

Study of physical properties and drug release kinetics of dendrimer hydrogel for ocular drug delivery

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I. Introduction

The anatomy, physiology, and biochemistry of the eye are one of the most complex and unique systems in the human body.¹ Lacrimation (production of tears), effective drainage by the nasolacrimal system, the inner and outer blood-retinal barrier, the impermeability of the cornea, and inability of absorption by other non-corneal structures cause the eye to be exceedingly impervious to foreign substances.^{1,2} While these innate barriers are advantageous for hindering the invasion of undesired molecules, pathogens, and particulates, they pose significant challenges to delivering ocular drugs. Currently, many drug delivery systems are utilized for ophthalmic treatment, including eye drops, ointments, inserts, implants, colloids, and suspensions.^{2,3,4} However, all of these systems are highly ineffective in delivering therapeutic drugs. For example, when a drug is administered topically by eye drops, less than 10% of the drug is absorbed into the system.⁴ Additionally, high doses of vigorous drugs can cause systematic and ocular side effects.⁴ To increase residence time and to dissolve hydrophobic drugs, ointments are prescribed, but these often cause blurriness and poor patient compliance.³

Many sources list “ideal” characteristics for delivering ocular drugs, some of which include:

- A sustained, controlled, or continuous drug delivery system²
- Maximizing corneal drug absorption and minimizing pre-corneal drug loss²
- Delivery through eye drops without blurred vision or irritation for convenience and high patient compliance^{1,4}
- Number of administrations limited to once or twice a day or less¹
- Appropriate particle size and compatibility with ocular tissue¹
- Other considerations, including factors of preparation, such as preservatives and appropriate suspensions¹

Nanotechnology, which refers to engineering, physical science, or electronics, is working with materials or molecules on a scale from 0.1 to 100 nm.¹ Gene and drug therapy, drug delivery, imaging, and novel drug discovery techniques are promising biomedical applications.¹ As for drug delivery, nanotechnology’s main advantages include a more accurate targeted delivery and controlled drug release.¹ Therefore, because of their size and properties, nanoparticles are ideal for ocular drug delivery. Some of the current biomedical, ocular nanotechnology includes microemulsions, nanosuspensions, liposomes, niosomes, and dendrimers.¹

Of these diverse nanotechnologies, dendrimers are particularly auspicious. Dendrimers are highly branched polymers with a three-dimensional structure. These very monodisperse molecules are composed of an initiator core, interior layers of repeating units, and multitudinous terminal groups. They are classified by the number of branches and terminal groups. Various cores and units can be used, which can change the properties and shape of the dendrimer. Currently, polyamidoamine, or PAMAM, is the most studied and employed dendrimer.⁵

Concerning drug delivery, dendrimers can either attach to a therapeutic agent by a permanent or separable bond to the end groups or be enclosed within the dendrimer itself. Because of its multiple terminal groups and its polymer backbone, dendrimers can have multiple functionalities.⁵ Dendrimers are especially ideal for synthesizing hydrogels, cross-linked networks that increase in volume in aqueous solution and are more similar to living tissue than any other synthetic compound.⁷ By adding polyethylene glycol or PEG groups to the dendrimers, these hydrogels have applications including cartilage tissue production and for sealing ophthalmic injuries.⁷ These compounds can be utilized to control the release of dendrimers.

Therefore, by synthesizing a hydrogel composed of PEGylated dendrimers that contain, for instance, ocular drug molecules attached to the dendrimers, one could study how efficiently such a system could deliver aforementioned drugs to the eye.

II. Progress Report

Over this summer, I have activated polyethylene glycol (PEG) and conjugated it to G3.0 PAMAM dendrimers. By using ¹H NMR, I have attempted to characterize how much PEG was conjugated to the amine terminal groups of the G3.0 dendrimers. Additionally, I have acrylated the terminal hydroxyl group on PEG to allow the dendrimers to be cross-linked through photo-initiation. A G3.0 PAMAM was also acrylated as a control. Unfortunately, the photo-initiated cross-linking to form the hydrogel did not occur. Finally, two mucin standard curves were created for future mucoadhesiveness assays with the hydrogel.

III. Goals for the Academic Year

My main research goal is to study the physical properties and characteristics of this cross-linked PEGylated dendrimer hydrogel. This includes water swelling studies, degradation studies, water retention studies, and drug release kinetics. These studies will help characterize the hydrogel and determine what—if any—changes or modifications need to be made for optimal effectiveness.

IV. Plan for the Academic Year

Experimental Preliminary Set-Up

Optimistically, Dr. Yang's lab will send me either hydrogels that have already been cross-linked or acrylated PEGylated dendrimers that can be cross-linked at Ripon College using either an ultraviolet lamp or a helium cadmium or diode laser. If time permits, different wavelengths of light can be used to cross-link the dendrimers and the following studies can be evaluated with each wavelength to determine the optimal cross-linking wavelength for this hydrogel.

Water Swelling Studies and Degradation Studies

By emerging the hydrogel in DIH₂O, I could determine how much water the hydrogel absorbs overtime until degradation occurs by monitoring mass. This study will attempt to evaluate when equilibrium occurs, when degradation commences, and attempt to quantify how rapidly degradation occurs.

Water Retention Studies

By using a static environment—idealistically with temperature, humidity, airflow, and other factors, I will attempt to quantify, using mass, the rate in which the hydrogel loses water through evaporation. To maintain a static environment, a monitored incubator could be used long-term. The temperature and humidity would be set to average room temperature conditions.

Drug Release Kinetics

Using the glaucoma drugs brimonidine tartrate and timolol maleate, I could ideally determine how much of each drug is released from the hydrogel *in vitro* through rapid dialysis techniques. To simulate human body conditions, dialysis would occur in a stable 37°C water bath. Prior to performing the drug kinetics studies, a standard curve for both drugs would be generated with a UV/Vis instrument. Using this curve, I could quantify the unknown concentration of the drug being released throughout the kinetics study.

Courses

For Fall 2009, I will be taking marine ecology and nautical classes through SEA Semester at Woods Hole, MA and performing marine biological or chemical research on the Pacific Ocean south of Hawaii. For Spring 2010, chemistry courses that would aid this project would be CHM 422: Biochemistry, CHM 334: Physical Chemistry: Chemical Thermodynamics and Kinetics, CHM 413: Advanced Organic Chemistry, or CHM 342: Advanced Laboratory. Biology and other courses that would aid this project would be: MTH 121: Statistics, BIO 200: Scientific Writing and Communication, and BIO 327: Cell Physiology. I will most likely take CHM 422, CHM 334 or CHM 342 (or both), MTH 121, and BIO 200.

V. Tentative Timeline

My goal is to complete the water swelling, degradation, and retention studies and start the drug release kinetic studies before I leave for Woods Hole in mid-October. As for Spring 2010, I cannot predict what I can accomplish: depending on my course load, I may be forced to limit my research to just completing the drug release kinetic studies and literature research.

VI. Budget

With my allotted \$1400, I will likely spend most of it on laboratory supplies and chemicals.

<i>Supply</i>	<i>Amount needed</i>	<i>Cost</i>
Timolol maleate salt (Sigma-Aldrich)	1 g	\$301.50
Brimonidine tartrate		
Std. dialysis closures, 35 mm (SpectrumLabs)	10 closures	\$86
Spectra/Por 4 std. dialysis tubing (SpectrumLabs) (12-14 kD MWCO, 32 mm flat width, 3.3 mL/cm)	100 ft (30 m)	\$186
Shipping for above items		~\$50
		Total: \$623.50

VII. References

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8. Malaek-Nikouei B, Sajadi Tabassi SA, Jaafari MR. Preparation, characterization, and mucoadhesive properties of chitosan-coated microspheres encapsulated with cyclosporine A. *Drug Dev Ind Pharm* 2008;34(5):492-8.
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