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Stimuli-Responsive Drug Delivery Systems using Gold Nanoparticles and Phospholipid Vesicles

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abstract

In the near future, new pharmaceutical therapeutics will evolve to contain complicated protein molecules, gene therapies, etc., which must be transported in extremely specific environments such as a specific pH level or sodium concentration. The problem is that throughout the body there are many different environments that a drug could pass through. For example, gastric acid can have pH levels as low as 1 where blood is around 7.4. This is a problem because as the drugs pass through these harsh environments they may become rendered useless. Furthermore, these new therapeutics are not compatible with conventional drug delivery mechanisms and new strategies for drug delivery are required. To solve these problem phospholipid vesicles are being used with gold nanoparticles to transport these drugs. The vesicles encapsulate the drug of choice and protect it from the harsh environments of the body. The gold nanoparticles can be designed to either embedded in the lipid bilayer of the vesicles or decorate the vesicle exterior. When radiation is applied, the nanoparticles are excited and cause a disruption in the vesicle structure, leading to the release of the drug into the body. Our research is centered around how the stability of the lipid vesicles changes based on the size, surface chemistry, and distribution of the nanoparticles.

research goals

1. Perform various gold nanoparticle syntheses and analyze the varying size, surface chemistry, and hydrophilicity the nanoparticles to determine their effects on drug delivery.
2. Measure the leakage rate of fluorescent dye from lipid-nanoparticle vesicles to simulate stimuli responsive drug delivery.
3. Tailor nanoparticle surface chemistry to increase stability and bioavailability, decrease macrophage uptake, and enable site-specific targeting.

introduction

Gold Nanoparticles (GNPs)

Hydrophilic GNPs:

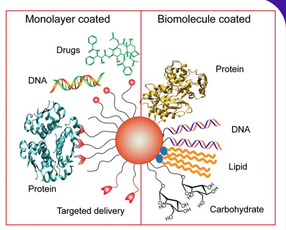
- Citrate(-)
- Carboxymethyl cellulose, CMC(-)
- Polyethylene imine, PEI(+)
- Polyethylene glycol, PEG(0)
- Dipalmitoylphosphatidylcholine, DPPC (+/-).

o Determine hydrophilic GNP effect on leakage when exteriorly bound to phospholipid vesicles

Hypothesis:

- Size and hydrophilicity will increase rate of fluorescent dye release.
- GNPs will cause enhancement of fluorescent dye

Hydrophobic GNPs:



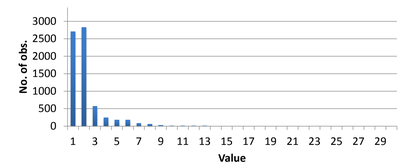
- DDT is used as capping agent
- Size range is 2-6 nm for averages
- Drugs are encapsulated in vesicle
- Particles embedded in bilayer
- GNPs are used to disrupt the vesicle

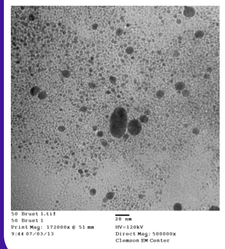
Experiments with GNPs:

- Determine how to control the size and distribution of size
- Conduct experiments varying size of nanoparticles in vesicles
- Conduct experiments to determine temperature of release

results

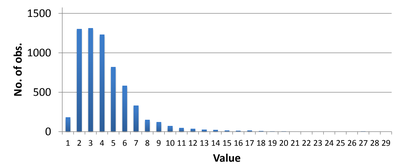
Histogram for 50% Fractionation

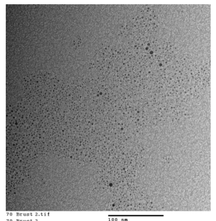




Mean	4.608
Standard Deviation	3.84
Range	60.62

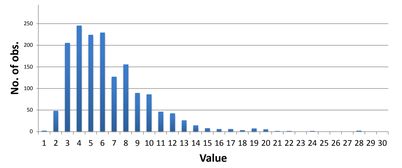
Histogram for 70% Fractionation

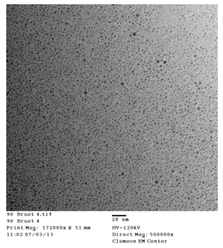




Mean	3.22
Standard Deviation	.9968
Range	10.52

Histogram for 90% Fractionation





Mean	2.95
Standard Deviation	.6636
Range	5.48

Results

As the data shows the fractionation does a very good job of creating different size dispersions. The range and the number average (mean) show exactly how well the fractionation process works. Also, the standard deviation continues to lower as the percent of methanol is raised. This is desired for the present because the lowest size is the most important, but more monodispersed distributions for higher averages will be required as research continues. Procedures will be developed to lower the standard deviation of the lower percent methanol fractionations.

Nanoparticle Characterization:

- Hydrodynamic diameter accounts for the gold core, the ligand length, and the hydrodynamic barrier surrounding the NP
- Poly-dispersity index (PDI) shows that our solutions contain a range of sizes, or conglomerates
- Zeta results need to be near +/- 30
- UV – VIS shows that colloidal gold exists in solution

Nanoparticle	Hydrodynamic Diameter (nm)	Volume %	PDI	Zeta (m.v.)	Confirmed through UV -Vis?
Citrate 5nm	10.09	99.7	0.564	-41.1	yes
Citrate 20nm	30.15	98.6	0.428	-46.2	yes
CMC	59.72	4.7	0.203	-58.1	yes
PEG	20.02	59.1	0.459	-1.41	yes
PEI 5nm	10.57	34.2	0.469	50.1	yes
PEI 10nm	23.06	97.4	0.421	49.8	yes

Table displaying the nanoparticles' characterizations:

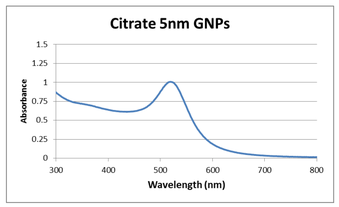
- Variance in expected sizes or zeta potentials display the need to perform dilutions of the samples and/or filter the samples to ensure no conglomerates are present in the samples which could skew results.

Importance of Characterization:

- Alterations in the nanoparticle surface chemistry and ligand types can engender different effects on the leakage rates and stability.
- Understanding the variances between the surface chemistries of the nanoparticles provides an accurate evaluation and analysis of these effects.

Nanoparticles and Liposomes:

- In order to create the vesicle-nanoparticle assembly, nanoparticles can be synthesized and then exteriorly associated with vesicles through electrostatic adsorption.



UV-Vis data displaying the wavelength and absorbance for 5 nm Citrate GNPs:

- Shows a peak approximately around 500 nm
- This peak demonstrates what wavelength the particles absorb at and, therefore, would have to be irradiated at in order to get nanoparticle heating.

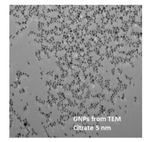
Image of various types of GNPs:
(Left to Right) CMC, 5nm PEI, PEG, Citrate 20 nm

Future Goals:

- To determine nanoparticle effects on drug delivery when exteriorly bound to lipid vesicles as well as determining the effect of the particles on fluorescent dye—quenching or enhancement
- The variations in surface chemistry can either produce a quenching or enhancement effect on the fluorescence emitted. Once these effects are analyzed and a control curve is obtained, the measurement of the leakage rate of dye will be determined.
- The development of the nanoparticle-lipid vesicle assembly will provide a new mechanism for drug delivery for patients that can provide site specific targeting upon thermal stimulation.
- This targeting system can be utilized to release the desired medication to specific sites within the body; thus, replacing the current technique of full body chemical treatment such as chemotherapy.

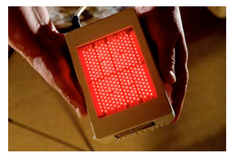
Experimental-Instrumentation

- **Instruments for Characterization**
  - Dynamic Light Scattering (DLS)
    - Hydrodynamic diameter, zeta potential
  - Ultraviolet Visible Spectroscopy (UV-Vis)
    - Approximate size, distribution, stability, surface chemistry
  - Transmission Electron Microscope (TEM)
    - Core GNP diameter, visual placement
  - Synergy H1 Plate Reader
    - Fluorescence intensity of dye



medical implications

The vesicles will help the medicine inside travel through the harsh conditions that they will have to endure while inside the body. The vesicles can be tracked in the blood stream and then leaked into the body when thermal radiation is applied. The vesicles must be stable enough to endure the temperature of the body without rupturing, but must also break under temperatures that the human body can easily tolerate. If this can be achieved, then the patient will be put under the least amount of stress and the medicine will be delivered most efficiently.



acknowledgments

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