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Development of a targeted and controlled nanoparticle delivery system for FoxO1 inhibitors

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Development of a targeted and controlled nanoparticle delivery system for FoxO1 inhibitors

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Abstract

Poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) are polymers approved by the United States' Food and Drug Administration due to their biocompatibility with humans. Drugs for various medical treatments have been encapsulated in PLGA-PEG nanoparticles for targeted delivery and reducing unwanted side effects. In this research, a flow synthesis method for PLGA-PEG nanoparticles with FoxO1 inhibitors and adipose vasculature targeting agent were studied. These drugs inhibit the FoxO1 pathway targeting white adipose tissues and converting them from an energy storing state to an energy burning state. A set of nanoparticles including PLGA and PLGA-PEG-P3 unloaded and drug loaded were generated. The particles were characterized by Dynamic Light Scattering, Fluorescence Spectroscopy, Transmission Electron Microscopy and Dialysis to measure hydrodynamic diameter, size distribution, zeta potential, stability, yield and encapsulation efficiency.

Introduction

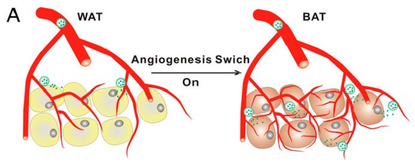


Figure 1. Schematic of the browning of white adipose tissue.[1]

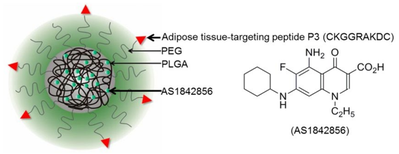


Figure 2. Representation of PLGA-PEG-P3-AS1842856 nanoparticle.

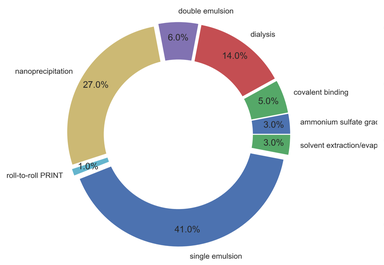
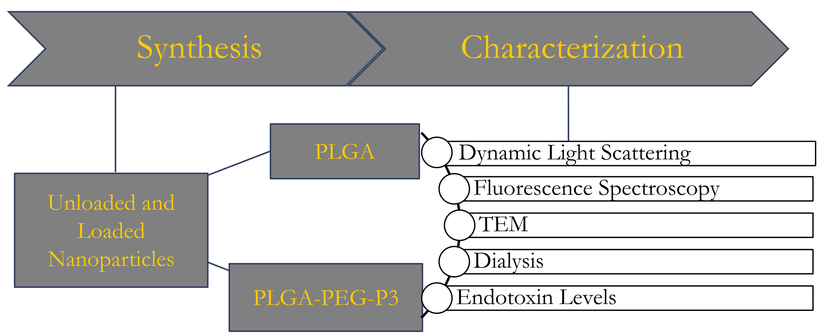


Figure 3. Method distribution for Nanoparticle synthesis.

- Around one third of the United States population is obese.
- The medical approach to treating this disorder is mainly focused on diet and exercise.
- Inhibition of the FoxO1 pathway allows for browning of adipose tissue to occur.
- Poly(lactic-co-glycolic acid) and polyethylene glycol are polymers used in the synthesis of nanoparticles for targeted drug delivery.
- Flow chemistry allows for more uniform particle formation as well as repeatability across batches.
- Our synthesis approach was compared to over 270 research articles using information extraction tools.

Experimental Design



Results

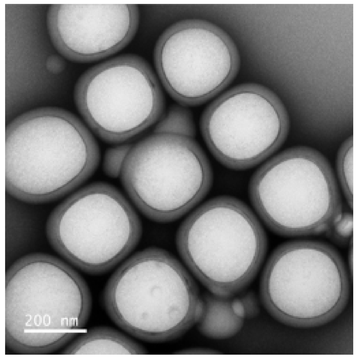


Figure 4. TEM image of PLGA nanoparticles.

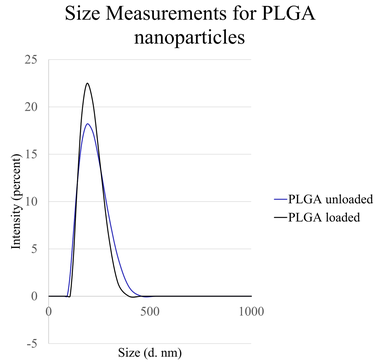


Figure 5. Size of PLGA nanoparticles.

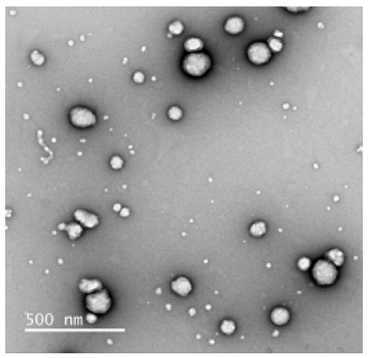


Figure 6. TEM image of PLGA-PEG-P3 nanoparticles.

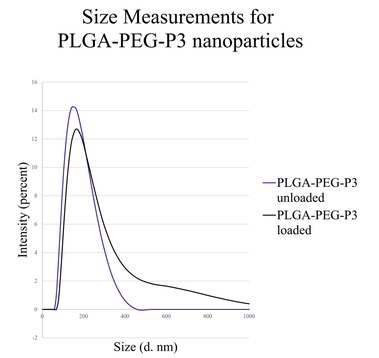


Figure 7. Size of PLGA-PEG-P3 nanoparticles.

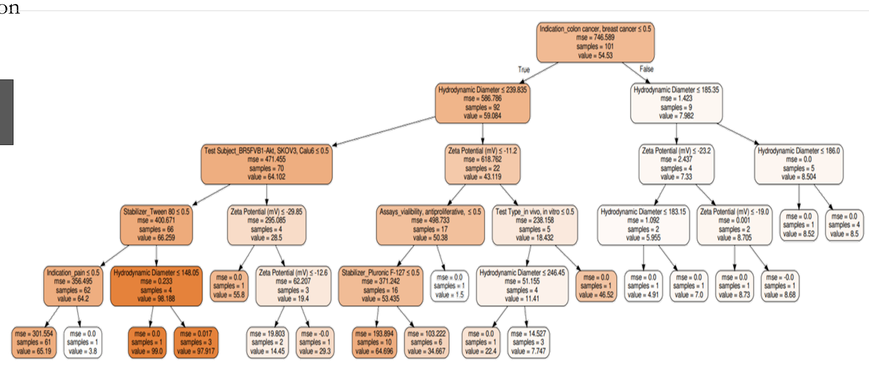


Figure 8. Decision tree based on nanoparticle data extracted from scientific papers.

- PLGA-PEG-P3-AS1842856 nanoparticles had a range of sizes from 142.4 ±0.4 d.nm to 208.7 ±3.5 d.nm. This was confirmed with TEM imaging.
- The polydispersity index was less than 0.500 for all the samples, ranging from 0.057 ±0.021 to 0.369 ±0.038.
- Zeta potential values for the nanoparticles synthesized ranged from -4.330mV ±0.214 mV to 13.40mV ± 1.89mV
- Stability testing indicated that the nanoparticles are stable for at least a month after production, based on particle size measurements.
- When comparing both PLGA and PLGA-AS1842856 nanoparticles it was evident that the drug is being encapsulated due to the change in size and fluorescence intensity. This was also the case with PLGA-PEG-P3 samples.
- Through fluorescence spectroscopy, the encapsulation efficiency was determined to be 100% for both AS1842856 drug loaded nanoparticles synthesized.
- Elevated endotoxin levels were measured in the synthesized particle suspensions.
- No nanoprecipitation occurred when using the same synthesis approach for two other hydrophilic drugs.

Future Work

- Control the release profile of the drug loaded nanoparticles in vitro.
- Develop PLGA-PEG loaded and unloaded nanoparticles for comparison.
- Determination of peptide conjugation efficiency.
- Carry out in vivo models with the developed nanoparticles.
- Manage the endotoxin levels in the nanoparticles.
- Study alternative syntheses such as water/oil/water emulsion or liposomal encapsulation for the other more hydrophilic drugs.

References

1. Xue, Y.; Xu, X.; Zhang, X.-Q.; Farokhzad, O. C.; Langer, R. Proceedings of the National Academy of Sciences USA 2016, 113 (20), 5552.

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College of Engineering