Modeling surface chemistry of gold nanoparticles for targeted inhibition of amyloid-beta aggregation.

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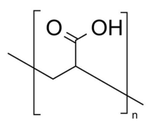
Introduction

Alzheimer's Disease (AD) is an irreversible and progressive brain disorder. AD is the sixth leading cause of death in the US, and it affects more than 6.2 million Americans and 44 million people in the world. Currently, there is no cure for AD. Researchers do not fully understand the cause of AD, but recent studies have led researchers to believe that aggregation of amyloid-β(Aβ) on the brain is an etiological factor for AD. Researchers believe that if the process of aggregation is inhibited that could delay the average onset of AD until after a human's life expectancy meaning that it could be a potential treatment. Nanoparticles (NPs) have caused a lot of excitement and interest in this field because of their highly tunable properties. NPs can be synthesized out of many different materials. Properties like size, shape, and surface chemistry can be tuned easily, making them a great tool for biological applications. The material used for the NPs in this research was gold because gold nanoparticles are readily synthesized, easily functionalized, and highly stale against oxidative dissolution. Gold Nanoparticles have another very interesting property, their ability to pass through biological membranes. The blood Brain Barrier (BBB) is a biological membrane in the brain that is extremely effective at excluding exogenous materials. Crossing the BBB is essential to achieve therapeutic success. The gold nanoparticles were coated with polyacrylic acid (PAA). The PAA was modeled using Self Consistent Field Theory (SCFT) using the program Fortran. The goal of this research is to determine which polymer-coated gold nanoparticle configuration would have the best results at halting the aggregation of Aβ in the Brain.

Methods

This research consisted of a computational approach.
The polymers were modeled using Fortran code.
The Fortran code used Self Consistent Field Theory to solve mathematical equations and give a well-grounded assumption for the model of the polymer.



Poly-Acrylic(Acid)	
Persistence Length	0.5 nm
Segment Length	0.3
Segment Volume	0.014 nm³
Pka	5
Tris Concentration	0.001m
Salt Concentration(NaCl)	0.1m
Ph bulk	8
Solvent Volume	0.03 nm³
Salt Volume	0.03 nm³

Worm Like Chain Equation for curvilinear coordinates

$$\frac{\partial}{\partial s}q(\mathbf{r},\mathbf{u},s)=\left\{-W(\mathbf{r},\mathbf{u})-\frac{\lambda}{2}\kappa^2(\mathbf{r},\mathbf{u})\right.$$

$$\left.-\mathbf{u}\cdot\nabla_{\mathbf{r}}+\frac{1}{2\lambda}\nabla_{\mathbf{u}}^2+[(\mathbf{u}\cdot\nabla_{\mathbf{r}})\mathbf{u}]\cdot\nabla_{\mathbf{u}}\right\}q(\mathbf{r},\mathbf{u},s),$$

Gaussian Model equation for planar coordinates

$$\frac{\partial}{\partial s}q(\mathbf{r},\mathbf{r}_0,s)=\left[\frac{a^2N}{6}\nabla^2-w(\mathbf{r})\right]q(\mathbf{r},\mathbf{r}_0,s) \qquad (1.24)$$

$$\frac{\partial}{\partial s}q^\dagger(\mathbf{r},\mathbf{r}_0,s)=-\left[\frac{a^2N}{6}\nabla^2-w(\mathbf{r})\right]q^\dagger(\mathbf{r},\mathbf{r}_0,s) \qquad (1.28)$$

Results

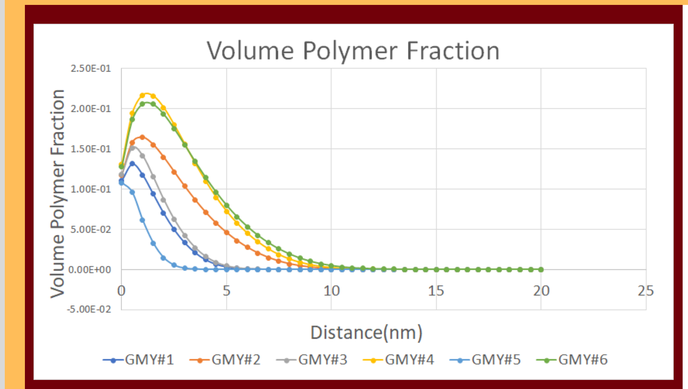


Figure 1.

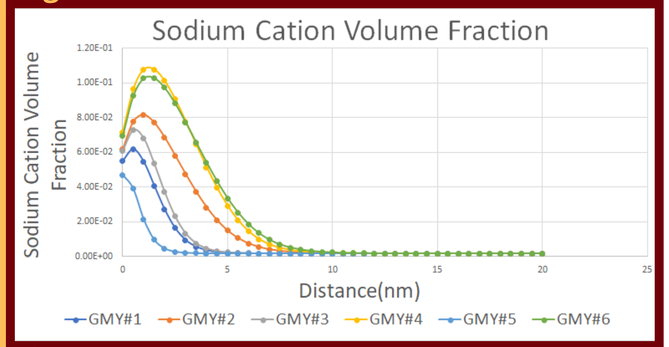


Figure 2.

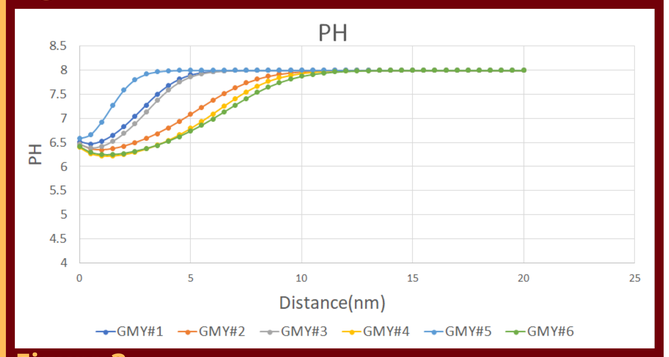


Figure 3.

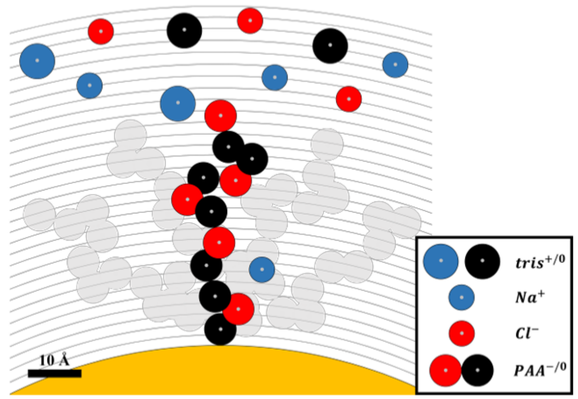
Gold Nanoparticles	Number of Segments	Radius (nm)	Contour Length (nm)	Bulk Polymer Fraction
Gmy #1	36	5	10.8	0.00004
Gmy #2	112	5	33.6	0.00012
Gmy #3	36	10	10.8	0.00015
Gmy #4	112	10	33.6	0.00047
Gmy #5	11	7.5	3.3	0.00003
Gmy #6	138	7.5	41.8	0.00033

Conditions for each gold nanoparticle modeled.

Figure 1. The surface coverage of the PAA is constant in all these calculations at 1 polymer / (squared nm), so the larger the nanoparticle, the more anionic polymer is coating the surface. The bulk pH is 8 to match experiments, and this is 3 units above the pKa of PAA, so the polymers are very stretched due to all the monomer units being charged. The very stretched polymers do not exhibit much regulation of charge due to curvature, so we can see that the only real curvature effect is increasing the charge on the nanoparticle for increasing nanoparticle size.

Figure 2. The high negative charge on the nanoparticle surface scavenges a lot of sodium cations from the surroundings. The larger nanoparticles with longer chains exhibit the most localization of sodium cation.

Figure 3. The local pH is greatly reduced at the surface of each nanoparticle. The value of the pH at the surface is consistent for each system studied in this work. The larger nanoparticles with longer chains exhibit the most influence of reducing the pH for a greater volume around the nanoparticles.



Conclusions and Future Work

The theory used for this research project models the chemistry of the molecular environment around gold nanospheres. The model explicitly accounts for the sensitivity of this system to the local aqueous environment. The PH effect shown on the graphs corresponds to the inhibition of aggregation confirmed experimentally. GMY#4 and GMY#6 show the best results for extended lag time on the aggregation assays. Using this theory, the shell of ph in a given solvent can be tuned by adjusting the particle diameter, tethered polymer length, and grafting density.

The long-term goal for nanoparticles would be to get them on in vivo experiments and eventually be approved for clinical trials. We are working on developing a similar theory to model Aβ aggregation from a thermodynamic perspective, that would allow for direct modeling of the interaction between Aβ aggregation and the local solvent effects produces by the NPs. This Theory would also allow testing of other polymers like PMMA to see their effect on aggregation. This could be a great design tool to engineer nanoparticles to inhibit Aβ and potentially stop the progression of Alzheimer's Disease.

References

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Acknowledgments

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