DESIGN OF BIOLOGICALLY ACTIVE EMBOLIZATION COILS FOR TREATING BRAIN ANEURYSMS

bettingergroup
biomaterials-based microsystems + electronics

JOET BAGGA[12] – ONYENMA ENWEREJI[12] – DARWIN KWOK[12] – DEREK LOH[13] – ANN RUTT[13]

1: BIOMEDICAL ENGINEERING
2: CHEMICAL ENGINEERING
3: MATERIALS SCIENCE AND ENGINEERING

BACKGROUND

ANEURYSM TREATMENT WITH ENDOVASCULAR COILING

- An aneurysm is a weakened portion of a blood vessel creating a bulge in the vessel wall
- If untreated, blood pressure can cause aneurysm rupture leading to serious health risks
  - 1 in 50 individuals unknowingly live with brain aneurysms
  - 1 in 10,000 aneurysms will rupture, 40% of which are fatal.
- Aneurysms can be treated with an endovascular coiling procedure.
  - A series of small platinum coils are packed into the aneurysm site causing blood flow to slow in the aneurysm site allowing a clot to form.
- The clot develops into tissue and blocks blood flow into the aneurysm
- Lowering the pressure in the aneurysm reduces the risk of rupture.

THE PROBLEM: RISK OF ANEURYSM RECURRENCE

- In 10-20% of cases recurrence occurs and the risk of rupture is only temporarily reduced
- The clot formed degrades restoring blood flow
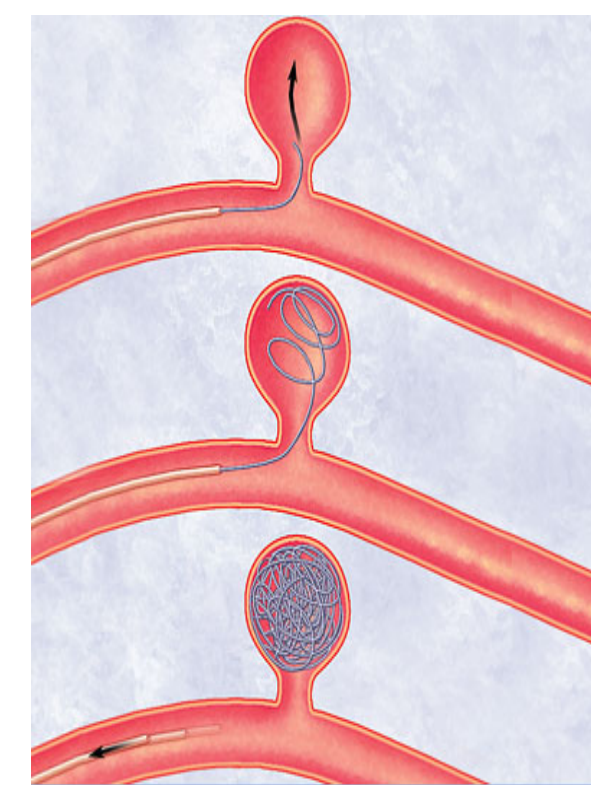- Recurrence typically occurs within 6 months after performing endovascular coiling

OUR APPROACH: USING GENIPIN TO INCREASE CLOT STABILITY AND PREVENT ANEURYSM RECURRENCE

- Genipin is a crosslinking agent capable of binding primary amines together
- Genipin would be able to crosslink proteins involved in clot formation
- Increasing the number and stability of bond in the clot will increase resistance to degradation reducing the risk of aneurysm recurrence
- Genipin can be loaded into a polymer coating on platinum coils used in endovascular coiling

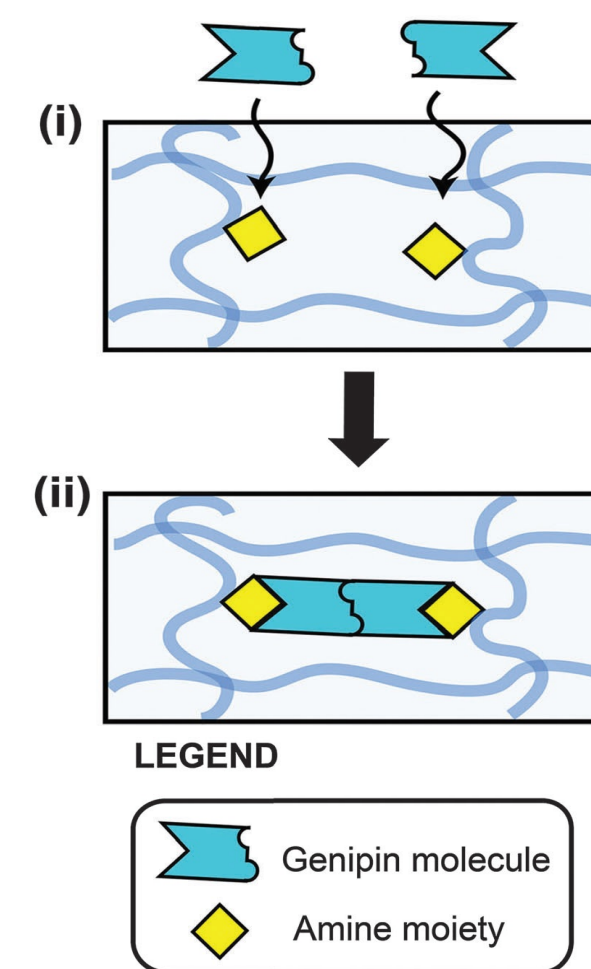Figure 1: A small platinum coil is packed into an aneurysm during endovascular coiling.

Figure 2: Genipin crosslinks amines in a two-step capping and coupling reaction

PROJECT GOALS

- Create polymer thin films that will release genipin in the correct time frame
- Delay the release of genipin until clot begins developing
- Utilize polymer crystallinity to influence the diffusion of genipin from the polymer for clot stabilization
- Increase understanding of results by applying a reaction-diffusion model

EXPERIMENTAL RESULTS

PLGA CRYSTALLINITY OF VARYING COMPOSITION AND CHIRALITY

POLYMER	DEGREE OF CRYSTALLINITY
PLDGA 50:50	2.3%
PLLGA 85:15	32%
PLLA 100:0	61%

Table 1: PLGA of varying compositions and chirality were selected and tested for degree of crystallinity. Polymers of greater crystallinity will resist hydrolytic degradation and slow the diffusion of genipin out of the polymer. Based on the measured degrees of crystallinity, PLDGA 50:50 and PLLGA 85:15 were further studied to determine their genipin release characteristics.
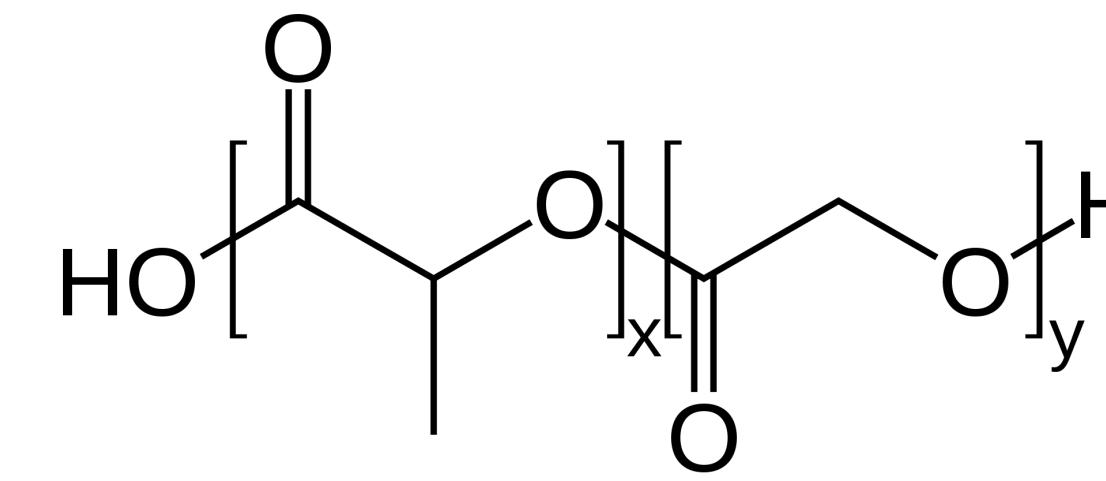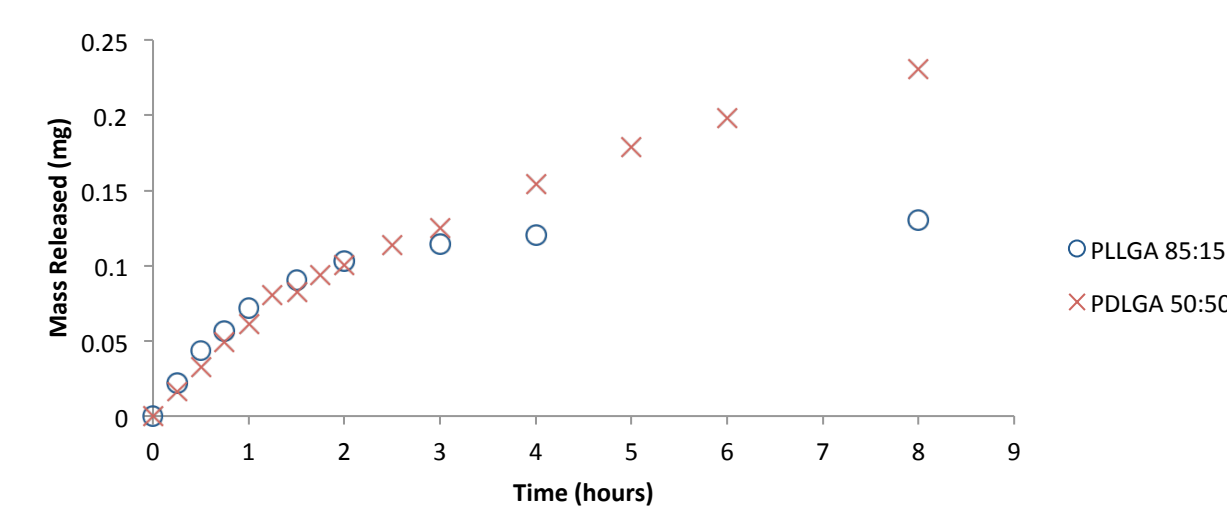

Figure 4: Structure of Poly(lactic-co-glycolic) acid (PLGA). The ratio of each of the subunits can be changed in order to change the degradation and diffusion properties of the polymer.
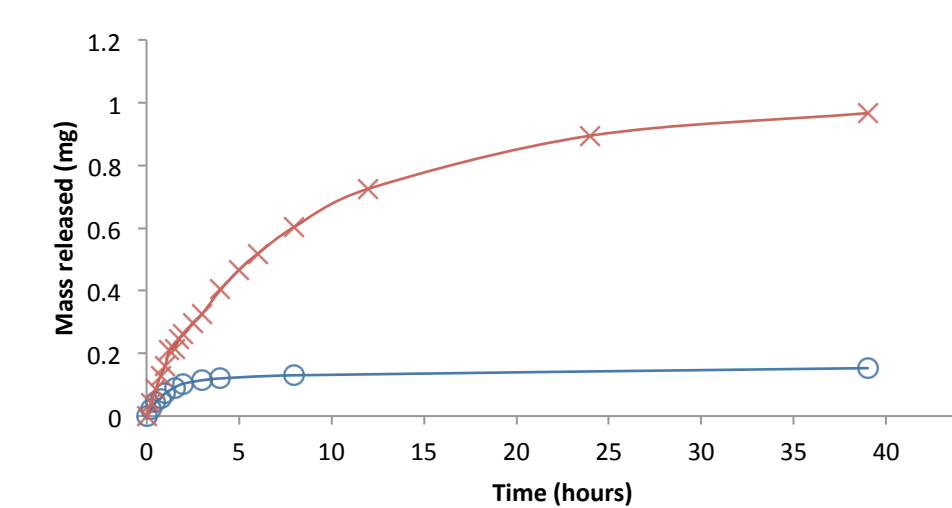

Figure 5:
The above plots represent the release of genipin from PLLGA 85:15 and PDLGA 50:50 thin films. The plot on the right shows the release of the genipin during the first 8 hours and the plot on the left represents the release of the genipin over 39 hours.

MODELING

- The following model was developed for coils coated with a film composed of 50% genipin and 50% polymer by weight and with an initial film thickness of 30 microns. Altering these parameters in the model to predict an optimal release rate can provide insights into future experiments.
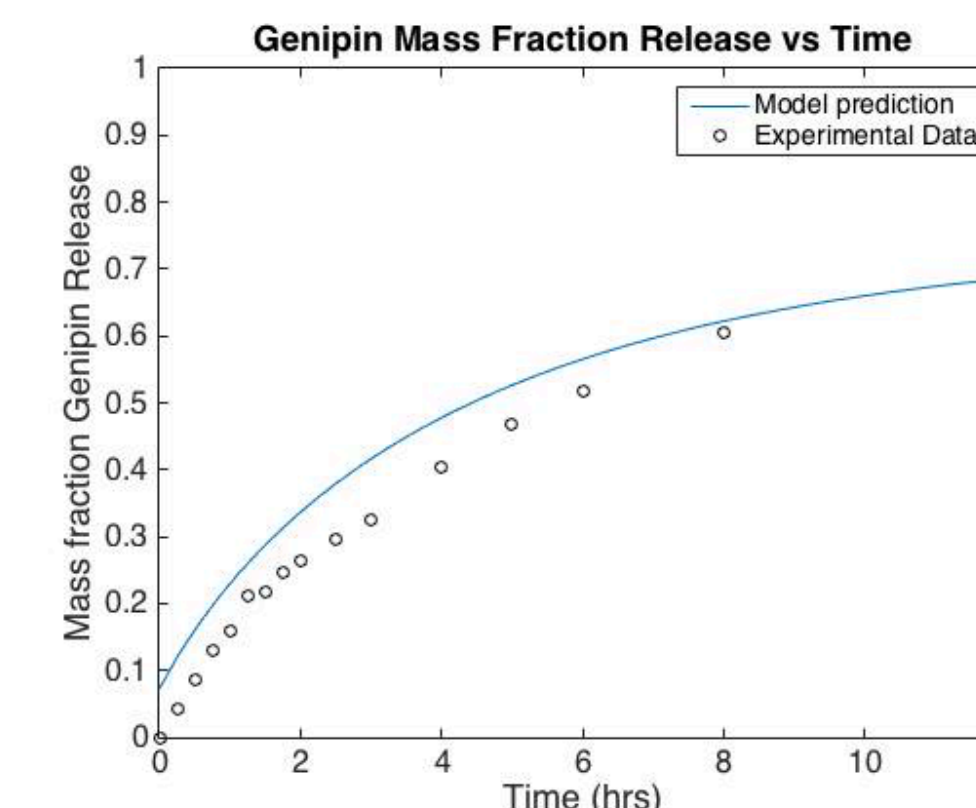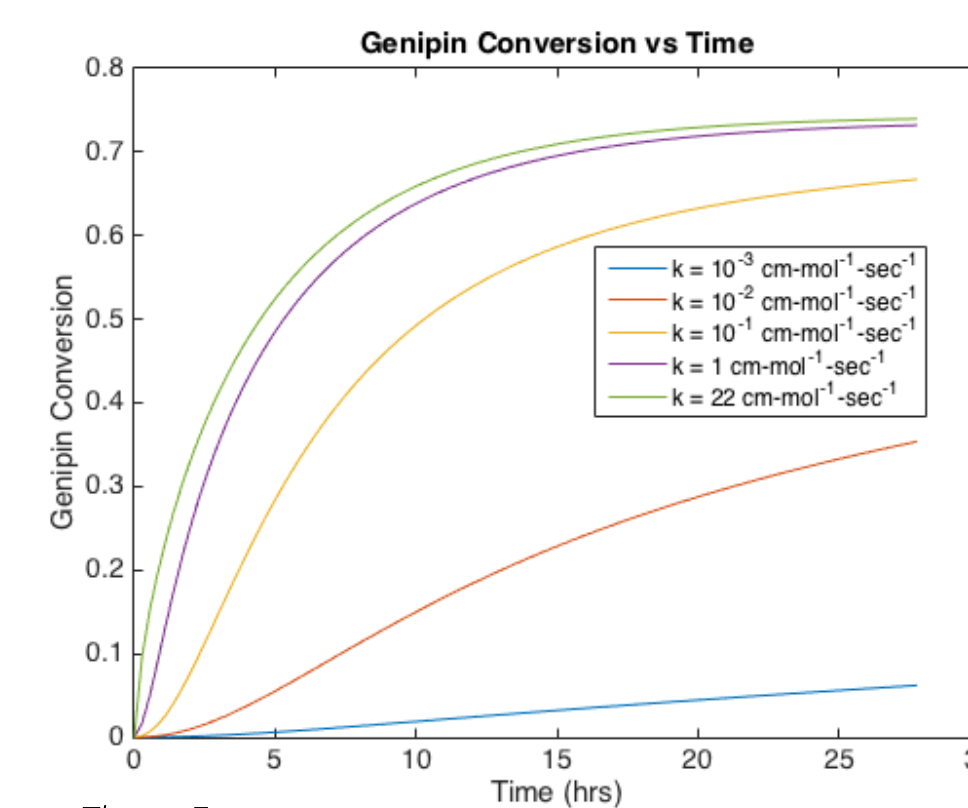

Figure 5:
The plot on the right was obtained by developing a 1-D model and displays genipin consumption over time. Taking into account diffusion and reaction kinetics, the model represents how long it takes for the genipin to diffuse out of the coil and to bind to an amine for clot stabilization. The plot on the left compares values obtained from a variation of the model to data acquired from a controlled release experiment (50:50 w/w Genipin: PDLGA)

COMPARISON TO EXPERIMENTAL RESULTS

- Since the concentration of amines is variable and difficult to determine, the analysis was run over a variety of reaction rate constants.
- From the plot, it is evident that reaction rate constants above 1 cm-mol^{-1}-sec^{-1} do not significantly increase the rate of consumption.

METHODS

- Different types of PLGA were characterized for their crystallinity using differential scanning calorimetry (DSC)
- The PLGA was dissolved with genipin in a solution for casting thin films
- Spin coating was used to coat the solution on a substrate creating a thin film to simulate a coating on an endovascular coil
- The thin films loaded with genipin were exposed to a solution of phosphate buffer solution (PBS) at 37C
- The release of the genipin from the thin films was determineed by characterizing the PBS solution at several time points using UV-vis spectroscopy

CONCLUSION

- A reaction-diffusion model was made to predict genipin behavior in a variety of conditions
- Films can be casted to mimic genipin release from embolization coils for experimentation
- Model predictions align well with experimental data
- 85:15 PLLGA thin films releases less genipin than 50:50 PDLGA thin films in vitro
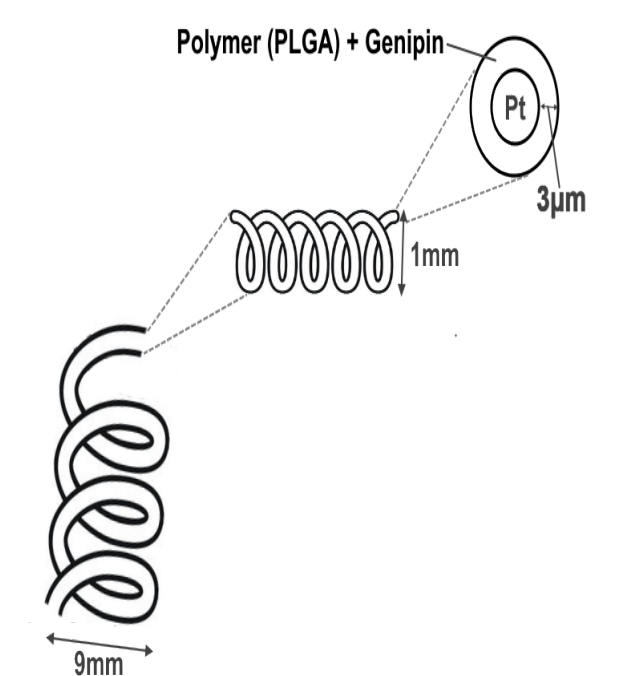

Figure 7:
A representative image of the proposed device which consists of a platinum embolization coil coated with a polymer layer loaded with genipin

FUTURE WORK

- Fabricate and characterize thin films with uniform properties to better understand the release of genipin over longer time scales
- Perform in-vivo experiments using genipin loaded polymer coated endovascular coils

REFERENCES

- http://ocw.mit.edu/courses/materials-science-and-engineering/3-051j-materials-for-biomedical-applications-spring-2006/lecture-notes/lecture19.pdf

ACKNOWLEDGEMENTS