Engineering Microstructures in Biomaterials for Drug Delivery

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Background

- Approximately **1 in 5** people contract cancer during their lives.
- **Chemotherapy** is one-way cancer is treated, but it has harmful side effects and often requires frequent hospital visits.
- Hydrogels as a drug delivery system could offer solutions to these problems, but raise some **problems** of their own, primarily in **burst/slow-release of drugs**.
  - Increased Blood Toxicity
  - Swift Decline in Effectiveness
  - Frequent Injections
  - Lack of Precision
- We sought to **solve these problems** by engineering hydrogels that utilize **sustained release**, which offers:
  - Reduced Blood Toxicity
  - Steady Effectiveness
  - Fewer Injections
  - More Precise Targeted Drug Delivery
- We utilized microstructured hydrogels comprised of **Dextran Methacrylate (Dex-MA)**, a polysaccharide modified with **hydrophobic** residues that undergoes phase separation in an aqueous solution with well-defined microdomains to accommodate **hydrophobic drugs** and **test dyes.**

Materials

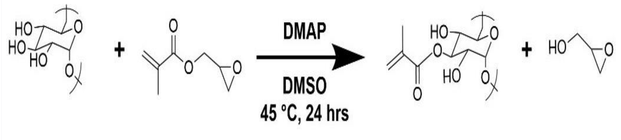
- **Dextran** is an uncharged hydrophilic Homopolysaccharide and FDA-approved material.
- **Rhodamine-B** is a hydrophobic dye.
- **Doxorubicin (DOX)** is a hydrophobic chemotherapy drug.
- **Irgacure 2959** is a photo-initiator initiating the photopolymerization of dextran hydrogel precursor.

Dex-MA Synthesis

- Modified Dextran (Dex-MA)

Dialysis Set-up

  - The Dextran was chemically modified by adding glycidyl methacrylate to make the resulting materials hydrophobic.
  - The reacted materials were precipitated in isopropanol and dialyzed for 3 days and lyophilized.

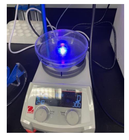


Synthesis of dextran methacrylate

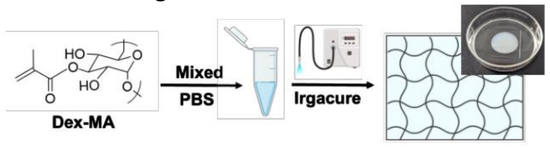
Photocrosslinked Microstructured Hydrogels

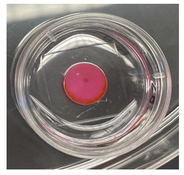
- Hydrogel solutions were prepared separately with dye and drug at a Dex-MA concentration of 50 mg/mL in PBS Buffer.
- Solutions were brought to different temperatures to promote differences in phase separation.
  - Cooled on ice for NPS
  - Heated to 24°C, 37°C and 45°C
- 2µL of photo-initiator Irgacure 2959 added to each 100µL sample.
- Each sample was exposed to 365nm wavelength UV light with intensity 25mW/cm^2 for 30s to 90s to crosslink.

UV Lamp

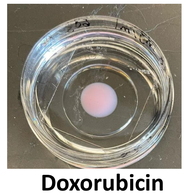


Crosslinking of Dex-MA in PBS Solution

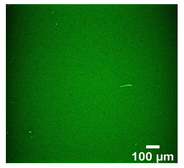




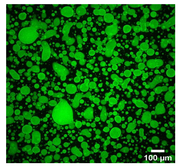
Rhodamine encapsulated Gel



Doxorubicin encapsulated Gel



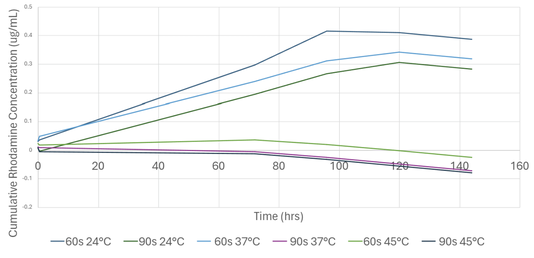
Non-Phase-Separated Gel



Phase-Separated Gel

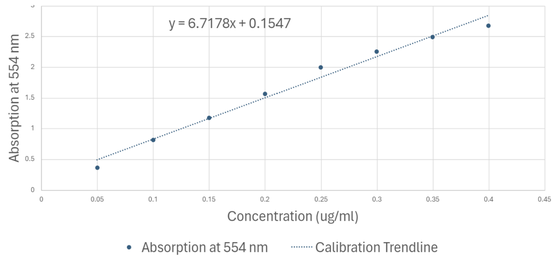
Results

Cumulative Rhodamine Concentration for Variant Temp and UV Exposure Times (50 mg/mL Dex-



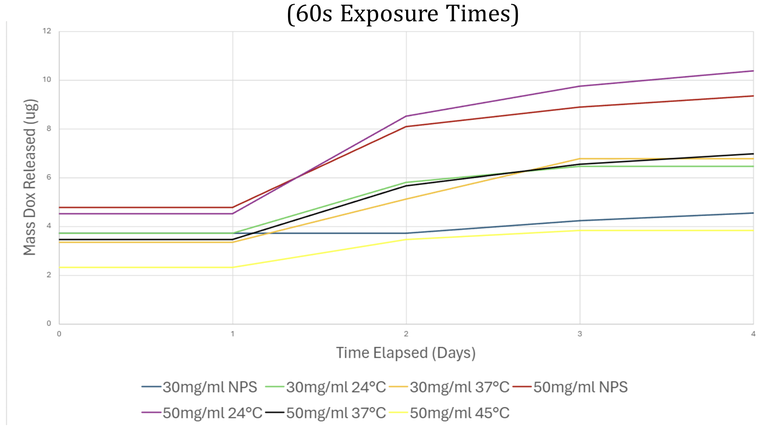
Increasing temperature or exposure time seems to decrease drug release, suggesting an inverse relationship between gel stiffness and rate of release.

Rhodamine-B Calibration Curve at 554nm



The absorption of Rhodamine increases linearly when concentration increases, allowing the concentration of Rh-B to be found from observed absorbance. Curve was created using absorption data from a Cary 3500 UV-Vis Spectrophotometer.

Cumulative Doxorubicin Concentration Variant Temperatures (60s Exposure Times)



- **The highest releases came from the 24°C 50mg/mL and NPS 50mg/mL samples.**
- **All samples expressed rapid release followed by a plateau, suggesting burst release.**

Standard curve equation used to calculate concentrations of Doxorubicin: y = .01983x - .00558

Discussions

- Hydrogels made from a phase-separated Dex-MA solution contain well defined microdomains that can effectively hold hydrophobic substances such as:
  - Test dye Rhodamine B
  - Chemotherapy drug Doxorubicin
- Such hydrogels can control the release patterns of the encapsulated drugs/dyes when exposed to a buffer solution such as PBS, allowing diffusion from the gel.
- Cumulative concentration of Rh-B released seems most linear for the gel brought to 37°C and crosslinked for 60s.
  - Optimal conditions for Rh-B release.
- All Dox releases seemed to display sharp accelerations followed by plateaus.
  - This is indicative of a burst release.
- Dye and drug release depends on the stiffness of the gels and temperatures. Higher stiffness and temperature exhibited slower drug/dye release.

Conclusions and Future Works

- Drug is more hydrophobic than Rh-B, it is more likely to remain encapsulated in the Dex-MA gel than the Rh-B was, which may explain the low overall released concentration observed in drug encapsuled gels.
- Future work will likely include testing different means of encapsulation in terms of loading efficiency, tuning the stiffness of gels and perhaps other solutions conditions to achieve sustained/controlled release.
- Tests must also be done to test the true effectiveness of the drug released by the gel; specifically, cancer cells will be exposed to the gel and its response to the diffusing drug will be measured.

Acknowledgements

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References

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