Drug Delivery Applications of Carbon Dioxide Responsive Hydrogels

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Abstract

Stimuli-responsive hydrogels are polymers that swell in the presence of water and alter their properties based on environmental conditions. Hydrogel applications utilize this ability to encapsulate and release a drug on command. In this study, we used a NIPAM-co-VI polymer to create a hydrogel that responds independently to temperature and CO_2. By sparging (bubbling gas through) hydrogels with CO_2, we are able to increase the rate and final amount of drug release from a hydrogel.

Applications

Optimization of drug release is promising for a number of hydrogel - related applications. For example. water bath treatment for diabetic foot ulcers, and water treatment for the removal of toxic dyes. Foot ulcers are non-healing wounds that appear chronically, especially with diabetic patients. Frangez et. al. describes a method to stimulate healing via angiogenesis by exposing the wound site to CO_2 in a water bath. Frangez et. al. also cites in their research that VEGF (vascular endothelial growth factor) is effective at stimulating angiogenesis. It is possible that VEGF release at the wound site using hydrogel encapsulation may compliment the CO_2 bath treatment. A second potential application utilizes the capability of NIPAM-co-VI hydrogels to absorb toxic dyes from water. Garg et. al. synthesized hydrogels that were able to selectively absorb dyes such as methyl orange and methyl violet, implicating their use in water treatment plants. The gels absorbed dye well, and upon release and redrying demonstrated their ability to function over multiple trials. This is similar to the reusability found by Garg et. al. with their gels, thus it is possible NIPAM-co-VI gels could provide a similar functionality with an alternate material.

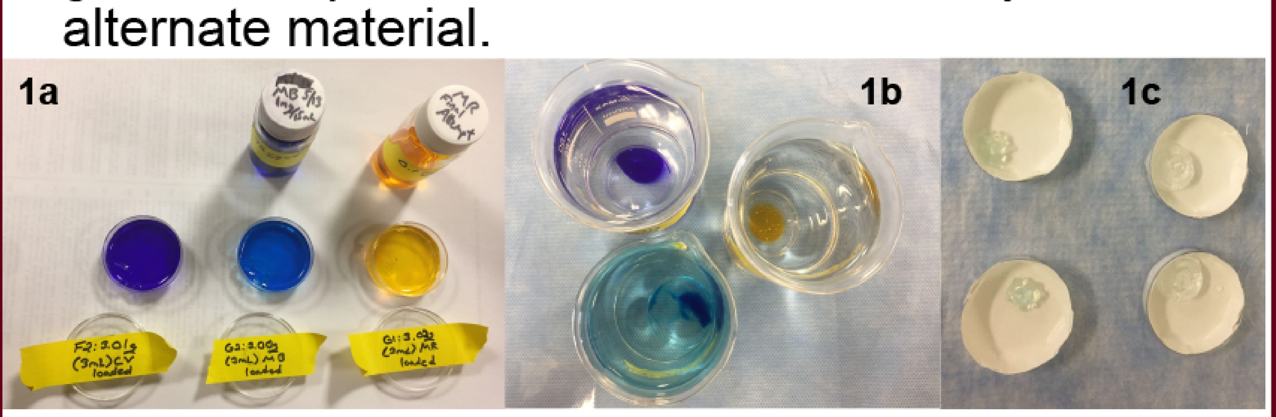
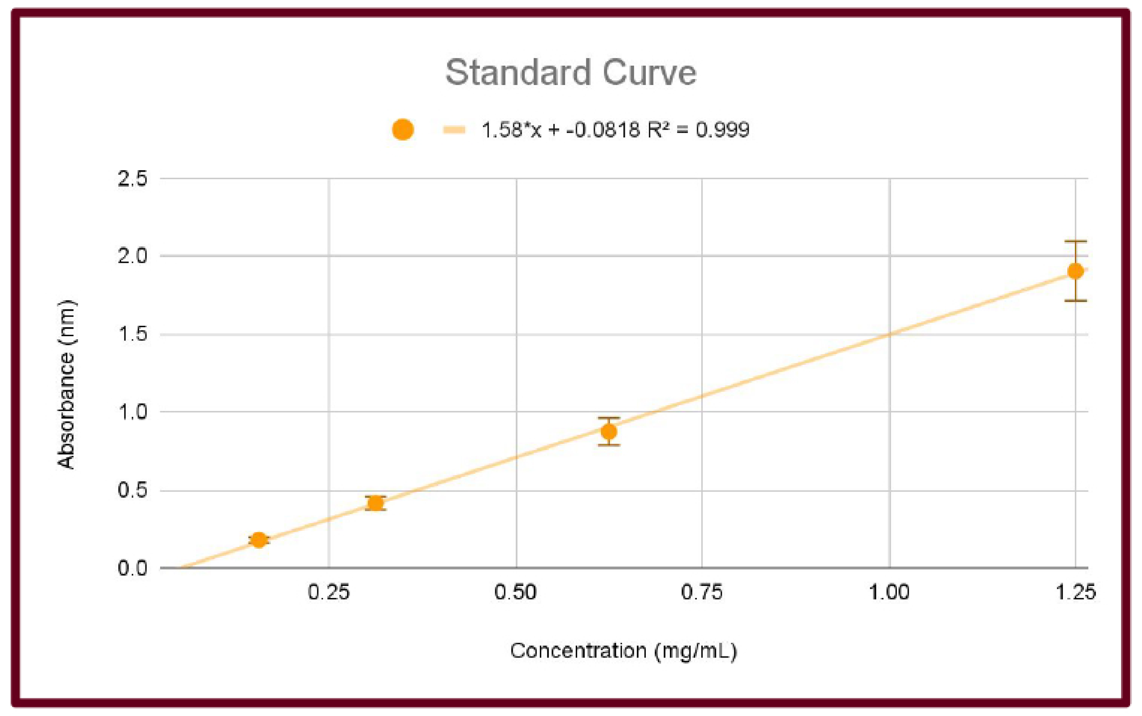
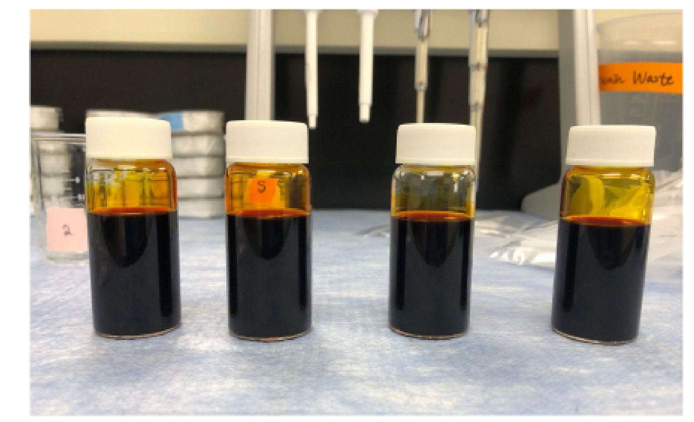


Fig. 1: The NIPAM-co-VI hydrogels during the loading phase (a), release phase (b), and redrying phase (c). The loading and release phase depict three different dyes: crystal violet, methylene blue, and methyl red (in order from left to right in Fig. 1a). The redrying phase depicts four partially dried methylene blue hydrogels -- note that two of the gels no longer retain methylene blue, allowing them to be reused in future trials. The gels depicted above were not sparged with CO_2 during release; if they were, it our results indicate that the methylene blue retained by the leftmost gels in fig. 1c would have been released over the same timescale.

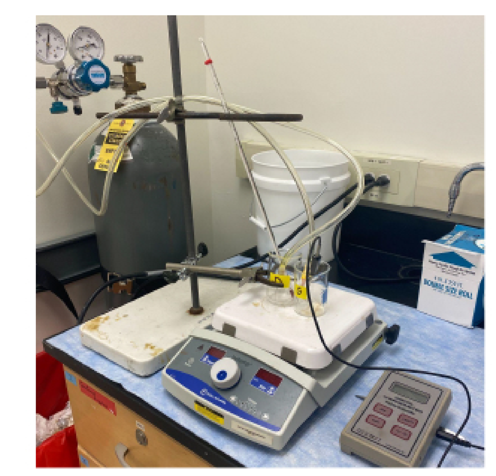
Methods





Above: Gels were loaded in a PEG/PBS curcumin solution. PEG was used to dissolve the curcumin due to curcumin's high solubility in PEG, and PBS was used to make the otherwise hydrophobic solution more readily absorbed by the hydrophilic gel.

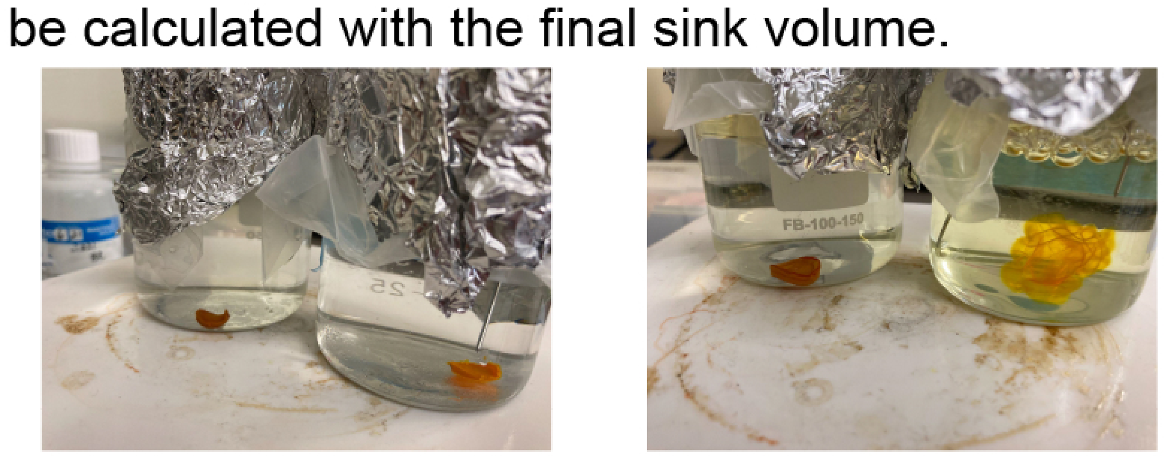
Below: Sparging set up for two gels. Beakers are kept at the LCST under careful observation using a hot plate, a temperature probe, a thermometer. The CO_2 is sparged using hoses with needles. The beakers are covered with aluminum foil to prevent evaporation and splashing.



The standard curve to the left represents curcumin in water. However, due to curcumin's low aqueous solubility, we loaded our gels in the PEG/PBS solution above. Gels were released in DI water. Thus the standard curve was not used in the final calculations, and volume - adjusted absorbance readings were instead used to obtain the relative release profile in the section below. While absolute measurements are not required for our research, further work in this area would allow us to asses the difference in final percent of loaded curcumin release in sparged versus unsparged gels.

Results

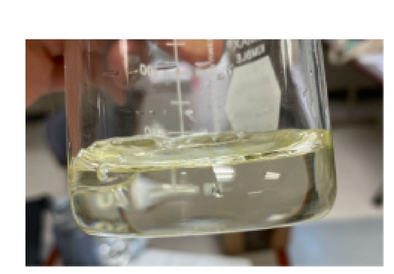
During a 45°C release trial, the CO_2 sparged gels released significantly more curcumin than unsparged gels. The mass of the cumulative release was determined by recorded absorbance values and volumes of each sink by a curcumin standard curve. The slope of the standard curve relates absorbance values with concentration, so the mass of curcumin release in each sink can be calculated with the final sink volume.



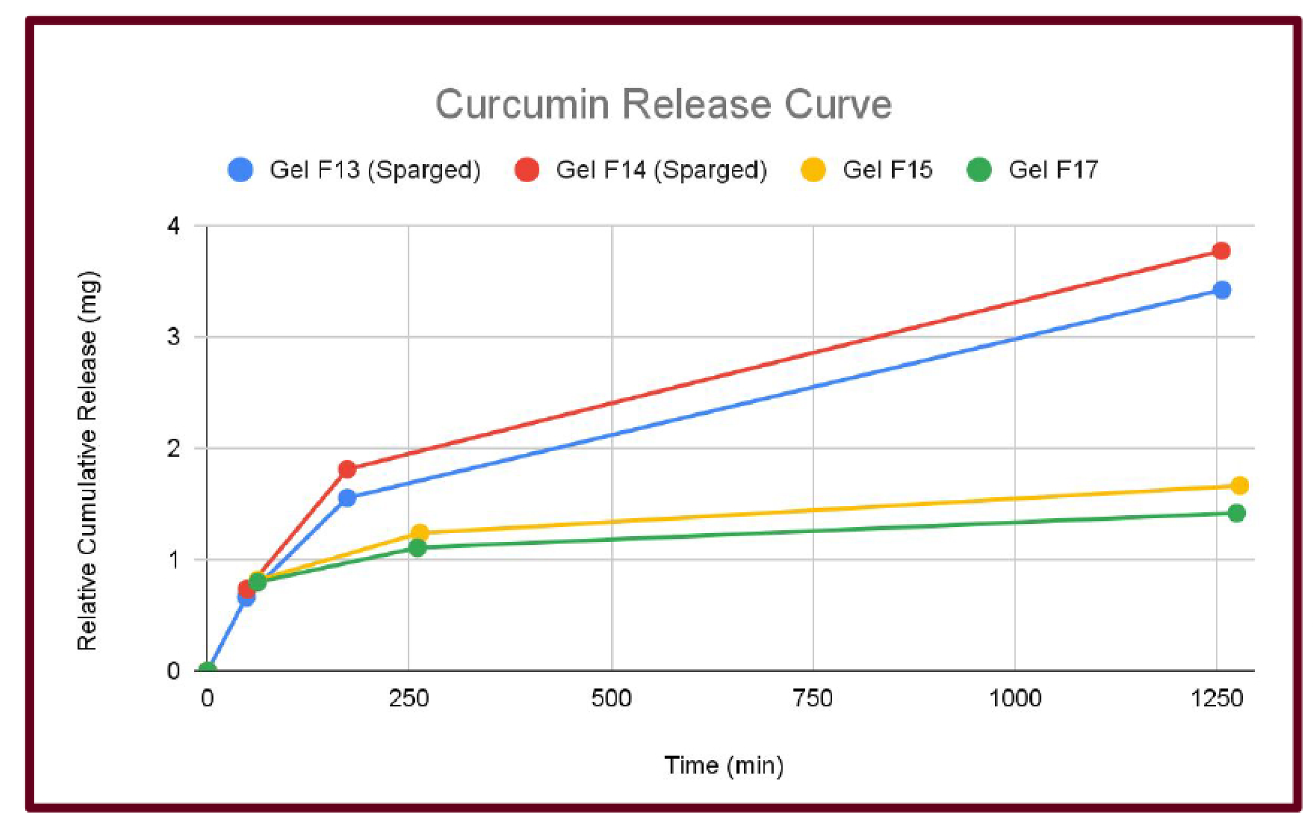
Unsparged (left beaker) and sparged (right beaker) curcumin-loaded hydrogels. The left image shows both gels at time zero, the right image shows the same gels after three hours of release. Note how the sparged gel exhibits far more swelling -- this is because the CO_2 raises the LCST of the gel, causing it to become hydrophilic and take on water. Subsequently, more curcumin is released.This is evident from the orange coloration of the sink, which we are able to quantify with an absorbance reader (see release curve to the right).

Hydrogel sparged with CO_2 in water.

Dried hydrogel, ~1cm in diameter.



Hydrogel sparged with CO_2 in water. The hydrogel has swollen to encompass the entire width of the beaker.



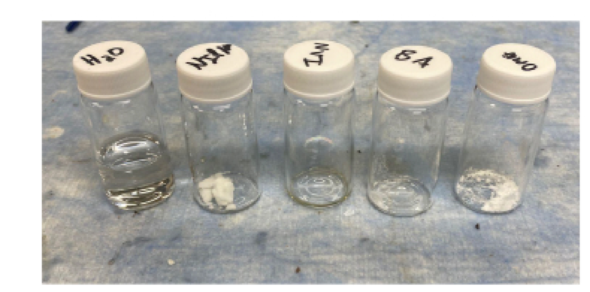
Hydrogels during synthesis (left) and after loading with methylene blue (above). While methylene blue was not found to be effective for sparging trials, the affinity of NIPAM-co-VI hydrogels for methylene blue and similar dyes supports potential applications in water treatment.

Hydrogel Synthesis

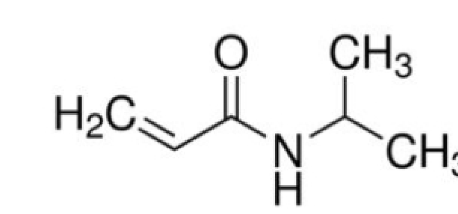
Materials

- Deionized Water (
- Poly(N-isopropylacrylamide)
- 1-Vinylimidazole
- methylene(bis)acrylamide
- Omnirad 2959

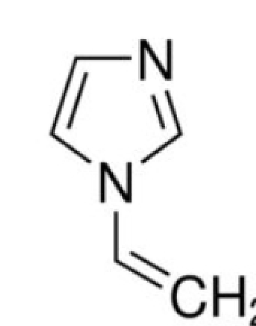
Combining and curing under a UV light, causes the gel to change from hydrophilic to hydrophobic at its LCST. Sparging with CO_2 causes the gel to swell, allowing it to absorb more water and expanding its hydrated state.



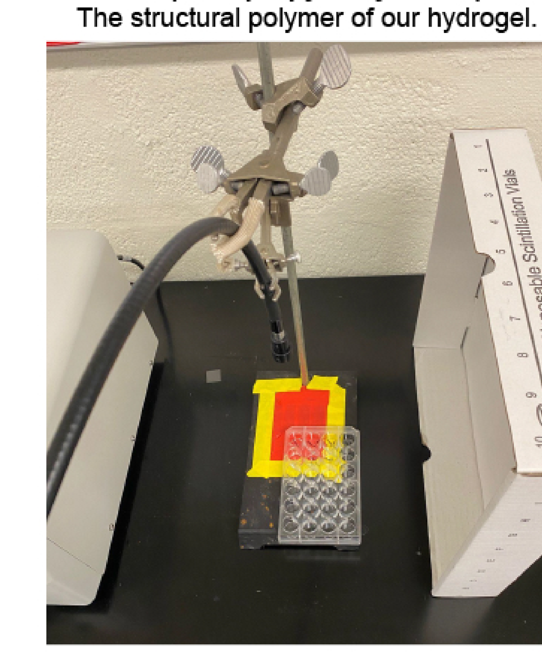
From left to right: DI, NIPAM, VI, BA, Omnirad.



NIPAM (N-isopropyl acrylamide):
The structural polymer of our hydrogel.



VI (1-Vinylimidazole):
The CO_2 - reactive moiety of our polymer.



Gels positioned to be cured under UV light.

References

I. Frangez, J. Colnaric, and D. Truden, *Clinical Research on Foot & Ankle.*, 2017, 05. 10.4172/2329-910X.1000232.
M. Garg, N. Bhullar, B. Bajaj, and D. Sud, *New J. Chem.*, 2021,**45**, 4938-4949

Acknowledgements

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