Optimizing Hydrogel Drug Release by Machine Learning on a Robotic Platform

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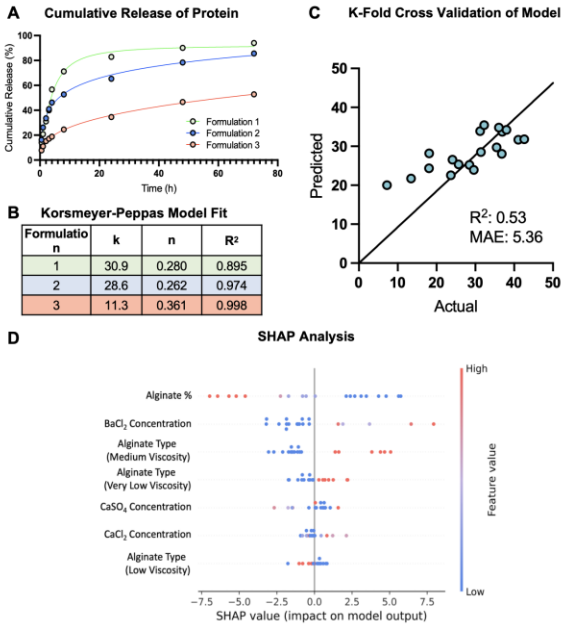
Statement of Purpose: Alginate hydrogels are useful materials for wound healing, drug delivery, and tissue engineering because of their biocompatibility and versatility [1]. Here, variable features for tuning performance include polymer concentration, the type of crosslinker, and the concentration of crosslinker [2]. Therefore, a platform that can efficiently survey these parameters would accelerate the development time of these materials. This study aims to test alginate hydrogels of various formulations and study their ability to deliver a protein payload. The release kinetics of the protein release will be modeled using machine learning to map the structure-function landscape. Results from this study may serve as a useful platform for other groups looking to predict the release kinetics of an alginate hydrogel prior to experimental testing.

Methods: Purified sodium alginate from brown seaweed of different molecular weights and concentrations were used for crosslinking. The hydrogels were crosslinked using various crosslinkers including calcium chloride, calcium sulfate, calcium carbonate, barium chloride, zinc chloride and strontium chloride. All hydrogels were formed in pH 7.4 phosphate buffered saline (PBS). Bovine serum albumin (BSA) was used as a model protein payload. Alginate hydrogels were prepared in 96-well plates by adding the sodium alginate, crosslinker, and protein payload in a 2:1:1 volumetric ratio. The hydrogel preparation process was automated using a Hamilton Vantage liquid handler. Sodium alginate of different concentrations were prepared by dissolving it in PBS. Next, a fixed 1% w/v BSA in PBS solution was prepared and added to the well and mixed with the alginate solution. Lastly, crosslinkers of various types and concentrations were added to the wells and mixed via shaking. The alginate hydrogels were allowed to cure overnight at 37°C to ensure complete gel formation. After successful hydrogel formation, payload release was measured by adding and aspirating 100 µl PBS at set timepoints between 0h – 72h. The protein release was quantified via BCA protein quantification assay. The release profiles of the various formulations were plotted and subsequently modeled in Python using the Korsmeyer-Peppas model (Figure 1A). The protein release of the hydrogels was modelled using a random forest regressor using the scikit-learn python package and validated using a k-fold cross validation method.

Results: By testing a wide array of formulations, we managed to produce a diverse dataset comprising of 93 unique release profiles. The release kinetics were modeled using Korsmeyer-Peppas with an average R-squared of 0.91 (Figure 1B). The random forest regressor showed promising predictive ability with an R-squared value of 0.53 and a mean average error of 5.36 (Figure 1C). When performing a feature importance analysis using Shapely Additive Explanations (SHAP), it was found that the alginate concentration was the feature that had the highest impact on the machine learning model (Figure 1D).

Conclusions: This preliminary exploration showcases the potential for utilizing machine learning and automation for alginate hydrogel testing and release profile optimization. Future directions for this study will look to broaden the dataset to include more commonly used formulations. This will look to fill in areas of uncertainty within the model with the aim of increasing the overall predictive ability.



Formulation	k	n	R^2
1	30.9	0.280	0.895
2	28.6	0.262	0.974
3	11.3	0.361	0.998

Figure 1. A) Release profiles of payload from alginate hydrogels. B) Korsmeyer-Peppas fit of the release profiles and their respective values for constants k, n, and R-squared. C) k-fold cross validation of the machine learning model. D) SHAP analysis showing feature importance of the machine learning model

References:

1. Hariyadi, D.M. and N. Islam, Adv Pharmacol Pharm Sci, 2020. **2020**: p. 8886095.
2. Mirtič, J., J. Ilaš, and J. Kristl, Carbohydrate Polymers, 2018. **181**: p. 93-102.