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Design and Synthesis of Polymers for Enhanced Solubility

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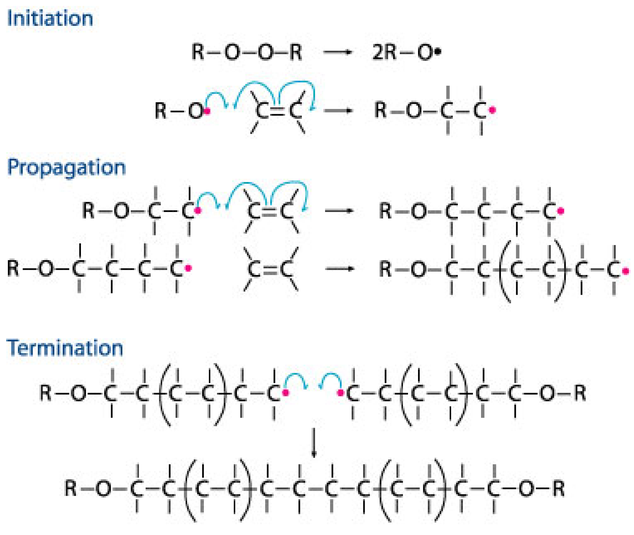
Introduction

- Drugs with low solubility are poorly absorbed and will have decreased bioavailability.
- Surfactants are amphiphilic agents that can increase drug solubility.
- The aim of this ImPaCT project is to address the issue of low drug solubility by synthesizing novel low molecular weight surfactants.

Methods

- Stage 1-Synthesis and Characterization of Surfactants
  - Free radical polymerization was used to prepare the surfactants.



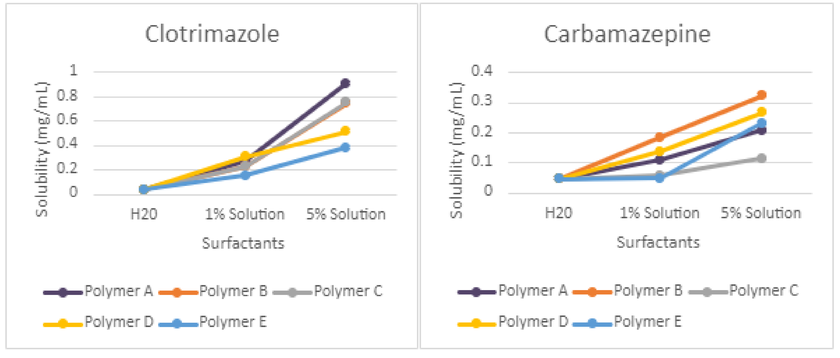
  - The polymer structure was analyzed using spectroscopic (MS and NMR) and chromatographic (GPC) methods.
- Stage 2-Solubility Testing
  - The known concentration of study drugs in methanol was used to determine the solubility in water via HPLC and LCMS..
  - Calibration curves were created from the drug/methanol LCMS results
  - Polymers were prepared in batches of 1% and 5% solutions and combined with each study drug and ran through HPLC and LCMS.
  - Calibration curves were then applied to the drug/water and drug/polymer LCMS results in order to determine drug/polymer solubility.

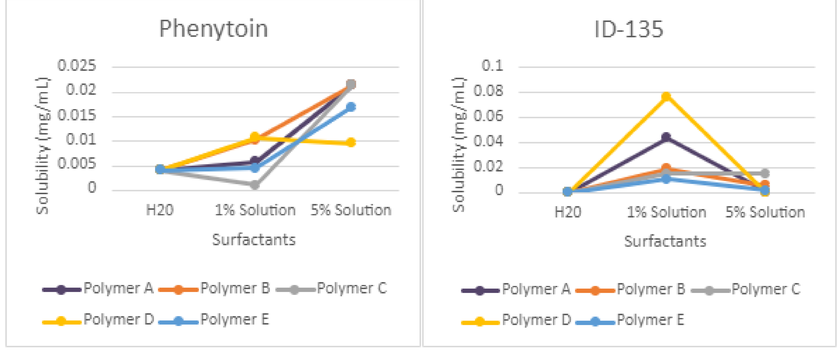
Results

- The methodology used for the synthesis of the 6 surfactants was successful with yields ranging from 1.54 to 2.96 grams.
- NMR analysis peaks were identified, confirming the formation of the modified polymer.
- The size of the polymer was determined using the ratio of the integration of the peaks from the vinyl group of the polymer and the terminal methyl group of the fatty acid.
- Four of eleven drugs tested showed solubility improvements, so they were the only drugs with calibration curves calculated.

Calibration Curves

Drug	Calibration Curve	r^2	Wavelength (nm)
Clotrimazole	y=1.04e+008X - 4.16e+005	0.998188	225
Carbamazepine	y=3.98e+007X + 2.47e+006	0.976014	250
Phenytoin	y=9.88e+006X + 6.44e+004	0.966209	240
ID-135	y=8.80e+007X + 4.04e+004	0.906573	290





Discussion

- Polymers A-E were successfully prepared following the free radical methodology. The transfer agent served as the modified portion of the polymer and a ratio was used for controlling the size of the polymers.
- NMR confirmed the proposed structure of Polymers A-E and GPC was used to estimate the size of the polymer. NMR also helped in determining the average number of monomers.
- Clotrimazole, carbamazepine, and phenytoin all showed a direct relationship between solubility and surfactant concentration.
- ID-135 demonstrated much greater improvements in solubility when combined 1% surfactant solutions compared with a smaller increase in solubility when combined with 5% solutions.
- Clotrimazole demonstrated the greatest percent increase with a 645% average increase in solubility when prepared in a 1% surfactant solution of polymer D.
- Among 5% surfactant solutions, polymer A resulted in a 2,119% increase in solubility for clotrimazole.
- Future study recommendations
  - Include more drugs with low solubility.
  - Repeat tests with the four study drugs that showed improvement, especially ID-135 since it displayed confounding results.
  - Modify the percentage of the surfactant solutions.

Conclusion

- Novel surfactants were synthesized and did show improved solubility in select drugs.
- If surfactant synthesis can be refined and the optimal ratio of surfactant to drug can be identified, the surfactants studied may be able to be added to the study drugs during the manufacturing process.
- As a result of this study, pharmaceuticals can be manufactured to be more soluble and have greater bioavailability within the body. Overall, this will increase the level of patient care.