Southern Illinois University Edwardsville School of Pharmacy

Design and Synthesis of Polymers for Enhanced Solubility

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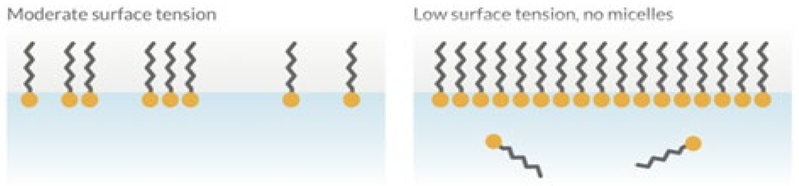
Introduction

- Absorption is the first step in a drug's ADME process within the body and is affected by the degree of their water solubility.
- 70% of new drugs have poor water solubility, which has a negative effect on their bioavailability.
- Using surfactants (amphiphilic agents) is one strategy to improve the solubility of a drug.
- Aim of ImPaCT Project: Design and synthesize modified PVPs that will improve solubility of poorly water-soluble drugs

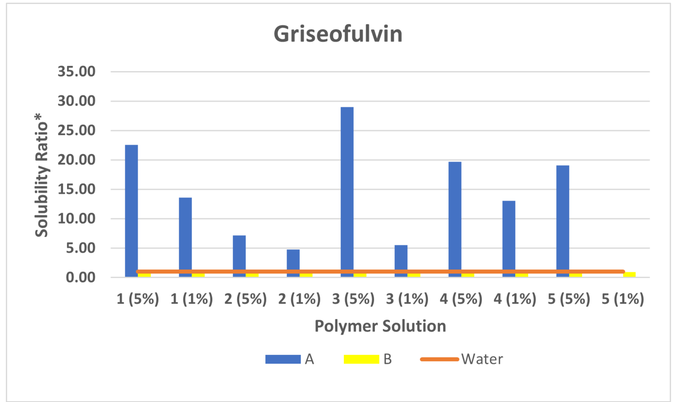


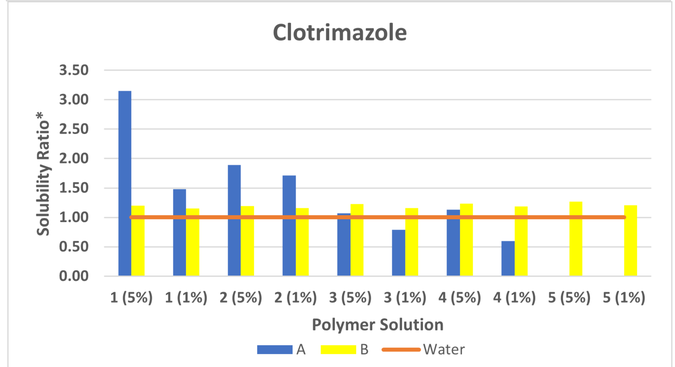
Methods

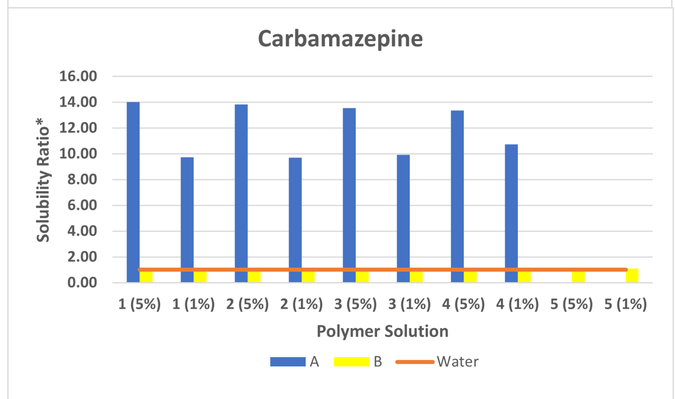
- Stage 1-Synthesis and Characterization of Surfactants
  - Free radical polymerization was used to prepare the surfactants.
  - The polymer structure was analyzed using spectroscopic (MS and NMR) and chromatographic (GPC) methods.
- Stage 2-Solubility Testing
  - Polymers were prepared in batches of 1% and 5% solutions and combined with each study drug and ran through HPLC and LCMS.
  - AUCs of the largest peaks as determined by HPLC results were used to assess solubility without determining exact solubilities.
  - AUCs of drug-polymer solutions were compared to that of drug (alone) in water, which was used as the reference solubility benchmark for each drug (S=1.0).
  - Results reported as a calculated "Solubility Ratio" (SR).
  - SR > 1: Improved solubility

Results

- The methodology used for the synthesis of the 10 surfactants was successful with yields ranging from 2.2 to 14.9 grams.
- Formation of modified polymers were confirmed by NMR analysis peaks.







* Solubility Ratio = AUC of drug in polymer divided by AUC of drug in water

Discussion

- Polymers A1-A5 and B1-B5 were successfully prepared from the free radical methodology.
- Griseofulvin experienced the largest SRs overall throughout the A1-A5 polymers with minimal differences in B1-B5 polymers.
- Griseofulvin's largest SR= 29.02.
- Overall, greatest increases in SR were found in polymer solutions A1-A5, with smaller increases in solutions B1-B5.
- SRs were generally higher with a more concentrated polymer solution (5% vs. 1%).
- Six drugs (griseofulvin, estrone, amiodarone, clotrimazole, carbamazepine, phenytoin) all showed improvements in solubility when added to polymer solutions A1-A5.
- Four drugs (griseofulvin, clotrimazole, sulfadiazine, carbamazepine) showed improvements in solubility when added to polymer solutions B1-B5.
- Improvements in solubility seem to be related to the fatty acid cap as well as the length of the modified PVP polymers.
- Although it was not done in this study, Log(P) could be calculated for each drug utilized in this study to gain a better idea of their overall lipophilicity.
- Future study recommendations
  - Include more drugs with low water solubility.
  - Determine optimal ratio of surfactant to drug to optimize solubility.

Conclusion

- The novel surfactants produced in this study have shown to improve the water solubility of certain drugs.
- These modified PVPs may potentially increase the bioavailability of these drugs in the human body as well.
- Drugs that may have failed approval due to poor water solubility could have future opportunities for approval if combined with these polymers.
- If combined with already-approved medications, combination with such polymers could potentially reduce the strength at which they are administered or even given less frequently.