Cross-linked Amino Acid-containing Polyanhydrides for Controlled Drug Release Applications

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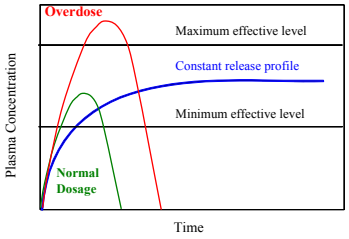
1. Introduction and Motivation

Rationale for Using Drug Delivery Systems



Advantages

- Continuous maintenance of drug levels
- Minimize side effects
- Decrease amount of drug and dosages
- Improve patient compliance

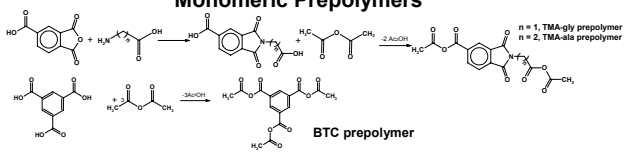
Disadvantages

- Potential toxicity of the drug support material
- Initial burst effect
- Discomfort from device placement
- Costly manufacturing of some modalities

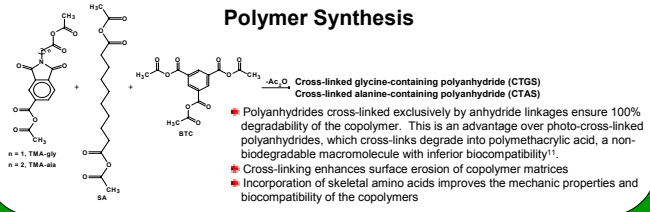
- Polyanhydrides have been known for several decades and are FDA-approved[1].
- Amino acid-containing polyanhydrides[2-5] and photo-cross-linked polyanhydrides[6-10] have shown superiority to linear polyanhydrides.
- The goal of this project is to develop cross-linked amino acid-containing polyanhydrides for controlled drug release applications.

2. Polymer Design and Synthesis

Monomeric Prepolymers



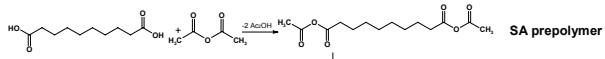
Polymer Synthesis



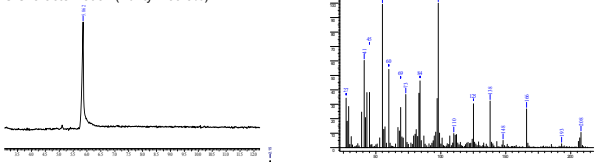
- Polyanhydrides cross-linked exclusively by anhydride linkages ensure 100% degradability of the copolymer. This is an advantage over photo-cross-linked polyanhydrides, which cross-links degrade into polymethacrylic acid, a non-biodegradable macromolecule with inferior biocompatibility[11].
- Cross-linking enhances surface erosion of copolymer matrices
- Incorporation of skeletal amino acids improves the mechanic properties and biocompatibility of the copolymers

3. Prepolymer Characterization

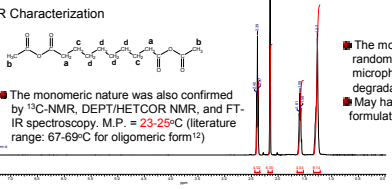
Monomeric Sebacic Acid (SA) prepolymer



GC-MS Characterization (Purity > 99.5%)



NMR Characterization



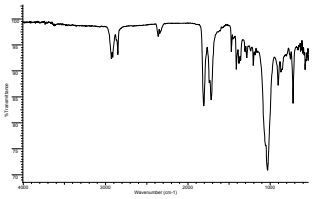
- The monomeric nature was also confirmed by ^{13}C-NMR, DEPT/HETCOR NMR, and FT-IR spectroscopy. M.P. = 23-25ºC (literature range: 67-69ºC for oligomeric form[12])
- The monomeric SA structure ensures a truly random structure for the copolymer, eliminating microphase separation, and allowing predictable degradation and controlled drug release.
- May have a positive impact on current Gliadel® formulation technology.

TMA-gly, TMA-ala, and BTC prepolymers

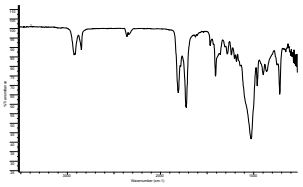
Each prepolymer was prepared according to the literature[2-4, 13].

4. Polyanhydrides Characterization

ATR-FTIR Analyses

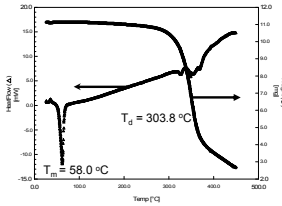


ATR-FTIR spectrum for the CTAS copolymer.

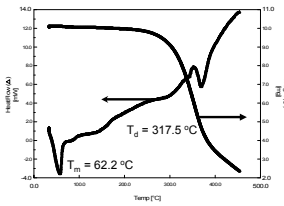


ATR-FTIR spectrum for the CTGS copolymer.

Thermal Analyses



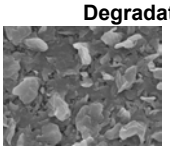
DSC and TGA profiles for the CTAS copolymer.

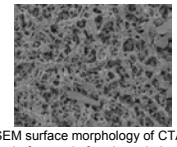


DSC and TGA profiles for the CTGS copolymer.

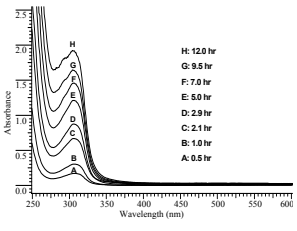
5. In Vitro Degradation and Solute Release Kinetics

Degradation of drug-free polymer matrices



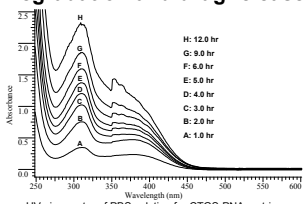


SEM surface morphology of CTAS before and after degradation

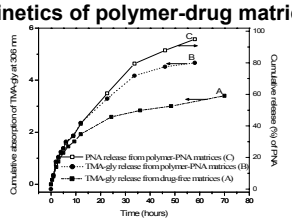


UV-Vis spectra of PBS solution for drug-free CTGS matrices

Degradation and drug release kinetics of polymer-drug matrices



UV-vis spectra of PBS solution for CTGS-PNA matrices



TMA-gly and PNA release from CTGS matrices

Conclusions

- Several thermoplastic cross-linked amino acid-containing polyanhydrides were synthesized and characterized by FTIR, NMR, DSC, and TGA.
- Due to their low degree of cross-linking and high hydrophilicity, their degradation and drug release characteristics were found to be similar to those of their linear counterparts.
- Changes in their chemistry including degree of cross-linking and hydrophobicity and in the formulation protocol are being evaluated in order to extend their useful life and range of applications.
- The monomeric form of the sebacic acid prepolymer was prepared for the first time.

Acknowledgements

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