####

CROSSLINKED AMINO ACID-CONTAINING POLYANHYDRIDES FOR CONTROLLED DRUG RELEASE APPLICATIONS

Guanglou Cheng[1], María A. Aponte[2], and Carlos A. Ramírez[1]
[1]Department of Chemical Engineering and [2]Department of Chemistry
University of Puerto Rico, Mayagüez, PR 00681
g_cheng@rumac.uprm.edu

ABSTRACT SUMMARY:

Crosslinked amino acid-containing polyanhydrides were synthesized by polycondensation. p-Nitroaniline (PNA) was formulated with the polymer, and the degradation and release behavior of the polymer-drug matrix studied. Results showed that for the hydrophilic polymer prepared, crosslinking has little effect on its degradation and drug release kinetics.

INTRODUCTION:

Polyanhydrides have been tested extensively as bioerodible supports in controlled drug release (CDR) applications. Some polyanhydride-based formulations are now clinically available for treating glioblastoma multiforme, a universally fatal form of brain cancer[1]. Linear amino acid-containing polyanhydrides were first developed in 1990[2], and later tested in orthopaedic[3-5] and CDR applications[6]. Photo-crosslinked polyanhydrides for load-bearing applications were also synthesized[7-9] by irradiating prepolymers containing methacrylate end groups. Degradation of these polymers produced poly-(methacrylic acid)s, sebacic acid, and other water-soluble molecules. Alanine-containing crosslinked polyanhydrides were also prepared by a similar method[10]. Likewise, branched polyanhydrides were prepared using 1, 3, 5-benzenetricarboxylic acid (BTC) and poly(acrylic acid) as branching agents. Degradation of the drug-free matrices was faster and drug release from the polymer-drug matrices was slower relative to their linear counterparts[11].

In this report, crosslinked poly(anhydride-co-imide)s based on trimellitylimido-glycine (TMA-gly), sebacic acid (SA), and BTC were prepared and tested as new polymeric supports for CDR applications. The polymers degraded completely into water-soluble molecules such as sebacic acid and amino acid. *In vitro* degradation and drug release from the polymer-drug matrices were quantified for up to 70 hours.

EXPERIMENTAL METHODS:

Polymer synthesis and characterization

Trimellitylimidoglycine prepolymers (TMA-gly) and sebacic acid prepolymers (SA) were synthesized as previously described[2]. The BTC prepolymer was prepared according to Maniar et al[11]. The three prepolymers were mixed (TMA-gly/SA/BTC; 30/70/5 molar ratio) and melt-polymerized at 180°C under high vacuum (5×10^{-3} mbar). The mixture gelated after 30 minutes, and the reaction was continued for another 30 minutes. The polymer was then crushed and immersed in ether to remove residues of acetic anhydride. The reaction was carried out twice with identical results. The crosslinked polymer product was denoted TMA-gly : SA : BTC (30 : 70 : 5), and characterized by ATR-FTIR spectroscopy (Bio-Rad FTS 300MX, Digilab Division, Cambridge, MA).

In vitro degradation and drug release experiments

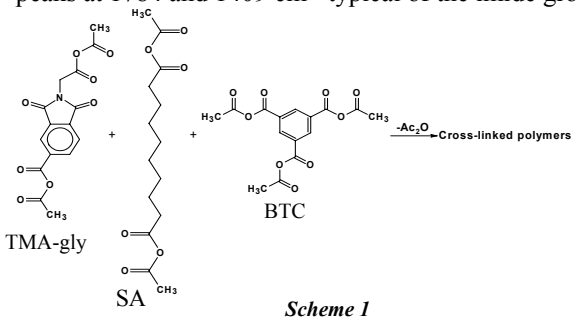
To formulate polymer-drug matrices, the polymer and a model drug (PNA, Aldrich Chemical Company Inc., Milwaukee, WI) were ground using either a mortar or a Scienceware Micro-mill Grinder (Bel-Art Products, Pequannock, NJ) and sieved to obtain microparticles (< 212 μm). The polymer and PNA (10% wt. loading) were vortex-mixed and compression-molded in a benchtop press (Carver Inc., Wabash, IN) into discs (0.207 ± 0.001 g, 13.0 ± 0.1 mm diameter, 1.20 ± 0.05 mm thick), by applying 5000 pounds per square inch for ten minutes at room temperature. Drug-free matrices were prepared by a similar procedure.

In vitro degradation and drug release studies were performed by placing the discs in Pyrex® bottles containing 200 ml of 0.1 M phosphate-buffered saline (PBS, pH = 7.4, Sigma Chemical Co., St. Louis, MO). The bottles were placed in an incubator-shaker (Infors AG, Bottmingen, Switzerland) set at 37°C and 100 rpm. At predetermined intervals, aliquots of the incubating media were withdrawn and assayed in a Beckman DU Series 7000 UV-vis spectrometer (Beckman Instruments Inc., Fullerton, CA). The optical densities at 306 nm (characteristic absorption maximum for TMA-gly) and 381 nm (absorption maximum for PNA) were used to monitor the degradation and drug release processes, respectively. The experiments were stopped at about 60% weight loss for the drug-free polymer matrices and at about 75% weight loss for the polymer-PNA matrices because of severe cracking of the discs. The PNA release curve for the polymer-drug matrices was normalized by the theoretical absorption at 381 nm for 100% PNA release. All experiments were performed in duplicate.

RESULTS AND DISCUSSION:

Under carefully selected conditions, monomeric TMA-gly prepolymers and SA prepolymers were prepared and characterized spectroscopically by GC-MS, NMR, and IR. The SA prepolymer had a melting point of 23 - 25°C, which is significantly lower than that reported for oligomeric SA prepolymers (67 - 69°C)[12]. By using the BTC prepolymer as a crosslinking agent in the copolycondensation of TMA-gly with SA prepolymers, crosslinked poly(anhydride-co-imide)s were prepared as

shown in Scheme 1. The polymer obtained was insoluble in the common solvents, but readily formed gels in certain organic solvents such as chloroform, THF, and dioxane. The identity of the poly(anhydride-co-imide) was confirmed by FTIR spectroscopy. For example, the FTIR spectrum showed peaks at 1811, 1724, and 1028 cm^{-1} characteristic of the carboxylic anhydride groups, and peaks at 1784 and 1409 cm^{-1} typical of the imide groups.



Scheme 1

Fig. 2 shows UV-visible spectra of the spent PBS solution for the drug-free matrices during the first 12 hours. TMA-gly was released steadily from the polymer discs with the overall degradation kinetics (shown in Fig 4A) being similar to its linear counterpart TMA-gly : SA (30 : 70)[5], where the degradation was monitored by cumulative change of UV absorption at 253 nm. These results indicate that crosslinking has little effect on the degradation behavior of this hydrophilic polymer.

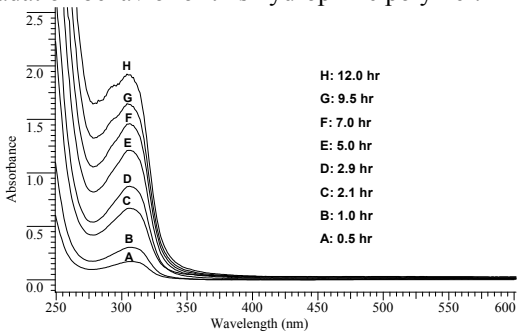


Fig. 2 *UV-vis spectra of PBS solution for drug-free polymer matrices*

Fig. 3 shows the UV-visible spectra of the spent PBS solution for polymer-PNA matrices during the first 12 hours. TMA-gly and PNA were released simultaneously from the discs, with the patterns (Figs. 4B and 4C) following closely that of drug-free polymer degradation (Fig. 4A). The degradation of the polymer-PNA matrices was faster than that of the drug-free matrices possibly due to a more open disc structure caused by the presence of the drug.

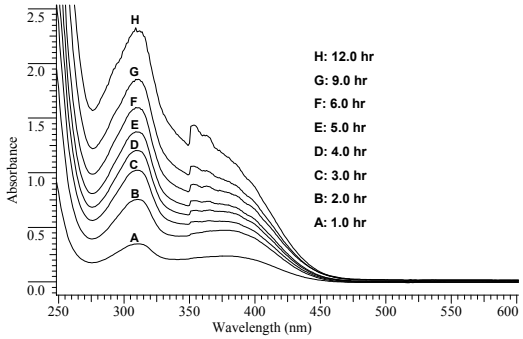


Fig. 3 *UV-vis spectra of PBS solution for polymer-PNA matrices*

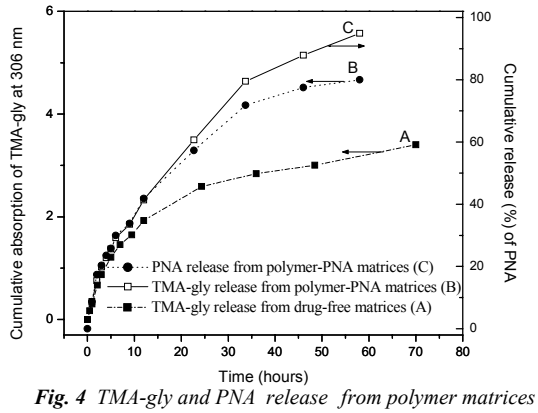


Fig. 4 *TMA-gly and PNA release from polymer matrices*

CONCLUSION:

Crosslinked amino acid-containing polyanhydrides were synthesized by polycondensation and their use in controlled drug release applications examined. Relative to their linear counterparts, crosslinking has little effect on the degradation and drug release behavior of these specific polymers. Changes in their chemistry and in the formulation protocol are being evaluated in order to extend their useful life.

REFERENCES:

(1) Dang, W.; Daviau, T.; Ying, P.; Zhao, Y.; Nowotnik, D.; Clow, C. S.; Tyler, B.; Brem, H. *J. Controlled Release* **1996**, *42*, 83-92.

(2) Staubli, A.; Ron, E.; Langer, R. *J. Am. Chem. Soc.* **1990**, *112*, 4419-4424.

(3) Ibim, S. E. M.; Uhrich, K. E.; Attawia, M.; Shastri, V. R.; El-Amin, S. F.; Bronson, R.; Langer, R.; Laurencin, C. T. *J. Biomed. Mater. Res.* **1998**, *43*, 374-379.

(4) Uhrich, K. E.; Larrier, D. R.; Laurencin, C. T.; Langer, R. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 1261-1269.

(5) Uhrich, K. E.; Thomas, T. T.; Laurencin, C. T.; Langer, R. *J. Appl. Polym. Sci.* **1997**, *63*, 1401-1411.

(6) Cuebas, L. E.; Ramírez, C. A.; Aponte, M. A.; Barbosa-Cánovas, G. V. *J. Controlled Release* **1992**, *18*, 145-151.

(7) Burkoth, A. K.; Anseth, K. S. *Biomaterials* **2000**, *21*, 2395-2404.

(8) Domb, A. J.; Mathiowitz, E.; Ron, E.; Giannos, S.; Langer, R. *J. Polym. Sci., Part A: Polym. Chem.* **1991**, *29*, 571-579.

(9) Quick, D. J.; Anseth, K. S. *Macromol. Rapid Commun.* **2001**, *22*, 564-572.

(10) Young, J. S.; Gonzales, K. D.; Anseth, K. S. *Biomaterials* **2000**, *21*, 1181-1188.

(11) Maniar, M.; Xie, X. D.; Domb, A. J. *Biomaterials* **1990**, *11*, 690-694.

(12) Domb, A. J.; Langer, R. *J. Polym. Sci., Part A: Polym. Chem.* **1987**, *25*, 3373-3386.

ACKNOWLEDGEMENTS:

Funding for this study was provided by the NIH-MBRS SCORE Program (grant S06GM08103).