297f Incorporating Eg Chains into Polyanhydrides: Consequences for Protein Stabilization and Delivery

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The overall goal of our research is to design a novel biodegradable polyanhydride system suitable for the stabilization and sustained release of peptides and proteins. It has been suggested that the use of carriers containing both hydrophobic and hydrophilic entities may provide a gentler environment for proteins. Previous research has demonstrated that the hydrophobic nature of polyanhydrides prevents water penetration into the bulk, thus eliminating water-induced covalent aggregation of proteins. However, protein inactivation by non-covalent aggregation due strong hydrophobic interactions between the polymer and the protein may lead to inactivation.

Our hypothesis is that incorporation of hydrophilic entities, such as oligomeric ethylene glycol, to an aromatic anhydride may create a suitable amphiphilic protein carrier. Accordingly we have synthesized random copolymers of the anhydride monomers 1,6-bis(p-carboxyphenoxy)hexane (CPH) and 1,8-bis(p-carboxyphenoxy)-3,6-dioxaoctane (CPTEG), which contains oligomeric ethylene glycol moieties. Random copolymers of CPTEG and CPH have been synthesized to obtain tailored chemistries and nanostructure, which may play a major role in peptide stabilization.

The phase behavior of the CPTEG:CPH system was ascertained using a combination of atomic force microscopy, small angle x-ray scattering, and molecular simulations. Mucin-based polypeptides, which are promising antigens for pancreatic cancer, were encapsulated in polyanhydride microspheres using a novel cryogenic atomization method, which is non-aqueous, and maximizes protein loading in the microsphere. The primary and secondary structures of the released polypeptide were monitored using gel electrophoresis and circular dichroism respectively. The interplay between the polymer chemistry, protein release, and protein stabilization is discussed in the context of developing sustained delivery systems for cancer vaccines.