Blood-Material Interactions of Polyurethanes

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Synopsis: It has been more than 40 years since John Boretos suggested that polyether based polyurethanes might have potential as a biomaterial. Much has transpired since the 1960's and indeed microphase separated polyurethanes have had notable successes and some remarkable failures as scientists and engineers have sought to exploit their unique properties in biomedical applications. My early work on polyurethanes related to studies of their synthesis and properties especially as related to their underlying morphology. Colleagues at the University of Wisconsin Medical School sought me out in order to include polyurethanes in blood contacting applications as assessed using a vena-cava ring test and also as a non-fouling membrane for biosensor implants. It soon became apparent that such collaborations made proposal applications to NIH possible and things took off from there. Most of our early efforts were around the question of achieving improved blood compatibility-whatever that is. Our end points were low platelet activation and thrombus formation in an ex-vivo canine animal model. While we made some progress it is safe to say that today there is still no truly "blood compatible" material available for clinical application. In addition the question of biostability of polyurethanes has been a significant issue in some of those applications where implanted polyurethanes were employed as pacemaker insulation and in foam form as a covering for breast implants.

Polyurethanes gained acceptance in the biomedical field because they have good physical properties and biocompatibility. The name "polyurethane" describes a class of polymers that can be synthesized to possess a variety of properties, from hard and brittle to very elastic. The polyurethanes that have found use in biomedical applications have elastomeric properties accompanied by good toughness, tear resistance and abrasion resistance. They have been widely used in applications such as the artificial heart and pacemaker lead insulation, among others. Surface properties believed to affect biocompatibility include the interrelated properties of hydrophobicity, polarity and surface charge. The presence and mobility of microdomain surface morphologies may also affect protein adsorption and thrombus formation.

We have also learned from hard experience about failure mechanisms when polyurethanes are used as implant materials. These include hydrolysis, especially in polyester based polyurethanes, oxidative degradation in polyether polyurethanes and enzymatic attack in all polyurethanes. In pacemaker insulation a new mechanism of metal induced oxidation was discovered and extensively characterized. The fate and toxic potential of aromatic isocyanate components in degraded polyurethanes have also received much attention. Fortunately much was learned about the mechanisms of degradation and materials with improved biostability are becoming available. Indeed there have also been advances in the utilization of deliberately biodegradable polyurethanes synthesized using peptide based aliphatic isocyanates and hydrolysable soft segments for use in tissue engineering.

In an attempt to find polyurethanes suitable for contact with blood, we modified their structure to include functional groups which have the potential to exhibit bioactivity. Polyurethanes containing sulfonate groups exhibit hydrogel and anticoagulant behavior compared to unmodified polyurethanes. The sulfonated polyurethanes affect the ability of fibrinogen to polymerize and they consume thrombin, an important enzyme in the coagulation pathway. Another way to improve the blood contacting performance of a biomaterial is to enhance its ability to bind endothelial cells.

Progress in understanding the interactions of the Arg-Gly-Asp (RGD) peptide sequence and integrins has stimulated a great deal of interest in the development of novel biomaterials, which may improve endothelial cell attachment and growth. Rather than immobilization of peptide to the polymer surface, an alternative approach was taken in that a polyurethane block polymer was modified so that it contained free carboxyl groups (PEU-COOH). Two cell adhesive peptides, GRGDSY (based on the fibronectin sequence, RGDS) and GRDVY (based on the vitronectin sequence RGDV), and an inactive peptide GRGESY were then grafted to the polyurethane backbone through the formation of amide linkages. The effects of peptide incorporation on polymer surface properties and endothelial cell adhesion were evaluated.

Lastly we have been working with phage display technology to identify highly specific ligands which will bind endothelial progenitor cells to biomaterial surfaces. We are investigating the binding of these ligands to our carboxylate containing polyurethanes via amide bond formation.

References:

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