Biomedical Applications of Polyurethane Elastomers

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By

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Notes:

The Polymer Technology Group Incorporated (PTG) is located in the Emeryville Research and Development Center in Emeryville, CA, fifteen minutes from San Francisco. PTG was founded in 1989 to perform consulting and contract research, to license technology and to provide laboratory services to its clients.

PTG performs lab and pilot-scale polymer synthesis, characterization, conversion and cleanroom processing of biomaterials, membranes and specialty polymers. The company's activities range from the synthesis of new polymers, to the fabrication of implantable medical devices. This includes melt and solution processing/compounding, membrane and film casting and the fabrication and testing of polymer components.

PTG employees have more than 40 man-years experience in the development, regulatory approval and manufacturing of Class II and Class III medical devices and prostheses.
"BIOMEDICAL" POLYURETHANES

POLYURETHANES USED IN BIOMEDICAL DEVICES AND PROSTHESSES:

Developed for Non-medical Applications
• Estane 5707 & Estane 5714

Purified, Modified or Renamed for Medical Use
• Biomer, Tecoflex, Cardiothane-51, Pellethane, Angioflex / Cardiomat-610

Developed Specifically for Medical Use
• BPS-215, Mitranthane, "Lyman PUU"

Notes:

Biomedical Polyurethane is the term used to describe any of a number of different elastomers and plastics used in the manufacture of medical devices and prostheses.

Relatively few polyurethanes developed specifically for biomedical applications are in clinical use today. More commonly, materials developed for the much larger industrial markets have been adopted for use in medical devices.

Certain industrial polymers have been purified or modified for use as biomaterials, but in some cases industrial polymers have simply been renamed and offered as "biomedical" materials, albeit with more intensive quality control than may be applied to their industrial counterparts.

Considering the wide range of structures possible within the polyurethane family, only a tiny fraction have ever been evaluated as biomaterials. Fewer yet are in widespread use in the form of devices and prostheses.

Although catheters and tubing make up the majority of currently-offered polyurethane biomedical devices, the most widely-recognized device may be the 'artificial heart'. In fact one of the earliest successful uses of "biomedical polyurethane" was in another type of cardiac assist device, the intra-aortic balloon or IAB.
ADVANTAGES OF POLYURETHANES

- Biocompatibility
- Strength
- Flexlife
- Abrasion Resistance
- Thermoplastic Processing
- Solvent Solubility
- Wide Modulus Range
- Versatile Chemistry

Notes:

Polyurethanes and the closely-related polyureas have many properties that recommend them for use as biomaterials.

The attributes listed here are not necessarily available in all polyurethanes, but represent general features typical of the generic class of polymers.

In common usage polyurethanes are any elastomers which contain urethane groups, usually formed by reaction between an isocyanate and a hydroxyl, but may also include urea groups when amines are reacted with isocyanates.

Early polyurethanes were synthesized from low MW reagents (e.g. diisocyanates and diols) and were high modulus, nylon-like plastics suitable for fiber spinning. Most modern polyurethanes are so-called segmented polymers or block copolymers with "hard segments" (similar to the early polyurethanes) covalently bound to rubbery soft segments.

By varying the chemistry and concentration of the segments or blocks and the extent of branching/crosslinking, a nearly unlimited number of different polymers may be prepared.
VARIETY IN PU: Reactants

DIISOCYANATES: Aromatic, Aliphatic, Cycloaliphatic

POLYOLS *: Siloxanes, Ethers, Carbonates, Lactones, Adipates, Dienes,

CHAIN EXTENDERS: Diamines, Diols, Water

ADDITIVES: Surface Modifiers, Bulk Modifiers, Stabilizers

* Available with amine-termination in many cases

Notes:

Even if synthesis is limited to those reactants available commercially at reasonable cost, it is possible to prepare thousands of different polyurethanes, many of which could be candidate biomaterials. Additional variety is possible through the use of various modifiers and stabilizers.
MIXED SOFT SEGMENT PU

\[
\left[ \begin{array}{c}
\text{Nonpolar} \\
\text{Block}
\end{array} \right]_x \left[ \begin{array}{c}
\text{High CED} \\
\text{Polar} \\
\text{Segment}
\end{array} \right]_y \left[ \begin{array}{c}
\text{Polar} \\
\text{Block}
\end{array} \right]_z 
\]

PSX \quad \text{URETHANE or UREA} \quad \text{PEO} 

AMPHIPATHIC, SURFACE-ACTIVE ELASTOMER WITH GOOD THROMBORESISTANCE. USED AS SURFACE-MODIFYING ADDITIVE.

PTG

Notes:

We have used the concept of mixed soft segments to prepare polyurethanes with some interesting properties. The structure shown here is a solid, film-forming analog of siloxane-polyethyleneoxide surfactants which are normally liquids.

At "hard segment" concentration of fifteen to twenty five percent, the high cohesive energy density of the urethane or urea gives the polymer elastomeric properties.

This \([\text{ABC}]_n\) terpolymer has shown excellent blood compatibility when used as a minor additive to base polymers chosen for their bulk properties.
VARIETY IN PU: Synthesis

BULK: One Shot or Prepolymer

IN SITU: Cast or Sprayed Elastomers & Foam, RIM

SOLUTION: One Shot, Prepolymer, Multi-step

WATER-BORNE: Surfactant, Residual Solvent

ALL: Stoichiometry
    Catalysis
    Reaction Conditions
    Trace Water Level
    pH
    Addition Rate / Side Reactions
    Reactant Purity

Notes:

Another important determinant of the properties of polyurethanes is the method of synthesis employed. The same reactants combined in different ways can produce significant variations in material performance.

For example, cast elastomers are often prepared as "one-shots" in which all the reactants are combined in a single step, in the presence of a catalyst. This is a convenient way to prepare a solvent-free casting liquid or encapsulant that cures after being poured into the mold. Properties which depend on hard segment / soft-segment microphase separation are negatively-affected by the random nature of polymer produced by the one-shot method. If the same reactants are combined in solution by first combining the soft-segment polyol with the isocyanate, then "chain extending" with a diol or diamine, these properties improve (e.g. in spandex fibers).

Side reactions between isocyanate with preformed urethane and urea groups (to form allophanates and biurets, respectively) can produce branching or gelation, the rate of which depends on the pH of the system, the rate and temperature of chain extender addition and the presence of catalysts or catalytic impurities.

Control of the -NCO-to-active hydrogen ratio in a dry system can be used to produce essentially linear systems, with a slight deficiency of -NCO, or crosslinked systems with an excess.

Because of the thermolabile nature of allophanate and urethane groups, even slightly crosslinked polymers may be thermoplastic. Since bonds may break and reform in the melt, the structure of melt-processed polyurethanes may change relative to the structure produced by the initial synthesis step.

The variations possible through the synthesis step can be combined with the large number of possible polyurethane reactants to produce a huge matrix of candidate biomaterials.
NEED FOR NEW BIOMATERIALS

PACEMAKER LEAD INSULATION

VASCULAR GRAFTS

PROSTHETIC HEART VALVES

ARTIFICIAL HEARTS

DRUG DELIVERY SYSTEMS

→ HYBRID ARTIFICIAL ORGANS

Notes:

Despite the wide-spread use of polyurethanes in implantable prostheses and simpler biomedical devices, there are certain long-term implantables in which the safety of presently-available polyurethanes has not yet been proven. Much of the concern applies not only to polyurethanes, but to any biomaterial, other than living tissue, expected to perform for five or ten years without mechanical failure, adverse tissue reaction or thrombogenesis.

Advances in artificial organs and prosthetics are closely tied to advances in biomaterials. In order for multi-year implantations of life-sustaining devices to become practical, continuous improvement in biomaterials performance will be necessary. The versatile synthesis and chemistry of the polyurethanes suggests that this class of polymers will continue to yield new and useful biomaterials for many years to come.
HYBRID or BIO-ARTIFICIAL ORGANS

BIODEGRADATION RESISTANCE: *Long-Term Implantation*

THROMBORESISTANCE: *Blood-Contacting*

CONTROLLED TISSUE INGROWTH: *Fix In Surrounding Tissue*

COMPLIANCE MATCHED: *Optimize Anastomosis To Natural Vessels*

TISSUE COMPATIBILITY: *Reduce Inflammation / Encapsulation*

SEMI-PERMEABLE: *Nutrients and Metabolites Pass, Cells Don’t*

GOOD FLEX LIFE: *Exposed to Arterial Circulation*

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**Notes:**

One of the most exciting areas of biomedical development today are the so-called *bio-artificial organs* or *hybrid artificial organs*. These devices would combine synthetic biomaterials and living cells to perform the work of diseased or damaged organs, such as the liver or pancreas.

Cells grown *in vitro* are transferred to implantable devices which will be expected to perform for years with little or no attention and no physical link to external equipment.

The potential of hybrid organs to extend life and improve its quality is fantastic. However, major advances in biomaterials will be required to make them a reality.

Some of the properties required of a hypothetical hybrid organ are shown above. Of all the biomaterials available today, the polyurethanes are probably the most likely to provide the many functions required of a successful hybrid artificial organ.
DISADVANTAGES OF POLYURETHANES

In Long-Term Implants:

- In Vivo Durability / Stability
- Thromboresistance
- Carcinogenic By-products?

Notes:

In very long-term implantations of blood-contacting implants, nearly all potential materials problems are nearly related to durability and stability.

Assuming that the device can be designed to function properly when first implanted, the materials-related problems that may result in device dysfunction or failure are related to changes in surface or bulk properties of the material. These changes may be manifested in different ways: Surface degradation of a smooth blood-contacting surface can lead to thrombosis. Sorption of (noncellular) blood components can cause dimensional instability. Hydrolysis or enzymolysis can disrupt primary bonds. Even the release of potentially toxic degradation products is only a problem when degradation occurs and the toxins can migrate to surrounding blood or tissue.

The remainder of our discussion will deal with factors affecting in vivo stability of polyurethanes in the broadest sense. We consider stability to be related to any change that takes place following implantation, whether or not it involves the dissociation of primary chemical bonds.
(POLYURETHANE) BIODEGRADATION

ANY SIGNIFICANT CHANGE IN PHYSICAL PROPERTIES FOLLOWING IMPLANTATION:

1. Cleavage or Rearrangement of Primary Bonds
2. Dissociation of Secondary Bonds
3. Increase in Temperature to 37 °C
4. Water Absorption
5. Leaching
6. Sorption / Deposition (Other Than Water)

Notes:

Although degradation is often thought of as being associated with the disruption of primary chemical bonds, with molecular weight reduction or embrittlement, several other materials-related changes can occur when a polymer is implanted in the body. Any one of these changes can result in the dysfunction or failure of the device, and all must be considered when designing new biomaterials.
SOFT SEGMENT HYDROLYSIS

POLYOL: 1000 MW
POLYMER: 1/2/1 POLYOL/MDI/BD
CONDITIONS: 95% R.H. @ 80 °C

Notes:

It is well known from studies of environmental degradation of non-medical polyurethanes, that the chemistry of the soft segment is a strong determinant of the degradation resistance of the resulting polyurethane. For a series of polyols of similar molecular weight, incorporated in a series of unstabilized polyurethanes of equivalent hard segment chemistry and concentration, the thermal/hydrolytic stability of the series would probably be: polydimethylsiloxane > polytetramethyleneoxide (PTMO) = polypropyleneoxide > polyethyleneoxide (PEO) > polycaprolactone (PCL) > polybutyleneadipate (PBA) > polyethyleneadipate (PEA) > polybutadiene.
PTG BIODEGRADATION STUDY

- Synthesize Additive-Free Model Polyurethaneureas
- Fabricate Samples Under Controlled Conditions
- Implant Characterized Samples Subcutaneously
- Bulk and Surface Characterization of Explants
- Correlate In Vivo and In Vitro Results
- Use Results To Help Design Next Generation Biomedical Polyurethane For Chronic Implants

Notes:

In order to investigate the in vivo stability of a series of additive-free polyurethaneureas, we are synthesizing several reference materials and preparing them as thin films for subcutaneous implantation. Results of this feasibility study will be used to design materials and experiments for developing new biomedical polyurethanes for use in chronically-implanted devices.

The structure of some of the reference polyurethanes are shown on the following pages.
MODEL PUU: PTMO Soft Segment

Polytetramethyleneoxide Soft Segment

- Hydroxyl-Terminated Oligomer
- Ethylene Diamine Chain Extender

\[
\begin{align*}
\text{PTMO} & \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-0-\text{N}-\text{N} \\
\text{HO} & \quad \text{H} \\
\text{HO} & \quad \text{H} \\
\text{X} & \quad \text{X}
\end{align*}
\]

Notes:
This polymer is closely related to Biomer in structure, but contains no stabilizing additives.

Polytetramethyleneoxide or PTMO generally gives the best overall physical properties of the commercially-available polyols, and is used in several biomedical polyurethanes including Pellethane, Tecoflex, BPS-215M, Angioflex / Cardiomat-610, Cardiothane-51, etc.
Notes:

Polyetherurethanes based on both polypropyleneoxide and polytetramethyleneoxide have shown good in vivo biostability. In terms of physical properties, however, the PTMO urethanes are much preferred. This is especially true when continuous flexing and/or dynamic creep is required, as it is in an artificial heart.

In our experience, the best tensile properties, lowest dynamic creep, and best flexlife are obtained when hard segment / soft segment microphase separation is maximized and when the soft segment is capable of undergoing reversible crystallization upon extension.

One indication of crystallization at high strain is an increase in modulus. Here we have plotted the first derivative of the stress-strain curve of each elastomer from a fifth degree polynomial fit. This gives a graphic representation of how the PTMO polymer firsts 'softens' then 'stiffens' as it is elongated.

Although the PTMO soft segment is capable of strain-induced, reversible crystallization, the conditions of synthesis can affect the degree to which it occurs. Conditions which lead to maximum purity of the segments appear to enhance this important property.
MODEL PUU: PEO Soft Segment

Polyethyleneoxide Soft Segment

- Hydroxyl-Terminated Oligomer
- Ethylene Diamine Chain Extender

\[
\begin{align*}
&\text{X} \\
&\text{PTMO} \\
&\text{PEO}
\end{align*}
\]

Notes:

This polyetherurethaneurea is similar to the PTMO-based polymer shown on the previous page except that polyethyleneoxide or PEO is extremely hydrophilic. Depending on hard segment content this polymer can absorb large amounts of water. For this reason we expect it to be less stable than the otherwise similar PTMO-based polymer.
ABSORPTION AND BIODEGRADATION

DEGRADANT MUST PENETRATE BULK POLYMER TO PRODUCE SIGNIFICANT BIODEGRADATION:

High Equilibrium Absorption = High Degradation

High Surface-To-Volume = High Degradation

Induction Period of Surface Fissure Development

Siloxane Hydrophobicity May Improve Biostability

Notes:

The extent to which a candidate biomaterial absorbs water, enzymes and other potential degradants will determine the rate at which bulk degradation takes place. Without absorption little, if any change in physical properties will be detectable, although surface changes are still possible.

Factors which increase the rate of absorption and/or expose additional surface area will have a negative effect on biostability. In implants of polyester urethane films around 100 μM thick, the first change observed is increased surface roughness, apparently due to loss of low molecular weight degradation products. This increases the surface area for subsequent attack, probably increasing the rate of degradation. After about three months of implantation measurable changes in GPC-measured molecular weight and tensile properties occur.

This induction period for degradation may be greatly reduced in polymer implants with high surface-to-volume ratio, such as those used in several polyurethane vascular grafts now under development. That is, sufficient bulk degradation may occur after much shorter implant times.

Any chemical change of the polymer that reduces absorption of degradants can have a positive effect on bio-stability. Although the water permeability of PSX homopolymer is reported to be very high, it is the product of a very high diffusivity and low solubility of water. Thus, small amounts of siloxane additives or coreactants may be used to increase hydrophobicity and decrease water solubility in base polyurethanes with insignificant increase on water permeability. This is a desirable combination of properties for reducing biodegradation and may be partly responsible for improved biostability of siloxane-modified polymers.
MODEL PUU: Siloxane Soft Segment

Polydimethylsiloxane Soft Segment

- **Amine-terminated Oligomer**
- **No Chain Extender**

\[
\begin{array}{c}
\text{O} \quad \text{H} \\
\text{C} \quad \text{N} \quad \text{O} \quad \text{CH}_2 \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{CH}_2 \quad \text{O} \\
\text{H} \quad \text{O} \quad \text{H} \\
\end{array}
\begin{array}{c}
\text{CH}_3 \\
\text{Si} \quad \text{O} \\
\text{Si} \quad \text{N} \quad \text{CH}_2 \quad \text{O} \\
\text{CH}_3 \\
\text{PSX} \\
\end{array}
\]

Notes:

Several investigators have shown that silicone-containing polyurethanes may have enhanced biostability relative to siloxane-free analogues. This may be due to the surface-active nature of the silicone, its inherent resistance to thermal/hydrolytic stability and it hydrophobicity.

In Cardiothane-51 (Aveothane-51), a poorly defined silicone-urethane, the silicone exists as a mixture of crosslinked homopolymer and copolymerized siloxane chains which have apparently cocondensed with terminal hydroxyl groups on the base polyurethane. Nevertheless, the siloxane appears to provide protection against property reduction in vivo.

We have worked for several years on the synthesis of well-defined polydimethylsiloxaneurethanes. This reference material is intended to assess the stability of a linear polydimethylsiloxaneurea separate from the effect of polyether soft segment.
PROBLEMS OF SILOXANE OLIGOMERS

Silanol, -Si-OH

-NCO + HO-Si-      \(\rightarrow\) -Si-O-CO-NH-

Hydroxyalkyl, -Si-(CH\(_2\))\(_n\)-OH

- Side Reactions During Oligomer Synthesis
- PSX - PU Structure is Poorly Defined
  Physical Properties Suffer

PTG

Notes:

One problem in the synthesis of well-defined silicone-urethane (PSX-PU) copolymers is the availability of suitable reactive siloxane oligomers. Commonly-available silanol-terminated polydimethylsiloxane oligomers (used to make RTVs, for example) do not react with isocyanates to form siloxane-urethanes.

Hydroxyalkyl groups bonded to the siloxane chain do give silicone-urethanes, but side reactions in the synthesis of the hydroxyalkyl-terminated siloxane can change the oligomer functionality and structure. This gives the resulting PSX-PU less well-defined structure.

We have reported a difunctional siloxane oligomer with secondary hydroxyl groups which apparently overcomes the problem with the primary hydroxyalyl PSX in polyurethane synthesis.
LOSS OF STRENGTH: Hydrated @ 37 °C

<table>
<thead>
<tr>
<th>POLYURETHANE</th>
<th>TYPE</th>
<th>TENSILE STRENGTH (psi)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BPS-215M</td>
<td>PTMO-ED-MDI</td>
<td>6140 ± 540</td>
<td>5430 ± 255</td>
<td>-11%</td>
<td></td>
</tr>
<tr>
<td>Biomer (Sln.)</td>
<td>PTMO-ED-MDI</td>
<td>6255 ± 535</td>
<td>5100 ± 300</td>
<td>-18%</td>
<td></td>
</tr>
<tr>
<td>Pellethane 80A</td>
<td>PTMO-BD-MDI</td>
<td>4625 ± 730</td>
<td>3280 ± 375</td>
<td>-30%</td>
<td></td>
</tr>
<tr>
<td>Tecoflex 80A</td>
<td>PTMO-BD-HMDI</td>
<td>4595 ± 985</td>
<td>3060 ± 285</td>
<td>-33%</td>
<td></td>
</tr>
</tbody>
</table>

Notes:

Within the group of PTMO-base polyurethanes, the hard segment also determines ultimate physical properties. This is especially true when measured fully hydrated at body temperature.

Polyurethanes based on three different hard segments are presented in the table above. ED = ethylene diamine. BD = butanediol. MDI = diphenylmethanediisocyanate and HMDI is the hydrogenated analogue of MDI.

In terms of cohesive energy density and phase separation the hard segments rank as: ED-MDI > BD-MDI > BD-HMDI. One result is that polymers with the higher CED hard segments undergo less tensile strength reduction upon implantation.

Although this is a reversible change in the properties of the polymers, it is a form of bio-instability in the broad sense that we have defined it. That is, any irreversible loss in strength of the polymer will be superimposed on the immediate strength reduction caused by water absorption and increase in temperature from room temperature to body temperature.
## Biaxial Flex Testing*

<table>
<thead>
<tr>
<th>Polyurethane</th>
<th>Type</th>
<th>Cycles</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPS-215M</td>
<td>PTMO-ED-MDI</td>
<td>&gt; 103 MM</td>
<td>OK</td>
</tr>
<tr>
<td>Biomer (Soln.)</td>
<td>PTMO-ED-MDI</td>
<td>93 MM</td>
<td>OK</td>
</tr>
<tr>
<td>Pellethane 80A</td>
<td>PTMO-BD-MDI</td>
<td>11 MM</td>
<td>SEVERE CREEP</td>
</tr>
<tr>
<td>Tecoflex 80A</td>
<td>PTMO-BD-HMDI</td>
<td>&lt; 2MM</td>
<td>BLOW OUT</td>
</tr>
</tbody>
</table>

*Dynatek M-2 Tester @ 50% Strain, In 37 °C Saline @ 550 Cycles Per Min.*

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**Notes:**

The results of accelerated biaxial flex testing at 50% strain further illustrate the effect of lower cohesive energy density and phase separation of BD-MDI and BD-HMDI hard segments relative to ED-MDI hard segment.

Flex testing results reflect the decrease in properties due to water absorption and heating to body temperature that we recorded for tensile strength on the previous page.

Of the three hard segments, the ED-MDI hard segment is clearly the best choice for devices that must flex repeatedly for prolonged period in vivo, e.g. vascular grafts, prosthetic valves and circulatory assist devices.
SURFACE-TO-VOLUME

Surface - To -Volume Ratio Determines Rate of Degradation of Formed Articles

$= S/V \text{ (cm}^{-1}\text{)}$

- **Tubing**, 1/16 inch Wall Thickness: 10
- **Film**, 10 mil (254 μM) Thickness: 80
- **Fiber, 1 Denier**: 400
- **Membrane, 10 μM Thickness**: 2000
- **Foam, 4μM Pores, 80% Void**: 100,000
- **Powder, 0.1 μM Particles**: 600,000

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**Notes:**

As the geometry of the implant changes toward increased surface-to-volume ratio, an increase in the reduction of physical properties can be expected. This is only true, of course, if the base polymer is inherently susceptible to biodegradation.

If we assume that all polymers will be degraded at some finite, though possibly very small rate, then high-surface-to-volume should be avoided in device design whenever possible.

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(PU) BIOMATERIALS FALLACIES

False: "Pure" Polymers are Better Biomaterials Than Additive-Containing PU:

True: Biostability Can Be Improved By Stabilizers

False: Air-Facing Surfaces of Solvent-Cast Films Are More Thromboresistant Than Mandrel-Facing Surfaces

True: Air-Annealing After Removal from Mandrel Equilibrates Surface

Notes:

Early work in the development of new biomedical urethanes often assumed that the "best" biomaterials would be ultra-pure, additive free polymers with narrow molecular weight distributions. In our experience the use of stabilizing additives can enhance in vitro and in vivo degradation resistance and are therefore useful in the development of new biomedical polyurethanes.

Rather than avoiding the use of stabilizers it would probably be more productive to develop polymeric analogues or functionalized versions that can be covalently bonded to the base polymer.

A significant amount of effort has been expended in the design and manufacture of critical devices (e.g. the Jarvik artificial heart) to provide air-dried blood-contacting surfaces. For a device solvent-cast on a mandrel, the air-dried surface is the one which dried with the air interface, not against the mandrel. It is often possible to achieve a smoother surface in solvent-cast films dried under the effects of air-liquid surface tension, e.g. in solvent polishing. However, chemical differences due to selective orientation of polymer blocks or components can be often be 'annealed out' of the part in subsequent oven drying, following removal from the mandrel. This can greatly simplify manufacture of certain devices.

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(PU) BIOMATERIALS FALLACIES

False: Vacuum Drying At Elevated Temperatures Quantitatively Removes Residual Solvents

True: Significant Amounts of Polar Solvents Remain In Thick Films When Dried Under Conditions Which Don’t Degrade The Polymer

False: Bulk Composition of PU Determines Surface Chemistry

True: Most Commercial PUs Have Surfaces Dominated By Processing Aids e.g. Fatty Amides. Soft-Blocks Orient In Air Surface

Notes:

Often, very little attention is given to the effects of residual solvent on the biocompatibility and biostability of solvent-cast films. Investigators often site the use of vacuum drying as 'evidence' that all residual solvent has been removed. We have used a sensitive gas chromatographic technique to determine the amount of residual polar solvents in cast polyurethanes. We have found that vacuum and/or elevated temperature atmospheric drying can often leave significant amounts of solvent behind, particularly in thick sections. In addition to increased cytotoxicity and hemolysis (see next page) residual solvent may be a concern in evaluating materials for biostability. If residual solvent content is sufficient to illicit an inflammatory response from surrounding tissue, the resulting local increase in enzyme concentration may produce a biodegradation rate many times faster than would occur without severe inflammatory response.

It is now fairly well known that block and segmented copolymers can orient at surfaces to increase the surface concentration of one or more blocks, relative to its average concentration in the bulk. The extent to which a polymer or polymer blend exhibits such surface activity depends on purity, polymer chemistry and structure, and thermal and processing history. This complicates the job of assigning biocompatibility to surface chemistry predicted from the average or bulk composition of the base polymer. It also argues for equilibration/annealing of test specimens and the use of sensitive surface analytical methods in characterizing samples.
RESIDUAL SOLVENT IN CAST FILMS

BPS-215M CAST FROM DIMETHYLACETAMIDE:

<table>
<thead>
<tr>
<th>DMAC Concentration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 35 ppm</td>
<td>Cytotoxic, Hemolytic</td>
</tr>
<tr>
<td>&lt; 35, &gt; 10 ppm</td>
<td>Cytotoxic, Non-hemolytic</td>
</tr>
<tr>
<td>&lt; 10 ppm</td>
<td>Non-cytotoxic, Non-hemolytic</td>
</tr>
</tbody>
</table>

Notes:

These are the results of in vitro cytotoxicity and hemolysis testing versus residual solvent content of a polyurethaneurea biomaterial (see previous page). Residual solvent was determined by a gas chromatographic method sensitive in the parts per billion range.

Additional cytotoxicity results suggest that the maximum value at which neither cytotoxicity nor hemolysis are measurable is $\approx 25$ ppm.
SUPER POLYURETHANE: Polymer

1. Pure MDI: *Low Isomer Content, High CED*

2. ED Chain Extender: *Short Chain, Urea Hard Segment*

3. Multi-Step Synthesis In Solution: *Control Structure & Stoichiometry*

4. Low/Narrow Water Concentration Spec: *Avoid Side Reactions, Maximize "Purity"/Reproducibility of Polymer Structure*

5. *pH and Addition Rate Control During Chain Extension: Avoid Gelation Side Reactions*

*PTG*

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**Notes:**

The following four pages summarize the author's experience in the synthesis of biomedical polyurethanes and their fabrication into critical blood-contacting devices for chronic implantation.

Clearly, a lot of work remains to be done in the development of new biomedical polyurethanes. Additional knowledge will add more items to this list. The points presented here are intended as recommendations for avoiding some pitfalls in material and device development and manufacture.
SUPER POLYURETHANE: Polymer

6. Purify Reactants and Solvents: Remove Nonvolatile and/or Catalytic Impurities

7. Glass Process Equipment: Minimize Metal Oxide Content

8. PTMO Soft Segment: Best Physical Properties and Flexlife, Lowest Hysteresis, Reversible Crystallization During Extension

9. PSX Co-Soft Segment: Reduce H2O Absorption, Improve Thromboresistance, Improve Biodegradation Resistance

10. Use Stabilizers: (Polymeric) Antioxidant + UV, Improve In Vivo Stability

Notes:

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SUPER POLYURETHANE: Polymer

10. Purify Polymer: Fractionate to Remove Low MW Impurities (Optional With 3. - 7.)

12. Stabilizing Additives: (Polymeric) Antioxidant + UV, Improve In Vivo Stability

13. Use (Functional) Polymeric Surface Modifiers: Improve Thromboresistance Without Changing Desirable Bulk Properties

PTG

Notes:
SUPER POLYURETHANE: Device

1. Water Extraction: Remove Residual Solvent To Reduce Inflammatory Response / Biodegradation and Improve Thromboresistance

2. Minimize Surface-To-Volume Ratio Of Formed Article: Minimize Interface Available for Sorption, Leaching and Degradation

3. Intelligent Device Design And Fabrication: Low Residual Strain, Low Dynamic Strain, Good Hemodynamics, No Metal Oxides, No Exposure To Degradants or Impurities During Manufacture or Storage

PTG

Notes:
CONCLUSION

1. Existing polyurethanes may not be suitable for multi-year implantation in the next generation of (bio) artificial organs and prostheses.

2. The versatility of polyurethane chemistry makes it attractive for developing new or modified biomaterials.

3. Siloxane coreactants or modifiers look promising for overcoming some of the known weaknesses of existing PU biomaterials.

4. Design, and fabrication methods and conditions are as important as materials.

Notes:

We have only scratched the surface in the development and application of polyurethane biomaterials. Refinements in chemistry, structure and conversion methods will continue, and will be combined with improved designs in the development of new and better artificial organs and prostheses.
FACTORS AFFECTING THE STABILITY OF
BIOMEDICAL POLYURETHANES:
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