### Absorbable Tissue Adhesives

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### Tissue Adhesive and Sealants

- Confluent Surgical
- Fibrin based Tissue by Baxter
- PEG based Cohesion Technology

To the best of our knowledge, currently there is no degradable polyurethane tissue adhesive or sealant in the market.

### Polyurethanes: Importance and Applications

- Polyurethanes comprise a diverse family of materials, including thermoplastic elastomers, flexible and rigid foams, fibers, coatings and sealants and thus impact many aspects of industrial applications. The toughness, versatility, durability, biocompatibility and biostability of polyurethanes makes them an excellent candidates for use in a wide variety of long term implantable biomedical device applications.

- Since MDI is the key aromatic diisocyanate which is used to synthesize most of biostable polyurethanes for biomedical and other commercial applications. It forms a very stable and non-degradable hard segment on reaction with chain extender.

- Our company decided to develop biodegradable aromatic polyurethanes will have toughness and durability along with bioabsorbability of biodegradable polymers.

### Biodegradable Polyurethane Tissue Adhesive

- The objective of our current work is to develop biodegradable polyurethane tissue adhesive based on novel aromatic diisocyanates.
- These aromatic diisocyanates (a) degrade into safe and biocompatible products (b) result in the formation of novel biodegradable aromatic polyurethane tissue adhesives when reacted with chain extenders, polyols or moisture. Furthermore, the ureaurethane hard segment of the derived polyurethane will have a hydrolyzable linkage for the first time. Moreover, the derived polyurethanes will have toughness and durability along with bioabsorbability of biodegradable polymers.

Since MDI is the key aromatic diisocyanate which is used to synthesis most of the commercial medical grade polyurethane elastomers in order to obtain favourable mechanical properties such as low permanent deformation and high elongation, Our company decided to develop biodegradable aromatic polyurethane tissue adhesives when reacted with chain extenders, polyols or moisture. Furthermore, the ureaurethane hard segment of the derived polyurethane will have a hydrolyzable linkage for the first time. Moreover, the derived polyurethanes will have toughness and durability along with bioabsorbability of biodegradable polymers.

### Our Mission

- Controlled degradation profile
- Degradation products: safe and biocompatible

- Degradable Aromatic Diisocyanate similar to MDI

- For the first time, our company has developed novel biodegradable polyurethane tissue adhesives and sealants based on aromatic isocyanates similar to MDI from safe and biocompatible monomers such as glycolide, lactide, p-dioxanone and caprolactone with controlled degradation profiles. Furthermore, we have also developed novel bioabsorbable chain extender amines.

- These polyurethane tissue adhesives and sealants derived from these novel aromatic isocyanates will have toughness and mechanical properties of that of commercially available medical grade polyurethanes and bioabsorbability of commercial bioabsorbable polymers.

- These polyurethane tissue adhesives and sealants will degrade into safe and biocompatible hydrolytic degradation products. Furthermore, the degradation rates of these polyurethanes can be controlled by varying the composition of degradable segment by changing glycolide with lactide and varying the length of degradable segment of isocyanate.

### Biocompatibility studies of Absorbable Thermoplastic Polyurethanes as per ISO 10993 Guidelines

<table>
<thead>
<tr>
<th>Test Article</th>
<th>Absorbable Thermoplastic Polyurethanes</th>
<th>Ratio (g/10 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot/Batch #</td>
<td>BB0001-110(b)</td>
<td>Serum-Supplemented (Complete) Medium (MIM)</td>
</tr>
<tr>
<td>Study</td>
<td>L509 MEN Elution Test – ISO 31161</td>
<td>Extraction Conditions</td>
</tr>
<tr>
<td>RESULTS</td>
<td>No signs of toxicity (Grade 0) were observed in the negative control article extract at the 48 hour observation.</td>
<td>57 ± 1°C for 24 ± 2 hours</td>
</tr>
</tbody>
</table>

CONCLUSION: The test article is considered non-cytotoxic and meets the requirements of the Static Test, ISO 10993-5 guidelines.

Results show that these thermoplastic absorbable polyurethanes are biocompatible.

### Summary

- For the first time, our company has developed novel biodegradable polyurethane tissue adhesives and sealants based on aromatic isocyanates similar to MDI from safe and biocompatible monomers such as glycolide, lactide, p-dioxanone and caprolactone with controlled degradation profiles. Furthermore, we have also developed novel bioabsorbable chain extender amines.

- The polyurethane tissue adhesives and sealants derived from these novel aromatic isocyanates, chain extender amines and polyols will not only be biodegradable but will also have hydrolytically unstable urethane and urea hard segment.

- These polyurethane tissue adhesives and sealants will have toughness and mechanical properties of that of commercially available medical grade polyurethanes and bioabsorbability of commercial bioabsorbable polymers.

- These polyurethane tissue adhesives and sealants will degrade into safe and biocompatible hydrolytic degradation products. Furthermore, the degradation rates of these polyurethanes can be controlled by varying the composition of degradable segment by changing glycolide with lactide and varying the length of degradable segment of isocyanate.

### Commercial Biomedical grade polyurethanes and their various applications

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Isocyanate</th>
<th>Chain extender</th>
<th>Polyol</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duraflex</td>
<td>VISCOR, Inc.</td>
<td>MDI</td>
<td>1,4-butanediol</td>
<td>PEG 400</td>
<td>Cardiac pacemakers, heart valves, heart catheters, dural, Daylite cathers, blood contact materials, bandages, Cardiovascular catheters</td>
</tr>
<tr>
<td>Tenflex</td>
<td>Novon</td>
<td>MDI</td>
<td>1,4-butanediol</td>
<td>PEG 400</td>
<td>Cardiac pacemakers, heart valves, heart catheters, dural, Daylite cathers, blood contact materials, bandages, Cardiovascular catheters</td>
</tr>
<tr>
<td>Tecothane</td>
<td>Novon</td>
<td>MDI</td>
<td>1,4-butanediol</td>
<td>PEG 400</td>
<td>Cardiac pacemakers, heart valves, heart catheters, dural, Daylite cathers, blood contact materials, bandages, Cardiovascular catheters</td>
</tr>
<tr>
<td>Ramer</td>
<td>Ethicon</td>
<td>MDI</td>
<td>1,4-butanediol</td>
<td>PEG 400</td>
<td>Cardiac pacemakers, heart valves, heart catheters, dural, Daylite cathers, blood contact materials, bandages, Cardiovascular catheters</td>
</tr>
<tr>
<td>Bionate</td>
<td>Polymer Tech Group</td>
<td>MDI</td>
<td>1,4-butanediol</td>
<td>PEG 400</td>
<td>Cardiac pacemakers, heart valves, heart catheters, dural, Daylite cathers, blood contact materials, bandages, Cardiovascular catheters</td>
</tr>
<tr>
<td>Polytane</td>
<td>Dow Chemical</td>
<td>MDI</td>
<td>1,4-butanediol</td>
<td>PEG 400</td>
<td>Cardiac pacemakers, heart valves, heart catheters, dural, Daylite cathers, blood contact materials, bandages, Cardiovascular catheters</td>
</tr>
</tbody>
</table>

Methylene Diphenyl isocyanate (MDI) is the key reactive aromatic diisocyanate that is used in the synthesis of majority of biostable polyurethanes for biomedical and other commercial applications. It forms a very stable and non-degradable hard segment on reaction with chain extender.

**Drawback:** In spite of excellent mechanical properties, the biostability and non biodegradability of all the commercially available medical grade polyurethanes limits their use in various biomedical applications where biodegradability of the polymer being used is a necessary prerequisite. Furthermore, degradation products of diisocyanates are toxic and mutagenic aromatic diamines.

**Biostable Isocyanates**
- Non-degradable aromatic diisocyanates
- Derived polyurethanes biostable

**Absorbable Isocyanates**
- Degradable Aromatic Diisocyanate similar to MDI
- Derived from safe and biocompatible monomers
- Degradation products: safe and biocompatible
- Controlled degradation profile

**Polymer 01**
- Crosslinked Tissue Adhesive
- Biocompatibility studies of Absorbable Thermoplastic Polyurethanes as per ISO 10993 Guidelines
- Summary

**Polymer 02**
- Biostable Tissue Adhesives
- Confluent Surgical
- Fibrin based Tissue by Baxter
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