Practical Considerations in the scale up and manufacture of Antioxidant UHMWPE made by blending the α-tocopherol version of Vitamin E

MediTECH Medical Polymers
Division of Quadrant EPP
Fort Wayne, Indiana USA
Key points for the conversion of UHMWPE with Alpha Tocopherol

• Relatively small doses required to be effective as an anti-oxidant.

• Higher doses, above approximately 1500ppm, have effects on color, properties and the cross-linking receptivity of UHMWPE.

• Vitamin E appears to offer new streamlined concepts for cross-linking material.

• An Alpha-Tocopherol Supplier specified by the implant manufacturer as not all suppliers are willing to support this application for their product.
Key points for the conversion of UHMWPE with Alpha Tocopherol

• A lot of work has yet to be done to take this process from the laboratory to the manufacturing floor. The path may be able to be shortened by the application of perspectives to be highlighted in this presentation.

• While the focus of this presentation is on Vitamin E, the concepts and suggested paths can be applied with appropriate modification to other potential antioxidants.
Creating the Specification: Key Elements

• Resin Type, Fabricated Form, and properties thereof as standardized by both ASTM and ISO standards.

• Vitamin E brand, specification, dose, measurement method and tolerance

• Blending protocol, whether pre-blended, left to MediTECH or customer specified.

• Standard (same as conventional) certification requirements.

• Other testing parameters and results expected as validated in preliminary characterization relating to the blend and any subsequent processing.
Creating the Specification; continued

• Any non-standard annealing specification.

• Cross-linking specification, dose, and tolerance.

• Post-radiation Annealing parameters
  • While it is understood that with the benefits of Alpha-tocopherol this may not be a requirement for free radical protection, it may still be desired to achieve other mechanical properties depending upon the overall specification.

• Final Fabrication
  • Material Removal on all surfaces, final shape
  • Yield Optimization will be done by MediTECH

• Final Storage, Packaging, and Shipping
Selection of base resin, fabrication method, and α-tocopherol dose

• Typical Characterization Protocol:
• Compression Molded or Ram Extruded
• Affects the certification and QA control plans because of batch size and logistics of production.
• Potential complexities of multiple doses, brands, types of anti-oxidant and fabrication type.

<table>
<thead>
<tr>
<th>Trial Piece</th>
<th>Resin</th>
<th>E-dose</th>
<th>Purpose</th>
<th>Post-Consolidation Anneal</th>
<th>Gamma Dose, kGy</th>
<th>Post-radiation anneal</th>
<th>Testing Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Virgin</td>
<td>1020</td>
<td>Conventional Control</td>
<td>MediTECH Standard</td>
<td>0</td>
<td>customer spec</td>
<td>Visual</td>
</tr>
<tr>
<td>1</td>
<td>Virgin</td>
<td>1020</td>
<td>Control</td>
<td>MediTECH Standard</td>
<td>A</td>
<td>customer spec</td>
<td>Visual</td>
</tr>
<tr>
<td>2</td>
<td>Virgin</td>
<td>1020</td>
<td>Control</td>
<td>MediTECH Standard</td>
<td>B</td>
<td>customer spec</td>
<td>Visual</td>
</tr>
</tbody>
</table>

Example Protocol for Alpha Tocopherol Characterization
Batch size considerations:

<table>
<thead>
<tr>
<th>E' Dose</th>
<th>kg resin</th>
<th>kg 'E'</th>
<th>gm 'E'</th>
<th>ppt 'E'</th>
<th>Resin accuracy requirement +/-Kg</th>
<th>E' accuracy +/-gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 ppm</td>
<td>1000</td>
<td>0.500250</td>
<td>500.25</td>
<td>500.00</td>
<td>52.00</td>
<td>25.0</td>
</tr>
<tr>
<td>500 ppm</td>
<td>900</td>
<td>0.450225</td>
<td>450.23</td>
<td>500.00</td>
<td>47.00</td>
<td>22.5</td>
</tr>
<tr>
<td>500 ppm</td>
<td>800</td>
<td>0.400200</td>
<td>400.20</td>
<td>500.00</td>
<td>42.00</td>
<td>20.0</td>
</tr>
<tr>
<td>500 ppm</td>
<td>700</td>
<td>0.350175</td>
<td>350.18</td>
<td>500.00</td>
<td>36.00</td>
<td>17.5</td>
</tr>
<tr>
<td>500 ppm</td>
<td>600</td>
<td>0.300150</td>
<td>300.15</td>
<td>500.00</td>
<td>31.00</td>
<td>15.0</td>
</tr>
<tr>
<td>500 ppm</td>
<td>500</td>
<td>0.250125</td>
<td>250.13</td>
<td>500.00</td>
<td>26.00</td>
<td>12.5</td>
</tr>
<tr>
<td>500 ppm</td>
<td>400</td>
<td>0.200100</td>
<td>200.10</td>
<td>500.00</td>
<td>21.00</td>
<td>10.0</td>
</tr>
<tr>
<td>500 ppm</td>
<td>300</td>
<td>0.150075</td>
<td>150.08</td>
<td>500.00</td>
<td>15.00</td>
<td>7.5</td>
</tr>
<tr>
<td>500 ppm</td>
<td>200</td>
<td>0.100050</td>
<td>100.05</td>
<td>500.00</td>
<td>10.00</td>
<td>5.0</td>
</tr>
<tr>
<td>500 ppm</td>
<td>100</td>
<td>0.050025</td>
<td>50.03</td>
<td>500.00</td>
<td>5.00</td>
<td>2.5</td>
</tr>
<tr>
<td>500 ppm</td>
<td>75</td>
<td>0.037519</td>
<td>37.52</td>
<td>500.00</td>
<td>3.75</td>
<td>1.9</td>
</tr>
<tr>
<td>500 ppm</td>
<td>1003.75</td>
<td>0.498370</td>
<td>498.37</td>
<td>496.26</td>
<td>3.75</td>
<td>1.9</td>
</tr>
<tr>
<td>500 ppm</td>
<td>996.25</td>
<td>0.502130</td>
<td>502.13</td>
<td>503.77</td>
<td>3.75</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Comments: Large batch sizes are conducive to tighter tolerances, assuming the inherent as yet unmeasured process repeatability is +/-5%, a good starting point for a dose range specification would be 450ppm to 550ppm, which equates to +/- 10%, until we have more confidence in the measurement techniques.
Selection and Storage of the α Tocopherol

• Selection of the α-Tocopherol ‘Brand.’

• Availability letter from the supplier for its intended use.

• Shelf life and storage recommendations from the supplier

• What we’ve found:
  • Minimize exposure to Oxygen: Sealed containment
  • Minimize exposure to Heat: Ambient storage except during processing.
  • Minimize exposure to Light: Stored in Light-proof containment
  • Compliance with these measures insures a shelf life of 1 year
  • Purchasing logistics and volumes will determine actual scenarios and affect price.
Blending the α-Tocopherol

• Among the basic options which exist:
  • Pre-blend by Ticona by proprietary method.
  • Blend at MediTECH by proprietary method.
  • Blend at MediTECH by proprietary customer specified and jointly developed method.

• What we’ve done so far:
Blending the α-Tocopherol in production scale sheets:

• In multiple presses (Vreden Germany and Fort Wayne, Indiana) by standard processing methods.

• Using pre-blended resin from Ticona at 500ppm

• Blended at 500ppm from direct blending the α-tocopherol and GUR 1020.

• Blended at 500ppm and 750ppm utilizing a 1% α-tocopherol master batch produced by Ticona.
Examples: Sheet from resin blended by Ticona at 500ppm α-tocopherol.
Examples: Sheet pressed from resin
direct blended by MediTECH with
α-tocopherol @ 500ppm
Blending the α Tocopherol

• Consolidate full sheets by direct blending α-tocopherol with GUR 1020 by means of 3 styles of blending equipment and varying processes within each.

• Consolidate material 150mm x 75mm x 45mm blended at 500, 750, 1000, 1500, 2000, 2500, 3000ppm utilizing a 1% master batch produced by Ticona.

• Consolidate material 150mm x 75mm x 45mm blended at 500, 750, 1000, 1500, 2000, 2500, 3000ppm from direct blending α tocopherol and GUR 1020.
Examples:
Examples:

11 month old blend     Day old blend
Both at 500ppm
Examples:

Virgin

500ppm From Master batch

750ppm From Master batch

500ppm direct blend
Current position on Blending methods:

• There are multiple methods by which α-tocopherol can be adequately dispersed within UHMWPE resin. Some are superior to others, and all that we have attempted can work providing adequate trialing is done in the name of process optimization.

• Ongoing work: What effect does the storage of α-tocopherol blended UHMWPE resin have on the outcomes of color, dispersion uniformity, and oxidation resistance?
Transporting / Storing Blended Resin

- Pharmaceutical Grade Equipment
- Dedicated lines to minimize cleaning requirements
- Virtually closed system
- Nitrogen Blanket
- Storage for Blended Resin before use
- Final pre-consolidation homogenization
Consolidating the Blended Resin

• MediTECH has tried multiple consolidation recipes for the material containing \( \alpha \)-tocopherol.

• As is the case with virgin material, properties can be manipulated

• All validated processes worked acceptably

• The \( \alpha \)-tocopherol is more sensitive to higher heats and residence times in the press and the evidence is color.

• There are inherent differences in residence times due to material thickness.

• No major difficulties are foreseen here, only optimization opportunities before and during validation efforts.
Annealing of the consolidated material

• Standard annealing methods have worked well for this material

• Annealing the material reduces the color intensity.

• Annealed and extensively cross-linked material in the 500ppm to 1000ppm range has color that is not so different from virgin cross-linked material. Is this a sign of α-tocopherol interaction with free radicals, or otherwise consumption of the α-tocopherol?
Cross-Linking of consolidated material

- **Can** be done in exactly the same way as is currently practiced for non-blended UHMWPE, with a potential factor applied if the α-tocopherol dose is high.

- Material removal of materials for all stock shapes has historically been in the range of a minimum 3mm per surface. This practice could be re-evaluated with respect to Oxidation Protection.
Post-radiation annealing of consolidated material

• Up to the device manufacturer to determine IF and WHAT

• While free radicals may not be the issue, there is still a further increase in crystallinity and increased uniformity of tensile and impact properties that may be beneficial.

• With nitrogen annealing in conventional material before, we still removed material afterward.

• Is it still of value now with α-tocopherol blended material?
Handling, long term storage and packaging of the consolidated material

• Internal work in process handling will not have to change, as material is typically stored in collapsible crates with covers, protecting the material from light.

• Light barrier packaging for individual bar stocks may be one consideration for preventing light effects in bulk storage, in transit, or at the device manufacturer’s cells.
Examples: 11 month comparison

Virgin

500ppm Stored in light

500ppm Stored in Dark drawer
Examples: 11 month comparison

Virgin GUR 1020
500ppm Blend Pressed
In November 2006,
Shelved in fluorescent
light

500ppm Blend Pressed
In November 2006,
Stored in a dark drawer
Testing of the consolidated material:

alpha-tocopherol blend property results for Ultimate Tensile and Modulus

![Graph showing the results of testing various materials.](image-url)
Testing of the consolidated material:

alpha-tocopherol blend density results

<table>
<thead>
<tr>
<th>Material</th>
<th>Density n/5* (g/cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virgin Material spanning 4 resin lots</td>
<td></td>
</tr>
<tr>
<td>Ticona 500ppm full Sheets, non-cross-linked</td>
<td></td>
</tr>
<tr>
<td>MedITECH 500ppm full Sheets, non-cross-linked</td>
<td></td>
</tr>
<tr>
<td>MedITECH 750ppm full Sheets, non-cross-linked</td>
<td></td>
</tr>
<tr>
<td>University of Torino Plaques @ 30kGy</td>
<td></td>
</tr>
<tr>
<td>University of Torino Plaques @ 100kGy</td>
<td></td>
</tr>
<tr>
<td>Ticona 500ppm full Sheets @75kGy, no post anneal</td>
<td></td>
</tr>
<tr>
<td>Ticona 500ppm full Sheets @75kGy, Below Melt post anneal</td>
<td></td>
</tr>
<tr>
<td>Ticona 500ppm full Sheets @100kGy, no post anneal</td>
<td></td>
</tr>
<tr>
<td>Ticona 500ppm full Sheets @100kGy, Below Melt post anneal</td>
<td></td>
</tr>
</tbody>
</table>
Testing of the consolidated material:

alpha-tocopherol blend property results

- Average Stress At Yield (Mpa)
- Average Peak Stress (Mpa)
- Average Izod
- Hardness n/5*

Virgin Material spanning 4 resin lots
Ticona 500ppm full Sheets, non-cross-linked
MediTECH 500ppm full Sheets, non-cross-linked
MediTECH 750ppm full Sheets, non-cross-linked
2004 University of Torino Plaques @ 30kGy
2004 University of Torino Plaques @ 100kGy
Ticona 500ppm full Sheets @ 75kGy, no post anneal
Ticona 500ppm full Sheets @ 75kGy, Below Melt post anneal
Ticona 500ppm full Sheets @ 75kGy, Above Melt post anneal
Ticona 500ppm full Sheets @ 100kGy, no post anneal
Ticona 500ppm full Sheets @ 100kGy, Below Melt post anneal
Ticona 500ppm full Sheets @ 100kGy, Above Melt post anneal
New Quality Assurance Challenges with Blended UHMWPE:

• Dispersion Uniformity Test Methods Under Consideration:
  • Infrared Spectroscopy
  • FTIR and spectral subtractions
  • DSC
  • UV Visibility Spectroscopy
  • Colorimetry

• Other Testing for efficacy:
  • Oxidation Index
  • Cross-Link Density
  • ESR

• Scale up concerns:
  • Practicality on a production basis
  • Testing of Resin form to reduce risk
New Quality Assurance Issues with Blended UHMWPE:

• Certifications:

  • Irresponsible logistics can make for significant work load increases for QA, and increases the risk for failed material.

  • Table shows how the number of discrete certificates could vary from ~400 to over 2600.

<table>
<thead>
<tr>
<th>Batch components</th>
<th>Size, kg</th>
<th>Certs per Resin Lot</th>
<th>Smallest Batches Possible, kg</th>
<th>Certs per Resin Lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resin Lot</td>
<td>100000</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Extrusion Run</td>
<td>1000</td>
<td>100</td>
<td>100</td>
<td>1000</td>
</tr>
<tr>
<td>a-tocopherol lot</td>
<td>50</td>
<td>1</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Resin Lots per year:</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Discrete Certificates:</td>
<td></td>
<td></td>
<td></td>
<td>204</td>
</tr>
<tr>
<td>Resin Lot</td>
<td>100000</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Compression Molding</td>
<td>500</td>
<td>200</td>
<td>75</td>
<td>1334</td>
</tr>
<tr>
<td>a-tocopherol lot</td>
<td>50</td>
<td>1</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Resin Lots per year:</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Discrete Certificates:</td>
<td></td>
<td></td>
<td></td>
<td>404</td>
</tr>
</tbody>
</table>
A novel way to view blended material in a blending method validation, although not practical on a production basis.
Examples:

- 0.254 mm film
- 0.381 mm film
- 3.81 mm film
Examples:

8x picture of small section of 3.81mm film
Examples:

8x pictures of .381mm and .254mm films, respectively
Continuing Efforts Summary:

- The Orthopaedic Community is already beginning to voice individual and collective opinions as to the benefits and opportunities of making UHMWPE oxidation resistant.

- There are significant steps to be taken in working with the enhanced material by the blender and converter:
  - How to quantify and verify dispersion uniformity (Resin & Sheet)
  - Assessing effectiveness of α-tocopherol for consolidated material
  - Post-Radiation Annealing considerations

- Explore Oxidative Performance of Production Processed UHMWPE and processing effects on α-tocopherol consumption.
Acknowledgements:

• Ticona, for their provision of virgin and blended resin to support these efforts

• Orthopaedic Device Manufacturers for partnering with us in development rather than working exclusively, which benefits us both.

• Dr. Luigi Costa, who for years has been spiriting this activity.

• The Universidad Autonoma de Madrid for hosting the forum to present this information.

• DISCUSSION