Summary

Alternative Solvents for Non-Targeted Extractables Analysis of Blood Contacting Medical Devices
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Plain Language Summary

An important aspect of safety evaluation for medical devices is to perform chemical analysis to understand the identities of chemicals that can be released from devices and their quantities. This work explores alternative solvents to simplify non-targeted extractables analysis of blood contacting medical devices.

Introduction/Purpose

The standard ISO 10993-18:2020, which describes chemical characterization approaches, includes statement “Based on published research, 40% (by volume) mixture of ethanol/water is considered an appropriate surrogate for blood and blood related substances.”. However, the published research on 40% ethanol/water approach relies on a very few material-extractable systems. This can be of concern since unreliable extractables systems can underestimate concentrations of extractables, leading to incorrect conclusions or greater uncertainties in toxicological risk assessment.

The goal of this study was to evaluate considerations for creating and justifying alternative solvents for non-targeted extractables analysis of blood contacting medical devices. We explore two approaches:

1. Create simpler simulators of blood with complex protein content that can be used in extractables studies.
2. Create simple solvents that may act like blood in certain extractables studies.

Materials and Methods

Two UHPLC/UV/MS systems were used (Dionex Ultimate 3000/Agilent 6540B UHD QTOF-MS and Thermo Vanquish Flex/Q Exactive HF) measuring both UV and MS signals. Also, target specific measurements were done by LC-MS/MS using Agilent 1290/Agilent 6495C QQQ-MS.

Current methods include:

- Bis(2-ethylhexyl) phthalate (DEHP - CAS number 117-81-7)
- Mono(2-ethylhexyl) phthalate (MEHP - CAS number 4376-20-9)

Methods are targeted for certain extractables. However, screening is also performed. The goal of this study was to evaluate considerations for creating and justifying alternative solvents and conditions and verifying with all LC based analytical methods.

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Results and Discussion

Table 1: Recoveries in verification experiment using human serum albumin (without syringe filters used). Total incubation time before centrifugation: 2 minutes

<table>
<thead>
<tr>
<th>Sample name</th>
<th>Concentration of added DEHP (µg/mL)</th>
<th>Measured concentration of free DEHP (µg/mL)</th>
<th>Calculated* concentration of bound DEHP (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Blank</td>
<td>53</td>
<td>53</td>
<td>&lt;ND</td>
</tr>
<tr>
<td>Albumin 30 µg/mL</td>
<td>53</td>
<td>43.2-45.0</td>
<td>8.0-9.8</td>
</tr>
<tr>
<td>Albumin 20 µg/mL</td>
<td>53</td>
<td>44.1-45.0</td>
<td>8.0-8.9</td>
</tr>
</tbody>
</table>

Table 2: Recoveries in verification experiment using human serum albumin (with syringe filters used). Total incubation time before centrifugation: 30 minutes

<table>
<thead>
<tr>
<th>Sample name</th>
<th>Concentration of added DEHP (µg/mL)</th>
<th>Measured concentration of free DEHP (µg/mL)</th>
<th>Measured concentration of bound DEHP (µg/mL)</th>
<th>Estimated Recovery %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Blank</td>
<td>53</td>
<td>53</td>
<td>&lt;ND</td>
<td>21 to 45</td>
</tr>
<tr>
<td>Albumin 30 µg/mL</td>
<td>10</td>
<td>2.1-4.5</td>
<td>&lt;ND</td>
<td>37 to 71</td>
</tr>
<tr>
<td>Albumin 20 µg/mL</td>
<td>10</td>
<td>1.3-4.0</td>
<td>2.3-3.1</td>
<td>63 to 86</td>
</tr>
</tbody>
</table>

Table 3: Determination of DEHP in PVC-Medical grade tubing by LC-MS technique (material was extracted at 37 °C for 24 hours at 100 RPM)

<table>
<thead>
<tr>
<th>Sample name</th>
<th>Test Solution</th>
<th>Average Calculated amount of DEHP (µg/mL)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVC-Medical grade</td>
<td>Hexane</td>
<td>80.037</td>
<td>23.58</td>
</tr>
<tr>
<td>PVC-Medical grade</td>
<td>Isopropanol</td>
<td>54.572</td>
<td>6.414</td>
</tr>
<tr>
<td>PVC-Medical grade</td>
<td>40% Ethanol</td>
<td>16.903</td>
<td>9.751</td>
</tr>
</tbody>
</table>

Acknowledgements

We appreciate feedback and opportunity to collaborate. We would like to hear from you. Please contact Berk.Oktem@fda.hhs.gov or Kanti.Sapkota@fda.hhs.gov

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Feedback

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