Special Rubber Stoppers

for heat sterilization

Dr. A. Schatzinger
Outline

• Introduction Lonstroff AG
• Composition of rubber compounds
• Processing issues
• Choosing a suitable rubber material
  ▪ mechanical properties
  ▪ chemical aspects
• Comparison of rubber compounds
• Testing of heat sterilized stoppers
Lonstroff AG

- established 1908 in Aarau, Switzerland
- manufacturer of elastomer parts for pharmaceutical packaging materials
- 170 employees (2010)
- turnover approx. 40 Mio CHF/a
- majority shareholder BV Holding AG
## Composition of rubber compounds

- **Rubber** – a curable polymer  
  - natural or synthetic material  
  - 50% to 90%

- **Filler** – minerals  
  - natural or synthetic origin  
  - up to 50%

- **Plasticiser**  
  - e.g. medicinal liquid paraffin  
  - 0 to 30%
- Processing agents 0 to 2%
  - e.g. flow promoters, dispersing agents.

- Curing agents 0.3 to 5%
  - classic ZnO/S, accelerators, peroxides, metall oxide...

- Antiageing agents 0.2 to 1%
  - antioxidants, light protection

- Pigments 0 to 1.5%
  - colour, whitener
Processing issues

raw materials check

analytical laboratory

chemical & physical testing e.g. ISO 8871, EP, USP

test certificate

compounding

prefoming

injection molding

trimming

cleaning, siliconization

visual inspection

packaging ready-to-sterilize ready-to-use

clean room

factory

customer
Siliconization of elastomer stoppers

- silicone oil applied against stickiness of rubber
  - for transport, further processing, manufacturing...
  - viscosity of silicone oil
    - usually 1'000 cSt (room temp.)
    - special applications 12'500 cSt
  - „Defect evaluation list for rubber parts“ (Editio Cantor Verlag):

<table>
<thead>
<tr>
<th>Degree of siliconization</th>
<th>mg of silicone oil per cm² of sample surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-siliconized</td>
<td>up to 0.005</td>
</tr>
<tr>
<td>Slightly siliconized</td>
<td>over 0.005 to 0.02</td>
</tr>
<tr>
<td>Moderately siliconized</td>
<td>over 0.02 to 0.04</td>
</tr>
<tr>
<td>Heavily siliconized</td>
<td>over 0.04 to 0.08</td>
</tr>
</tbody>
</table>
Choosing a suitable rubber material I

Requirements for the application?

Physics

- mechanical properties:
  - stability
  - tensile strength
  - penetration force
  - permeability
  - elasticity
  - …

Chemistry

- direct contact with a drug?
- stability of the compound
- environment, pH-value
- sterilization: dry heat, steam, irradiation, ETO
- …
Choosing a suitable rubber material II

• main properties are preset by rubber type!
  - e.g. permeability, heat stability, elasticity
• some adjustment can be made by filler and plasticiser
  - e.g. hardness
• curing system
  - curing system  mechanical properties
  - chemical cleanness
Comparison of rubber materials

- EPDM rubber
- Silicone rubber
- Bromobutyl rubber
- Fluoroelastomer
- Polyisoprene rubber, unfilled & filled

Test example: Stopper 20 mm
# Mechanical Properties overview

- values for typical pharmaceutical compounds

<table>
<thead>
<tr>
<th>polymer type</th>
<th>Silicone rubber</th>
<th>Ethylene-Propylene Diene</th>
<th>Fluoroelastomer</th>
<th>Bromobutyl rubber</th>
<th>Isoprene Rubber</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIN ISO 1629</td>
<td>MVQ</td>
<td>EPDM</td>
<td>FKM</td>
<td>BIIR</td>
<td>IR unfilled</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IR filled</td>
</tr>
<tr>
<td>tensile strength [N]</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>elongation at break [%]</td>
<td>550</td>
<td>580</td>
<td>400</td>
<td>330</td>
<td>700</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>550</td>
</tr>
<tr>
<td>tear strength [N/mm]</td>
<td>40</td>
<td>15</td>
<td>13</td>
<td>21</td>
<td>25 - 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>hardness [ShA]</td>
<td>30 - 60</td>
<td>40 - 55</td>
<td>45 - 65</td>
<td>35 - 65</td>
<td>25 - 35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35 - 45</td>
</tr>
<tr>
<td>compression set [%]</td>
<td>5</td>
<td>15 - 25</td>
<td>15</td>
<td>15</td>
<td>15 - 25</td>
</tr>
<tr>
<td>(1 day, 70°C, 25% deformation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 - 30</td>
</tr>
<tr>
<td>rebound resilience [%]</td>
<td>50</td>
<td>65</td>
<td>10</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>gas permeability (air, 25°C)</td>
<td>17000</td>
<td>700</td>
<td>10</td>
<td>&lt; 1</td>
<td>550</td>
</tr>
<tr>
<td>[cm³·mm/(m²·day·atm)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>550</td>
</tr>
</tbody>
</table>
## Chemical Properties overview

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<tbody>
<tr>
<td>DIN ISO 1629</td>
<td>MVQ/LSR</td>
<td>EPDM</td>
<td>FKM</td>
<td>BIIR</td>
<td>IR unfilled</td>
</tr>
<tr>
<td>chemistry, ISO 8871-1</td>
<td>type I</td>
<td>type I</td>
<td>type I</td>
<td>type I</td>
<td>type I,II</td>
</tr>
<tr>
<td>resistance against:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>type I,II</td>
</tr>
<tr>
<td>ethanol</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>acid, pH 6 - 3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>base, pH 8 - 11</td>
<td>(-)</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>ageing: UV-light, ozone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>steam sterilization</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>dry heat, &gt; 150°C</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
</tr>
<tr>
<td>dry heat, 200°C</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
</tr>
</tbody>
</table>
Conditions: untreated | 160°/2h | 170°/1h | 180°/0.5h

Silicone rubber

EPDM rubber

Fluoroelastomer

Bromobutyl rubber

Isoprene rubber
Functional & chemical testing of the stoppers

- ISO 8871 - Elastomeric parts for parenterals and for devices for pharmaceutical use (see also ISO 8362 - Injection containers for injectables and accories; closures for injection vials).

- Chemical tests of aquaeous autoclavates:
  - reducing substances
  - acidity/alkalinity
  - heavy metals (e.g. zinc)
  - UV absorbance etc...

- Functional tests
  - penetrability with a needle
  - Fragmentation of the rubber after piercing
  - self-sealing after removing the needle
# Heat sterilized stoppers: test results

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>DIN ISO 1629</td>
<td>MVQ</td>
<td>EPDM</td>
<td>FKM#</td>
<td>BIIR#</td>
<td>IR unfilled#</td>
</tr>
<tr>
<td>heat sterilization:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>160°C, 2h</td>
<td>+</td>
<td>not recommended</td>
<td>+</td>
<td>(+) slight discoloration</td>
<td>-</td>
</tr>
<tr>
<td>170°C, 1h</td>
<td>+</td>
<td>not recommended</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
</tr>
<tr>
<td>180°C, 0.5h</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
</tr>
<tr>
<td>tests ISO 8871-5:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>penetration force [&lt;10 N]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fragmentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>self sealing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# slightly siliconized
Conclusion

- suitable compounds for heat sterilization are:
  - Fluoroelastomers FKM - excellent heat stability
  - Silicone rubber MVQ - no change in properties after dry heat sterilization
  - limited recommendable: Bromobutyl compounds BIIR
Thank you