Rubber components selection for optimal drug packaging

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Manager Material Development

March 11th, 2019
Agenda

1. Composition of pharmaceutical rubber
2. Extractables and leachables from rubber
3. Expectations of extractables information sharing
4. Different rubber compositions to steer properties
5. Compound for gamma sterilisation
Stability and strength of a large industrial group

Swiss origin, established in 1915

Revenues of approx. CHF 1,200 million

Focused industrial player with two divisions: Sealing Solutions & Technical Components

Listed on the SIX Swiss Exchange
Multi-industry knowhow

**HEALTH CARE**

Applications:
- Prefilled syringe and cartridge drug delivery systems
- Medical devices
- Elastomeric closures and aluminium seals

**AUTOMOTIVE**

Applications:
- Brake systems
- Fuel and tank systems
- CNG and LPG
- Exhaust gas treatment
- Powertrain, suspension
- Thermoplasts and LSR
- E-Mobility, electrification

**GENERAL INDUSTRIES**

Applications:
- Consumer Goods
- Civil Engineering
- Oil & Gas
- Power tools, valves & fittings
- Machines for process industries
- Water and waste water
- Hydraulic and pneumatic
Datwyler Sealing Solutions – Health Care offer overview

High quality components and closures for injectable drugs
Datwyler Sealing Solutions – Health Care offer overview

High quality components and closures for injectable drugs

Vials
Datwyler Sealing Solutions – Health Care offer overview

High quality components and closures for injectable drugs

Vials

Syringes and cartridges
1. Composition of Pharmaceutical Rubber
Types of elastomeric closures

- Compounded material of:
  1. Elastomer
  2. Filler
  3. Cure system
  4. Pigment
  5. Other ingredients
Composition – 1. Elastomers

- **Halobutyl (BromoButyl, ChloroButyl)**
  - Cleanest curing system
  - Lowest permeability
  - High resistance to ageing
  - Regular butyl still on the market, and also newer types like **BIMS** (Brominated isobutylene para-methylstyrene)

- **Natural rubber / Polyisoprene**
  - Natural rubber: latex allergy discussions
  - Historically the oldest elastomer type
  - Need complex curing systems
  - Good elastic properties
  - Polyisoprene (synthetic) replaces Natural rubber

- **Nitrile rubber**
  - Typically used for mineral oil based drugs

- **Silicone rubber**
  - High permeability
  - Typically not used for parenteral applications

- **SBR** (styrene-butadiene rubber)
  - Intermediate permeability
  - Typically used for pre-assembled EtO sterilized components (e.g. Needle Shields)

- **EPDM** rubber
  - For niche applications
Composition – 2. Fillers

- Fillers give mechanical strength (stiffness) to a rubber
- Attributes physical properties to a rubber compound
  - More filler = Harder compound
    → Better for gliding profile plungers
    → Better against stickiness in bulk
    → Worse for stopper piercing (coring!)

- Inorganic fillers (‘white compounds’)
  - Aluminum silicate (clay)
  - Magnesium silicate (talc)
  - [Calcium carbonate] (calc)

- Carbon black (‘black compounds’)
  - Undesired for cleanliness reasons
  - May be associated with PNA’s
Composition – 3. Curing agents

• Cure system:
  – Crosslinking agent
  – Activator: gives the onset of vulcanization
  – Accelerator: speeds up the vulcanization
    • Easily extractable organic molecules such as thiurams, sulfonamides, thiazoles, ...

• Modern cure systems
  – Aim at giving little extractables

• Historic cure systems
  – Use easily extractable organic accelerators
Composition – 4. Color pigments

• Inorganic pigments
  – Grey colors:
    – Titanium dioxide → White
    – Traces of carbon black → Black
  – Red colors:
    – Oxides of iron → Red

• Organic pigments
  – Avoided in modern compounds
Composition – 5. Other ingredients

- Halobutyl polymer stabilizers
  - Calcium stearate
  - Epoxydized soybean oil (ESBO)

- Anti-oxidants
  - Already present in halobutyl elastomer
  - Hindered phenol type anti-oxidants
  - Additionally added to improve environmental stability (ageing)

- Plasticizer, Waxes, Oils
  - High polymeric weight plasticizers, Paraffinic oil
  - To tune a formulation (e.g. reduce coring)

- Processing aids
2. Extractables and leachables from rubber
E&L of elastomeric closures – Extractables profiles

- Too many ingredients should be avoided: negative impact on E-profile

→ “what you don’t put in, can’t come out”
Significant improvements in recipes and raw material selection

Fillers
- Silicates (Talc, Clay)
- No Carbon Black, No Calc

Curing systems
- Sterically hindered curing agents
- No doubtful accelerators

Color Pigments
- Inorganic (TiO\textsubscript{2}, C, Fe\textsubscript{3}O\textsubscript{4})
- No organic colorants

Additives
- High molecular weight, purified
- No simple waxes, oils
E profile: OLD vs MODERN

Difference in Extractable Results for an OLD vs MODERN rubber
(IPA Extract; GC/MS analysis)

“OLD” RUBBER

“MODERN” RUBBER
E profile: MODERN vs MODERN COATED

Difference in Extractable Results for a Coated vs Uncoated rubber, for the same rubber grade (IPA Extract; GC/MS analysis)
Extractable profile over time

- Extractables study is performed on the same batch at manufacturing date (0 year), after 1 year, 2 years and [ongoing:7 years]

- Negative trend in volatiles (Anti-Oxidant, Oligomers)
- No trend in non-volatiles (Fatty acid)
3. Expectations of Extractables information sharing
Information transfer

- **Sharing Pharmacopeial data**: ✔️

- **E-documentation from supplier**

- **L-study set up: Drug details drug company & E-doc. from supplier**

**Note**: Rubber compositions are extremely sensitive information to closure manufacturers
- Rubber compound recipes are in general not patented
- ‘Trust <-> control’
Extractables documentation throughout the years

<table>
<thead>
<tr>
<th>Extractable</th>
<th>Units</th>
<th>Water neutral</th>
<th>Water acidic</th>
<th>Water alkaline</th>
<th>Isopropanol</th>
<th>Hexane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al</td>
<td>s b</td>
<td>ppm</td>
<td>&lt; 0.02</td>
<td>0.03</td>
<td>&lt; 0.05</td>
<td>N/D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.02</td>
<td>0.03</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Zn</td>
<td>s b</td>
<td>ppm</td>
<td>&lt;0.01</td>
<td>0.04</td>
<td>0.19</td>
<td>N/D</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
<td>0.03</td>
<td>&lt; 0.09</td>
<td></td>
</tr>
<tr>
<td>Bromide</td>
<td>s b</td>
<td>ppm</td>
<td>1.5</td>
<td>1.5</td>
<td>1.6</td>
<td>N/D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
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</tr>
<tr>
<td>ID1</td>
<td>s b</td>
<td>ppb</td>
<td>0.02</td>
<td>0.02</td>
<td>2.2</td>
<td>10.0</td>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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<td>0.04</td>
<td>3.40</td>
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</tbody>
</table>

Theoretical list
+ actual study
+ semi-quantitative
+ screening
+ extra extract. media
+ gamma (if applicable)
Nelson Labs – Datwyler Partnership
… more than a decade

bringing analytical and rubber compounding experts together enabling the best services

• A premium service to the pharmaceutical packaging industry enabling a fast and safe regulatory approval.
• Common R&D programs show the ambition to continue offering the best-in-class knowledge and expertise in pharmaceutical elastomer formulations.
• Enjoy a discount for all your analytical study work.
4. Different rubber formulations to steer properties
Smart selection of ingredients can tune a rubber compound

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophobic ingredients</td>
<td>Improve E-profile with aqueous drugs</td>
</tr>
<tr>
<td>Halobutyl and SBR</td>
<td>Tune permeability</td>
</tr>
<tr>
<td>MgO</td>
<td>Replace ZnO to avoid Zn-ion extraction</td>
</tr>
<tr>
<td>Low water absorption compounds</td>
<td>For lyo applications</td>
</tr>
<tr>
<td>Soft compound</td>
<td>For multi piercings with needle</td>
</tr>
<tr>
<td>Omniflex coated rubber</td>
<td>For sensitive/large molecule drugs</td>
</tr>
</tbody>
</table>
Smart selection of ingredients can tune a rubber compound

E.g. recipe based on hydrophobic ingredients will show better E-profile with aqueous drugs.

E.g. blend of halobutyl and SBR can *tune* the permeability

E.g. MgO replaces ZnO to avoid Zn-ion extraction

E.g. low water absorption compounds for lyo applications

E.g. soft compound for multi piercings with needle

E.g. Omniflex coated rubber for sensitive/large molecule drugs
blend of halobutyl and SBR can tune the permeability

Ethylene oxide or steam sterilization:
NS or TC material must be permeable to gas (EtO or steam)!!
Smart selection of ingredients can tune a rubber compound

**E.g.** recipe based on hydrophobic ingredients will show better E-profile with aqueous drugs.

**E.g.** blend of halobutyl and SBR can *tune* the permeability

**E.g.** MgO replaces ZnO to avoid Zn-ion extraction

**E.g.** low water absorption compounds for lyo applications

**E.g.** soft compound for multi piercings with needle

**E.g.** Omniflex coated rubber for sensitive/large molecule drugs
Omniflex coated rubber for sensitive/large molecule drugs

- Key attribute: barrier effect!
  - Simplified extractables profile
  - Improved compatibility with drugs/excipients

Extractables: FM257 (Omniflex Coated v.s. Uncoated)

Concentration (mg/kg)

<table>
<thead>
<tr>
<th>R5</th>
<th>R3</th>
<th>R4</th>
<th>I1</th>
<th>I3</th>
<th>O2</th>
<th>A3</th>
<th>A2</th>
<th>O1</th>
<th>A4</th>
<th>T1</th>
<th>R3</th>
<th>R2</th>
<th>R1</th>
<th>K1</th>
<th>D1</th>
<th>D2</th>
<th>B1</th>
<th>B2</th>
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<td></td>
</tr>
</tbody>
</table>

Uncoated-FM257

Coated-Steam Sterilized
Smart selection of ingredients can tune a rubber compound

E.g. recipe based on hydrophobic ingredients will show better E-profile with aqueous drugs.

E.g. blend of halobutyl and SBR can tune the permeability

E.g. MgO replaces ZnO to avoid Zn-ion extraction

E.g. low water absorption compounds for lyo applications

E.g. soft compound for multi piercings with needle

E.g. Omniflex coated rubber for sensitive/large molecule drugs
Low water absorption compounds for lyo applications

Figure 4: Weight decrease in mg/gram stopper material by drying at 110°C after a steam sterilisation process (starting from delivery state condition)
5. Compound for gamma sterilization: FM457
Elastomers throughout the years

Natural → Butyl → Halobutyl → Exxpro → Coated
- 1950's
- 1970's
- 1990's
- 2008
- 2018

- FM257
- FM140
- FM457
- OMNIFLEX3G
- Coated
- FM460
- OCP
- FM480
- FM703

Gamma sterilized Ready to Use (RTU) components
Significant improvements in recipes and raw material selection

- Regular halobutyl still on the market, and also newer types like BIMS (Brominated isobutylene para-methylstyrene)

= **FM457**

No double bonds along the polymer chain.
### Physical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Unit</th>
<th>Irradiation level (kGy - gamma)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Modulus 100</td>
<td>N/mm²</td>
<td>1.56</td>
</tr>
<tr>
<td>Modulus 300</td>
<td>N/mm²</td>
<td>2.83</td>
</tr>
<tr>
<td>Tensile strength</td>
<td>N/mm²</td>
<td>4.78</td>
</tr>
<tr>
<td>Tear strength</td>
<td>N/mm</td>
<td>8.96</td>
</tr>
<tr>
<td>Elong. at break</td>
<td>%</td>
<td>408</td>
</tr>
<tr>
<td>Compression set</td>
<td>%</td>
<td>26</td>
</tr>
<tr>
<td>Hardness</td>
<td>° Shore A</td>
<td>51</td>
</tr>
</tbody>
</table>

The physical properties are similar before and after irradiation.
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<tr>
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<td>%</td>
<td>26</td>
</tr>
<tr>
<td>Hardness</td>
<td>° Shore A</td>
<td>51±5</td>
</tr>
</tbody>
</table>

Measure of the elasticity of the rubber
Measure of the capability to reshape after deformation
Functional properties

Penetrability

<table>
<thead>
<tr>
<th>Limit (N)</th>
<th>Storage Time</th>
<th>0 kGy (N)</th>
<th>25 kGy (N)</th>
<th>40 kGy (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>T = 0m</td>
<td>4.5</td>
<td>4.3</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>T = 6m</td>
<td>4.4</td>
<td>4.5</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>T = 1 year</td>
<td>4.7</td>
<td>4.7</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>T = 2 yrs</td>
<td>4.5</td>
<td>4.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Self-sealing

<table>
<thead>
<tr>
<th>Limit (number of leaks)</th>
<th>Storage Time</th>
<th>0 kGy (number of leaks)</th>
<th>25 kGy (number of leaks)</th>
<th>40 kGy (number of leaks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T = 0m</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T = 6m</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T = 1 year</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T = 2 yrs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Fragmentation

<table>
<thead>
<tr>
<th>Limit (fragments)</th>
<th>Storage Time</th>
<th>0 kGy (fragments)</th>
<th>25 kGy (fragments)</th>
<th>40 kGy (fragments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>T = 0m</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>T = 6m</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>T = 1 year</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>T = 2 yrs</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

The functional properties are similar before and after irradiation.

Limit: 10 N

Limit: no leak

Limit: 5 fragments
## Chemical properties

<table>
<thead>
<tr>
<th>Test</th>
<th>Unit</th>
<th>Pharm. limit</th>
<th>Irradiation dose (kGy - gamma)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Ca + Mg</td>
<td>ml Na-EDTA</td>
<td>0.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Chlorides</td>
<td>NTU</td>
<td>3.5</td>
<td>2.0</td>
</tr>
<tr>
<td>pH</td>
<td>-</td>
<td>5.0-7.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Reducing substances</td>
<td>ml 0.01 N KMnO4 (visual test)</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Ammonium</td>
<td>ppm</td>
<td>(colour)</td>
<td>pass</td>
</tr>
<tr>
<td>Zinc</td>
<td>-</td>
<td></td>
<td>0.058</td>
</tr>
<tr>
<td>UV absorb.</td>
<td>-</td>
<td></td>
<td>0.036</td>
</tr>
</tbody>
</table>

Gamma sterilized compounds are compatible for contact with WFI after irradiation.
E profile: OLD vs MODERN

Difference in Extractable Results for an OLD vs MODERN rubber (IPA Extract; GC/MS analysis)
E profile: MODERN vs MODERN COATED

Difference in Extractable Results for a Coated vs Uncoated rubber, for the same rubber grade (IPA Extract; GC/MS analysis)
Conclusions

1. Extractables can be complex and depends on the compound.

   “What we don’t put in cannot come out”

2. The composition of the rubber is never shared but detailed extractables reports are available.

3. Rubber properties can be steered to suit for a specific application.

4. Compounds specifically adapted for gamma sterilization are available.
Thank you