Basics of Blow-Fill-Seal technology

• From polymer granulates to filled and sealed containers
• Traditional BFS-process
• Multilayer options
BFS is worldwide well established in the market.

Some figures

established since 1964

1\textsuperscript{st} application for IV Solutions sold in 1965
1\textsuperscript{st} application for Eye drops sold in 1971
1\textsuperscript{st} application for Single dose Eye drops sold in 1976
1\textsuperscript{st} application for Inhalation Therapy sold in 1981
1\textsuperscript{st} application for Cough Syrup sold in 1982

more than 1800 BFS machines sold worldwide

Approx. 7 Billion of BFS containers per year

bp 312 from 1979
Within seconds BFS produces filled and closed containers from polymer granulate.

Traditional Blow-Fill-Seal (BFS)-Process

<table>
<thead>
<tr>
<th>EXTRUSION</th>
<th>BLOWING</th>
<th>FILLING*</th>
<th>SEALING</th>
<th>DEMOULDING</th>
</tr>
</thead>
</table>
| Polymer parison Extrusion | Bottles are blown into mould | Time-Pressure-Dosing system | Head mould closes | • Moulds open  
• Container removed |

15 sec


/2/ The manufacture of sterile Pharmaceutical Products Using Blow-Fill-Seal-Technology Parenteral Drug Association technical report No 77, 2017
Blow-Fill-Seal: How it works

https://vimeo.com/rommelag
BFS containers are mostly made of polyolefins.

<table>
<thead>
<tr>
<th></th>
<th>LDPE</th>
<th>HDPE</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory compliance</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Additives</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additives (potential extractables and leachables)</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thermal stability</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(important for terminal sterilization)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water barrier</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Transparency</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical strength</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Softness, flexibility</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>(e.g. squeezability for eye drops)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFS processing</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
BFS containers use medical grade polymers; polyolefins are preferred.

Some examples

PP, LDPE or HDPE
from e.g. LyondellBasell (Purell®), Borealis (Bormed®), INEOS, Total, Flint Hills, etc.

Autoclavable PE 106-115°C; PP 121°C

Extractables dossiers available for selected PE and PPs (by Toxikon)
Permeability: There are huge differences for polymers.

Typical polymers for BFS (mono and CoEx-systems)

**Literature data**

- Z. Zhang et al. Permeation of oxygen and water vapor through EVOH films as influenced by relative humidity, J. Appl. Polymer Science Vol.82 (8), 1866–1872, Nov.2001

**Typical polymers**

- PE-HD
- PE-LD
- PE
- PP
- PVC-P
- PS
- PC
- PLA
- PVC-U
- PET
- PEN
- PAN
- PVDC
- EVOH, 44%
- EVOH, 32%
- EVOH, 38%
- EVOH, 27%
- Cellulose

**Permeability**

- Oxygen permeation in cm³/m² d bar
- Water permeation in g/m² d at 23°C/85% RH
Small containers need special attention due to the filling volume to surface ratio.

<table>
<thead>
<tr>
<th></th>
<th>300 ml</th>
<th>15 ml</th>
<th>1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Filling volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Container surface</strong></td>
<td>311 cm²</td>
<td>57 cm²</td>
<td>8 cm²</td>
</tr>
<tr>
<td><strong>Wall thickness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Material</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Permeation rate at 25°C/40% RH</strong></td>
<td>2.3 mg/d</td>
<td>0.42 mg/d</td>
<td>0.06 mg/d</td>
</tr>
<tr>
<td><strong>Loss after 2 years at 25°C/40% RH</strong></td>
<td>0.6 %</td>
<td>2.1 %</td>
<td>4.3 %</td>
</tr>
</tbody>
</table>

LDPE (ρ=0.93 g/cm³)
Material properties can vary even in the same material class.

Some properties of different PEs

Source: Technical data sheets from different suppliers. Graph shows only general trends.
Functional requirement are key for proper material selection.

- functional requirements sometimes directly opposed
- development to find the best trade-off
- BFS offers a wide range of different polymers to cover different functional requirements
- different properties to be combined in multi-layer systems
Co-Extrusion of polymers to produce multilayer containers is well established.

**Principle**

- Flavors
- Oxygen
- CO₂
- Odors

**Examples**

- TANK STRUCTURE (6 layers)
  - Virgin HDPE
  - Adhesive
  - EVOH
  - Adhesive
  - Regrind
  - Virgin HDPE

**BFS-Co-Extrusion**

For pharma applications

- 5 Layers

- COC, COP, PP, ...
- EVOH, ...
- PE, PP, ...
- Nitrogen

**Picture Note**

The six-layer PP/EVOH squeeze bottle for Heinz ketchup, molded by American Can in 1983, was a breakthrough for barrier plastic bottles.
CoEx-BFS allows the improvement of barrier properties to minimize adsorption / permeation.

**EVOH** - excellent O$_2$ barrier properties for food and pharmaceutical packaging

**PA** - good gas barrier properties and chemical resistance, used for packaging of cosmetics and chemicals

**Cycloolefinpolymers COP (Nippon Zeon)**
inner layer for low adsorption used for parenteral packaging

**Cycloolefincopolymers COC (Topas)**
inner layer for low adsorption & low wvt used for parenteral packaging
Laser headspace spectroscopy offers fast, reliable and non-destructive testing.

- Test-kit containers in headspace testing

  - Tunable Diode Laser Absorption Spectroscopy at 760 nm
  - Test-kits filled with water
  - Conditioning at 40°C for 4 weeks
  - Storage at 40°C / 75% r.h. & 25°C / 60% r.h.

- Partners: Study performed by Wilco & Lighthouse

Oxygen head space data show strong barrier effect of EVOH.

O$_2$ headspace concentration over time

Michael W. Spallek, Johannes W. Geser and Martin Groh Characterization of Multilayer Blow-Fill-Seal Containers for Pharmaceutical Packaging
PDA Parenteral Packaging conference, 5-2015, Brussels