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.

bp 312 from 1979

Some figures

established since 1964

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

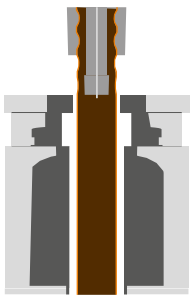
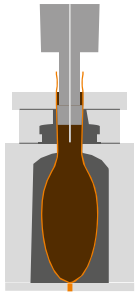
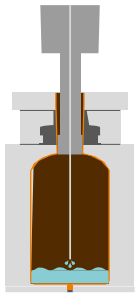
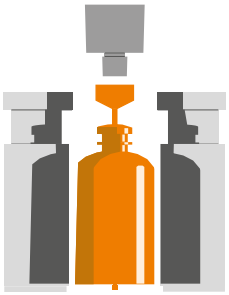
more than 1800 BFS machines sold worldwide

Approx. 7 Billion of BFS containers per year

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

Traditional Blow-Fill-Seal (BFS)-Process

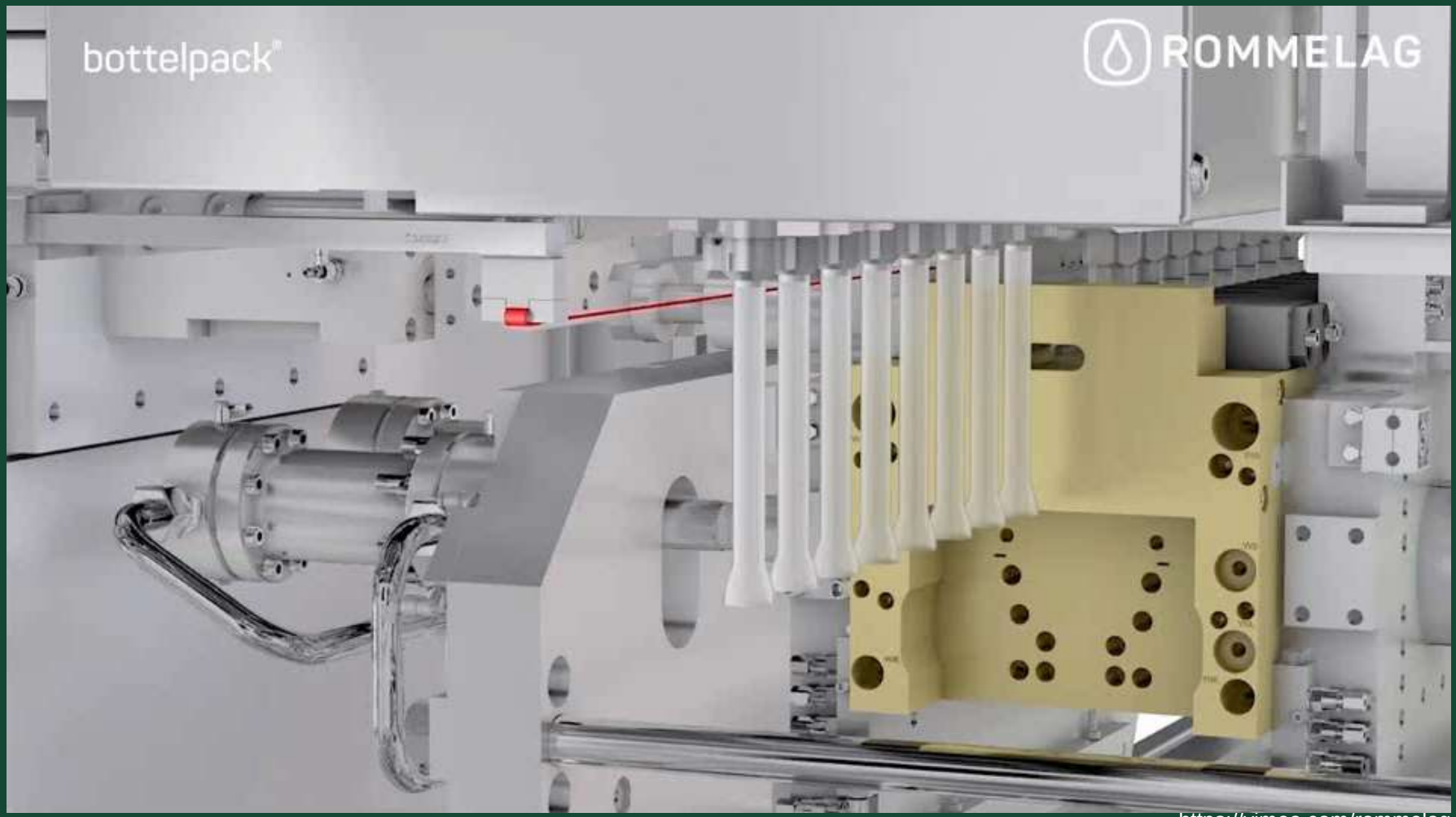
15 sec

EXTRUSION	BLOWING	FILLING*	SEALING	DEMOULDING
				
Polymer parison Extrusion	Bottles are blown into mould	Time-Pressure-Dosing system	Head mould closes	• Moulds open • Container removed

/1/ R. Oschmann, and O.E. Schubert, Eds, *Blow-Fill-Seal Technology*, (CRC Press, Stuttgart, 1999).
/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

Video



https://vimeo.com/rommelag

BFS containers are mostly made of polyolefins.

General comparison PE - PP

	LDPE	HDPE	PP
Regulatory compliance	++	+	++
Additives (potential extractables and leachables)	++	+	+
Thermal stability (important for terminal sterilization)	+	++	++
Water barrier	+	++	+
Transparency	o	-	o
Mechanical strength	o	+	+
Softness, flexibility (e.g. squeezability for eye drops)	++	-	+
BFS processing	++	+	+

BFS containers use medical grade polymers; polyolefins are preferred.

Some examples

PP **LDPE** **HDPE**

PP, LDPE or HDPE

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

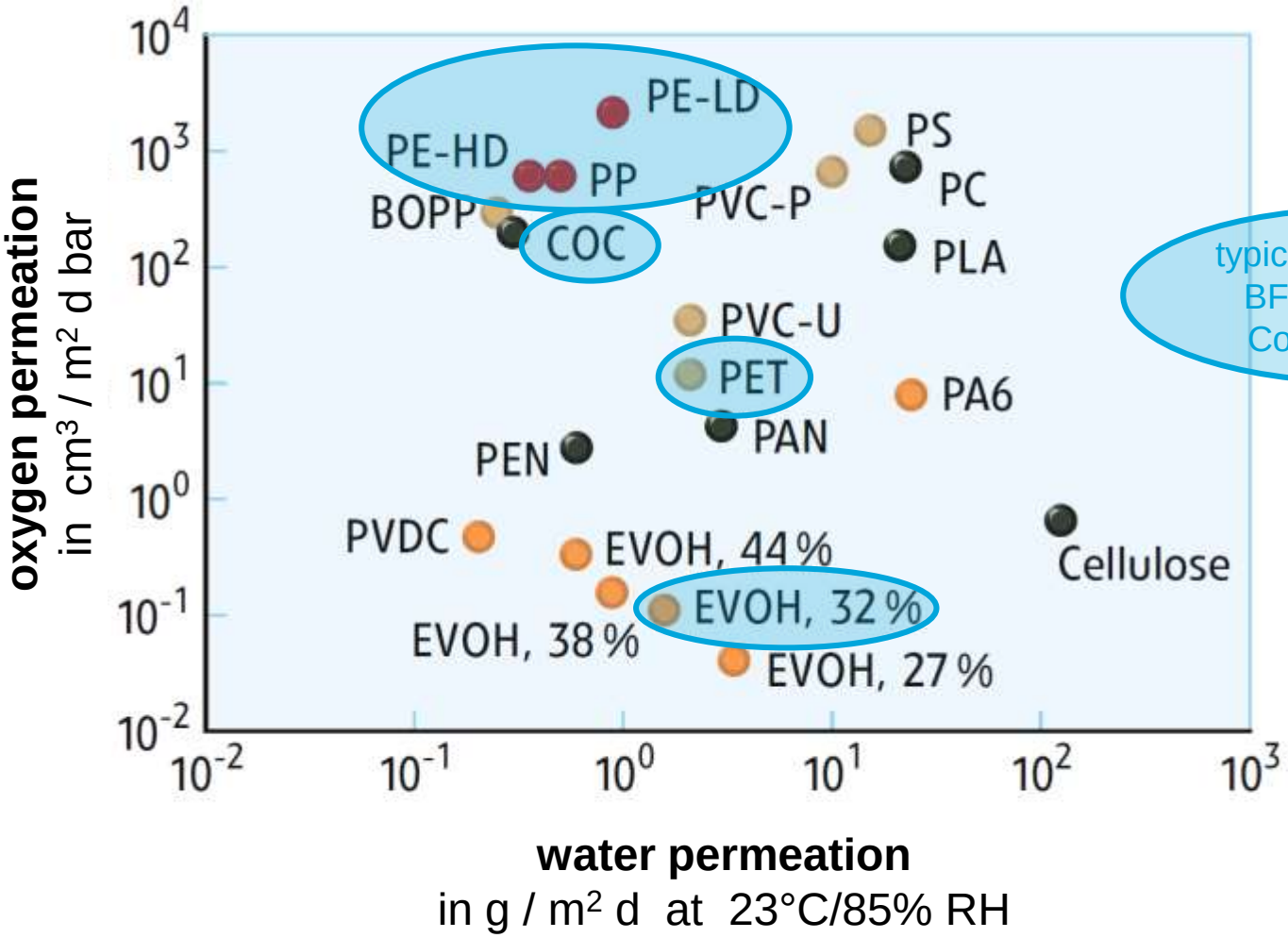
Autoclavable PE 106-115ºC; PP 121ºC

Extractables dossiers available for selected PE and PPs (by Toxikon)

P. Christiaens, M. Spallek The Importance of a thorough Material selection for Blow-Fill-Seal Applications… an E/L-Perspective PDA Parenteral Packaging Conference Venice April 13th, 2016

Permeability: There are huge differences for polymers.

Literature data



H.C. Langowski in O. Piringer (ed.) Plastic Packaging: Interactions with Food and Pharmaceuticals, 297-342, Wiley, 2008
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

Small containers need special attention due to the filling volume to surface ratio.

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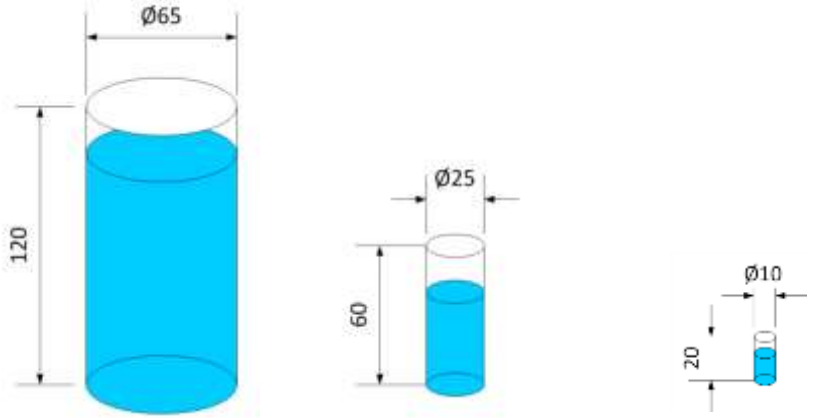
MVT-Calculations

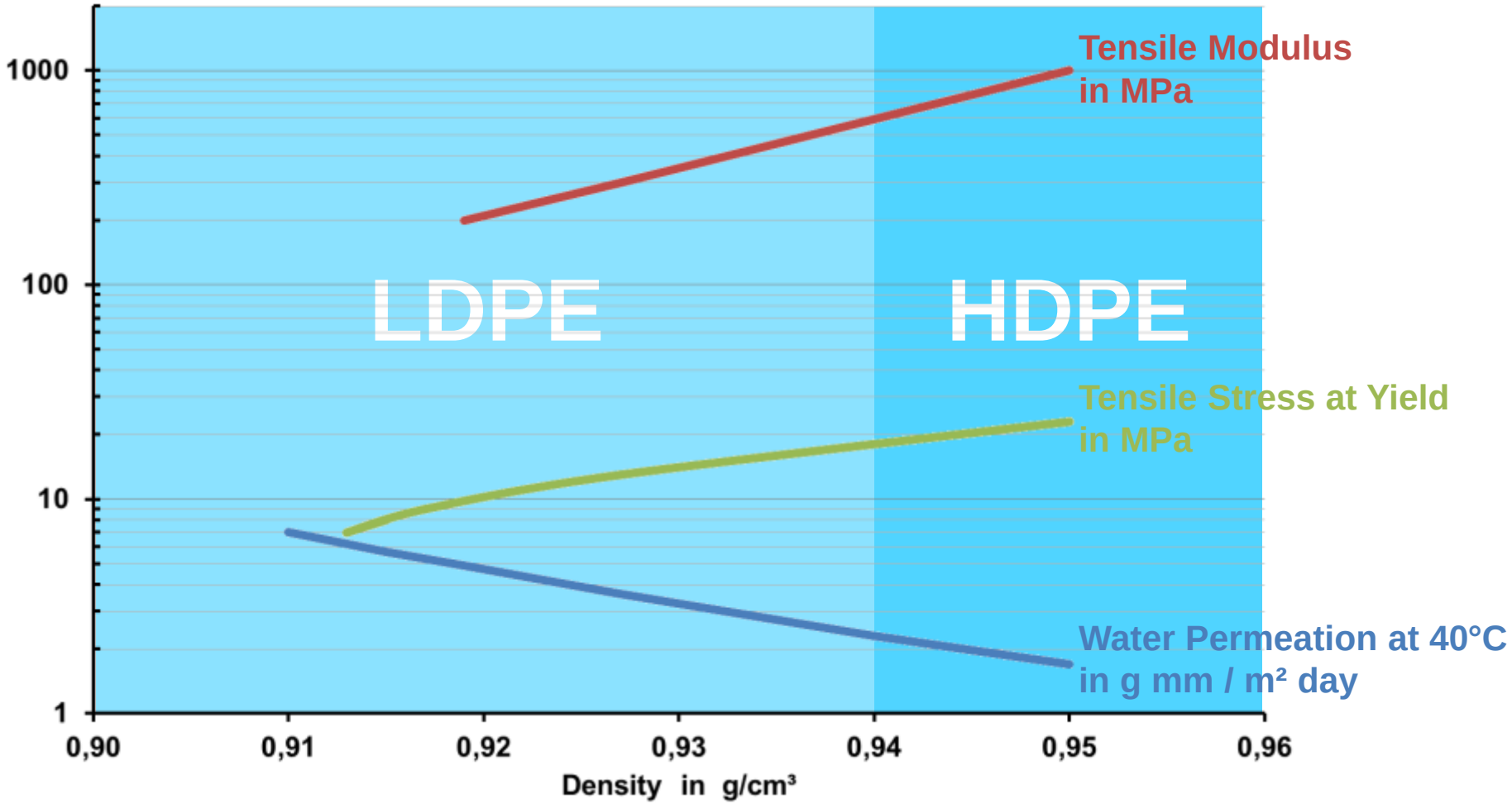


Filling volume	300 ml	15 ml	1 ml
Container surface	311 cm^2	57 cm^2	8 cm^2
Wall thickness	0.6 mm		
Material	LDPE (ρ=0.93 g/cm^3)		

Permeation rate at 25°C/40% RH	2.3 mg/d	0.42 mg/d	0.06 mg/d
Loss after 2 years at 25°C/40% RH	0.6 %	2.1 %	4.3 %

Material properties can vary even in the same material class.

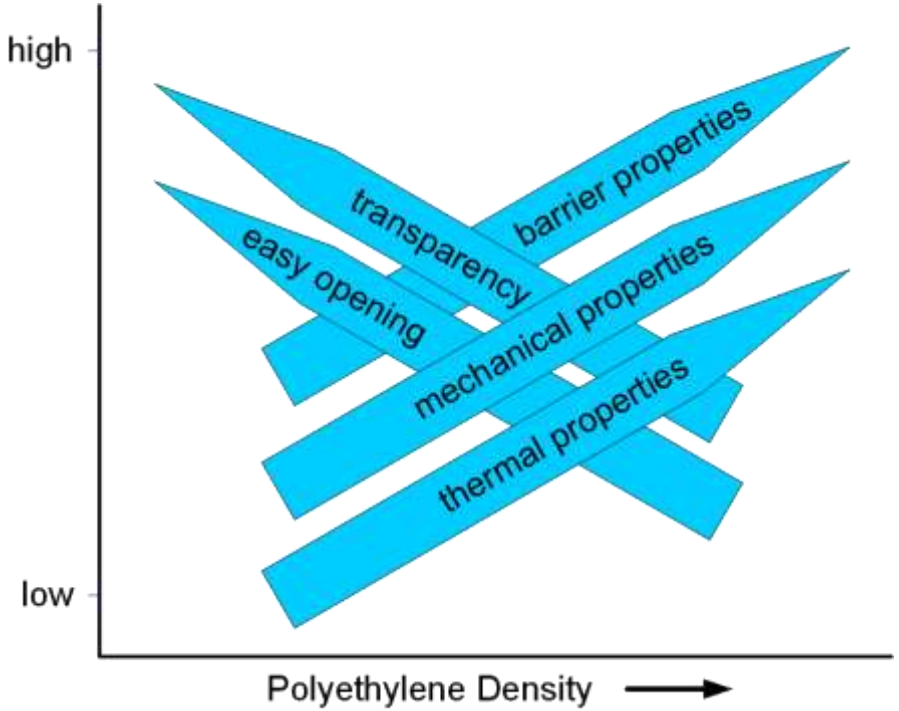
Some properties of different PEs



Source: Technical data sheets from different suppliers. Graph shows only general trends.

Functional requirement are key for proper material selection.

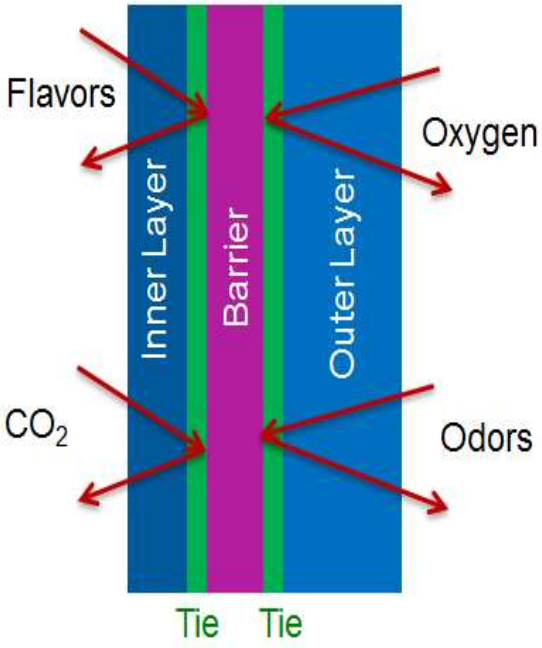
Some properties of Polyethylens



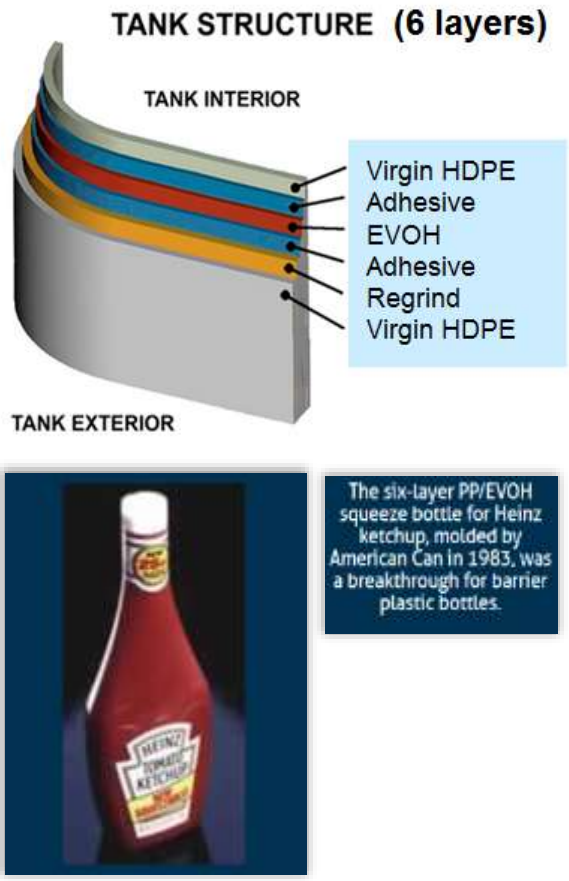
- functional requirements sometimes directly opposed
- development to find the best trade-off
- BFS offers a wide range of different polymers to cover different functional requirements
- different properties to be combined in multi-layer systems

Co-Extrusion of polymers to produce multilayer containers is well established.

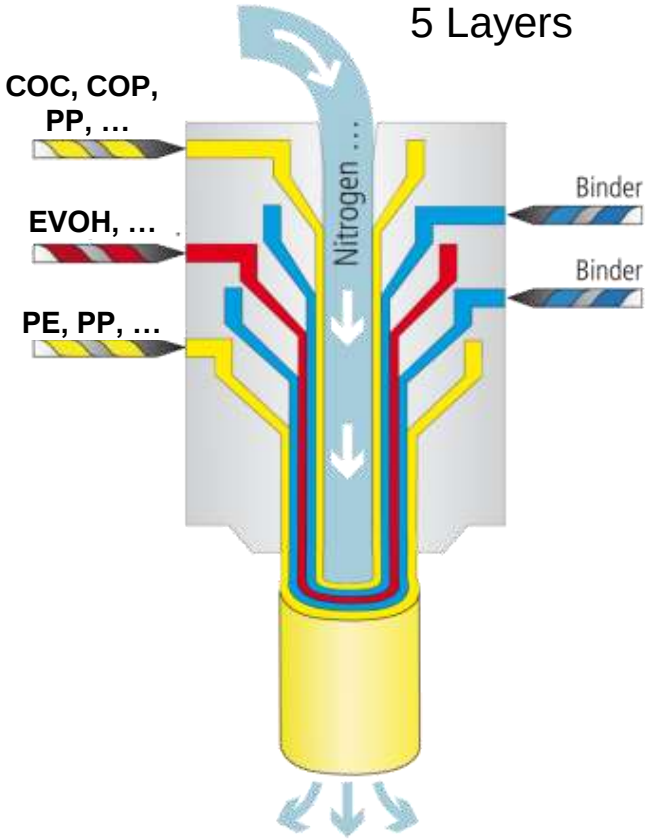
Principle



Examples

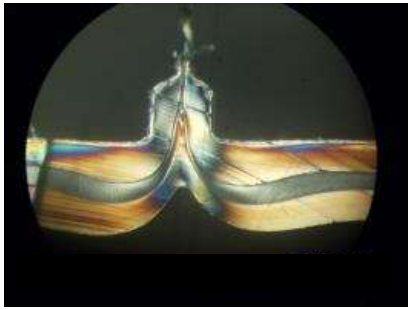


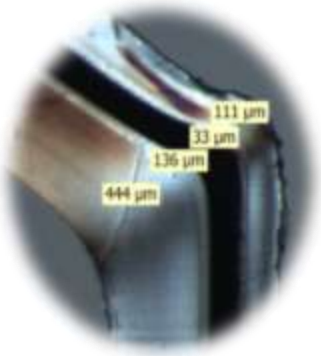
BFS-Co-Extrusion For pharma applications

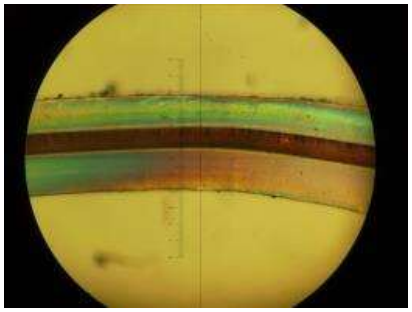


CoEx-BFS allows the improvement of barrier properties to minimize adsorption / permeation.

CoEx barrier materials







Cross sections of a
5 layer BFS-ampule

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

Test kit
container 10 ml

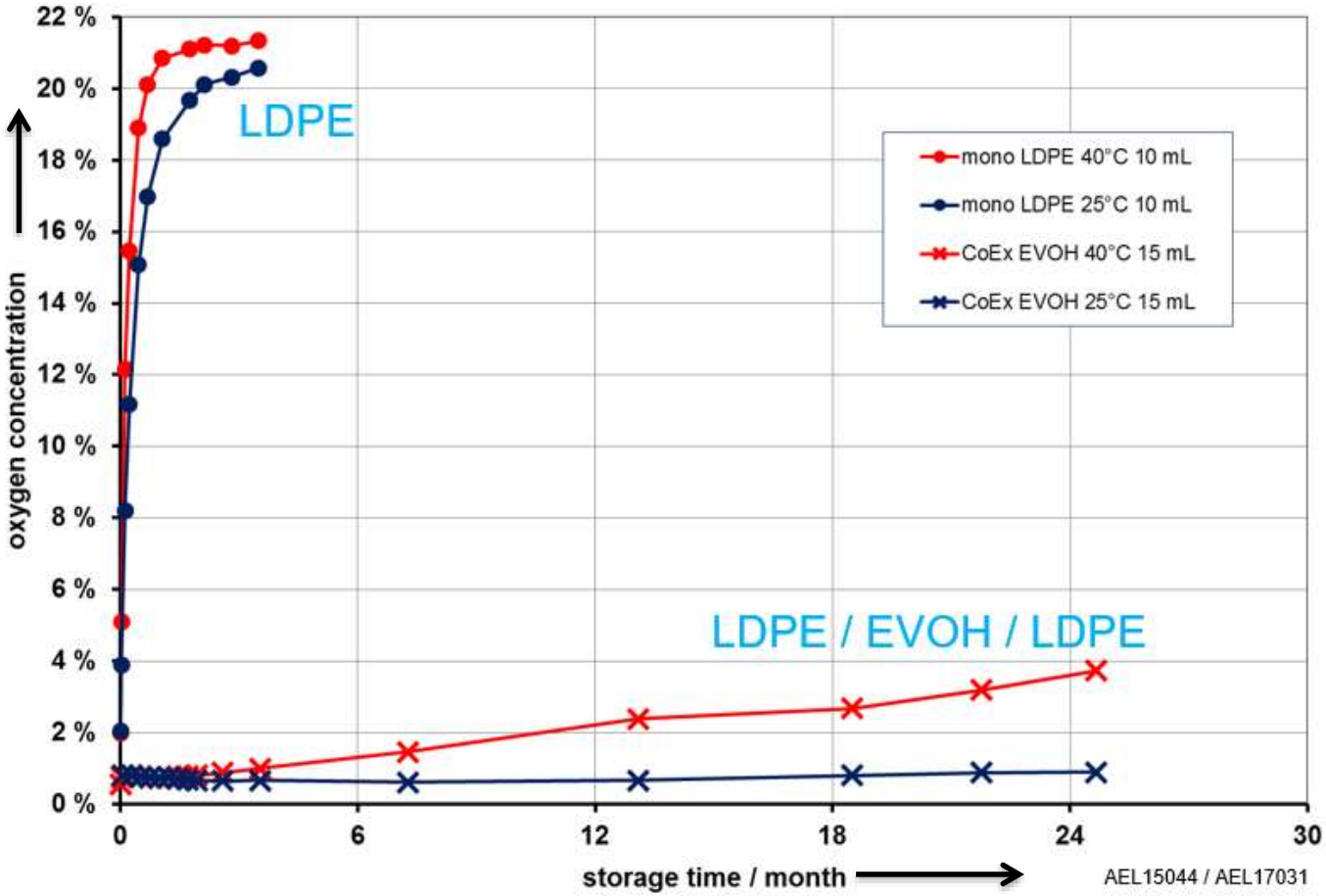
- Tunable Diode Laser Absorption Spectroscopy at 760 nm
- Test-kits filled with water
- Conditioning at 40°C for 4 weeks
- Storage at 40°C / 75% r.h. & 25°C / 60% r.h.

- Partners: Study performed by Wilco & Lighthouse

H. Sudo, G. Schramm et al. Development of a nondestructive leak testing method utilizing the head space analyzer for ampoule products containing ethanol-based solutions. PDA J Pharm. Sci Technol. 2012 Sep-Oct; 66(5): 434-44

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

