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Characterization of Multilayer Blow-Fill-Seal Containers for Pharmaceutical Packaging





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Overview

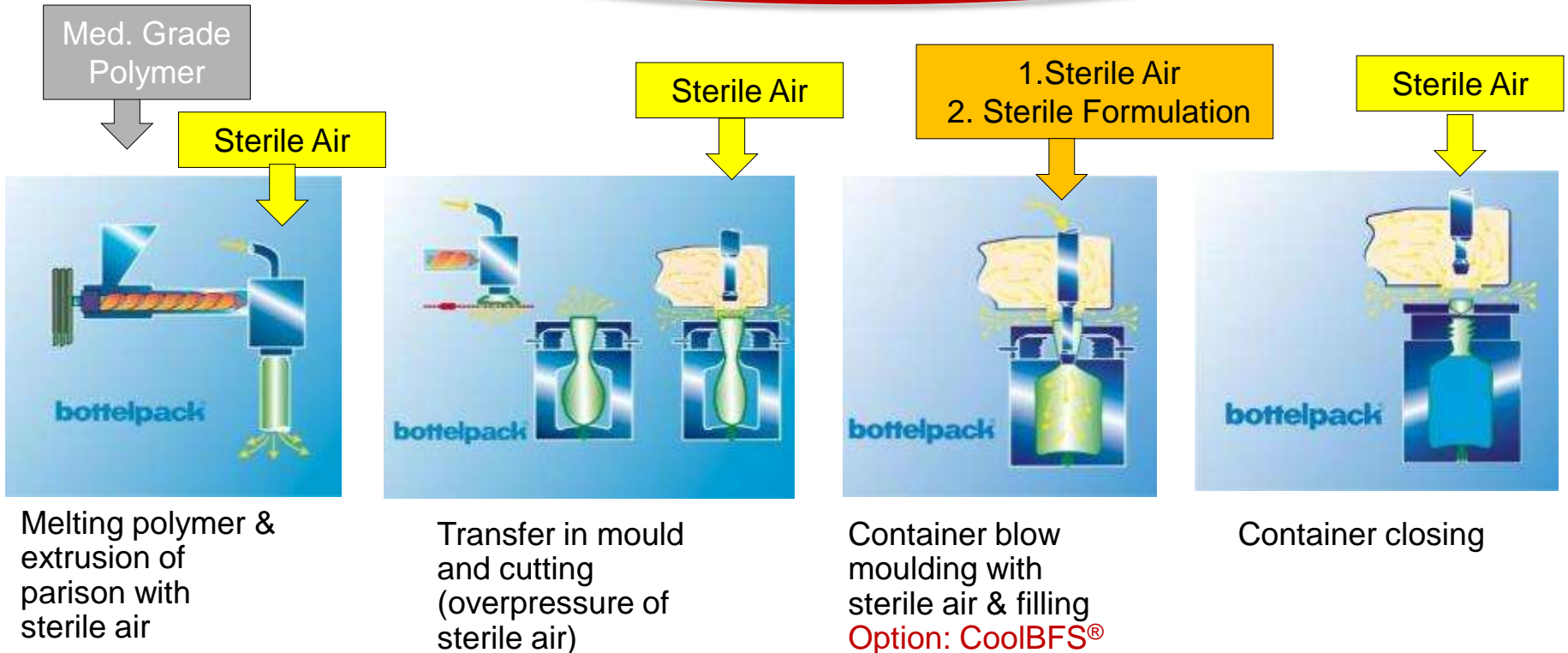


1. Introduction - the BFS process
2. Objective of the study
3. Methods
4. Results & Discussion
5. Summary & Literature.



Blow-fill-seal (BFS) is fast & straight forward.

Classical BFS Process: 6-13 seconds
Rotary technology: 3 seconds



CoolBFS®:

M. Spallek et al. Biotech Formulations and Modern Blow-Fill-Seal processing – Still a Contradiction? PDA Conference The Universe 10-2014

M. Spallek et al. Heat effects on sensitive formulations during blow-fill-seal processing PDA Parenteral Packaging, Brussels, 3-2014



BFS processing provides containers with a typical set of properties.

Examples & key features



1. Ampules (0.2 ml to 50 ml) or bottles (>50ml)
2. Mono-material Contact
3. Twist-off closures or caps
4. Semi rigid & semipermeable
5. Cost-effective Monomaterials:

Traditional Polyolefines LDPE, HDPE or PP

+ good water barrier

- limited oxygen barrier

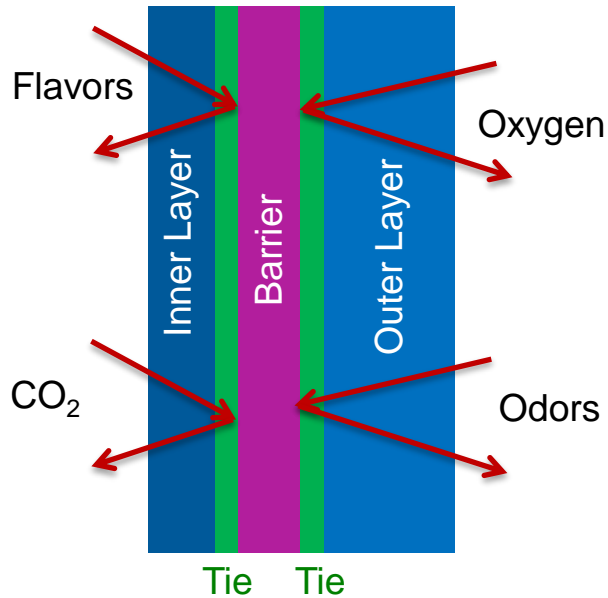
- limited flavor barrier.



Blow-Molded multilayer products are already well established in the food & automotive industry.

Multilayer-Products

Principle multi layers



Automotive: fuel tanks

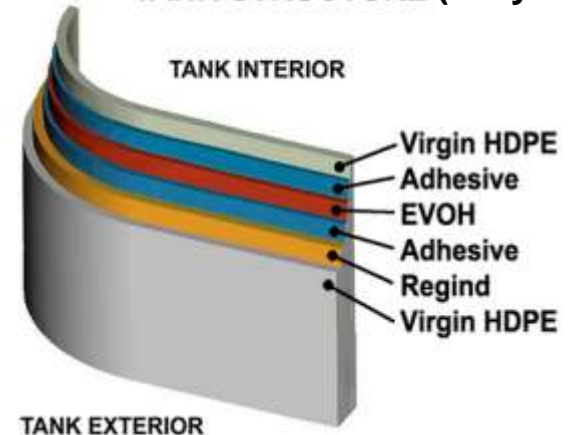


Food packaging



The six-layer PP/EVOH squeeze bottle for Heinz ketchup, molded by American Can in 1983, was a breakthrough for barrier plastic bottles.

TANK STRUCTURE (6 layers)





Pharmaceutical packaging is strictly regulated.

Key Issues from Health Authorities

See Presentation by
Cornelia Lipperheide,
BfArM



Description of container closure system

Suitability of packaging system for the intended use
protection
compatibility
safety (→ extractables, leachables)
performance

Quality Control of packaging components

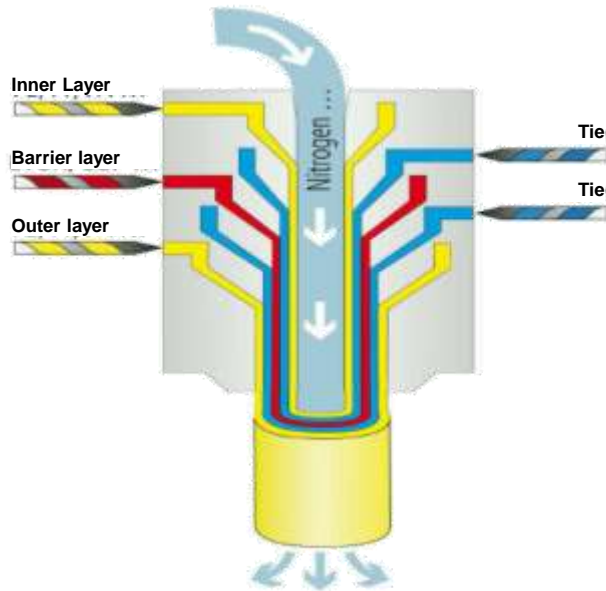
Stability of drug product (i.e. incl. container closure system)

FDA Guidance, Container Closure Systems for Packaging of Human Drugs and Biologics, May 1999
EMA Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03)



Objective “CoEx-BFS”: Improve BFS container performance by multilayer container designs.

Some Suitability Criteria for Pharmaceutical Packaging



Multilayer parison head

- BFS-suitability incl. process & container design
- Selection of suitable functional/barrier material
- Classification (secondary protective)
- Protective function over time
- Extractables / Leachables
- Container closure integrity (CCI)

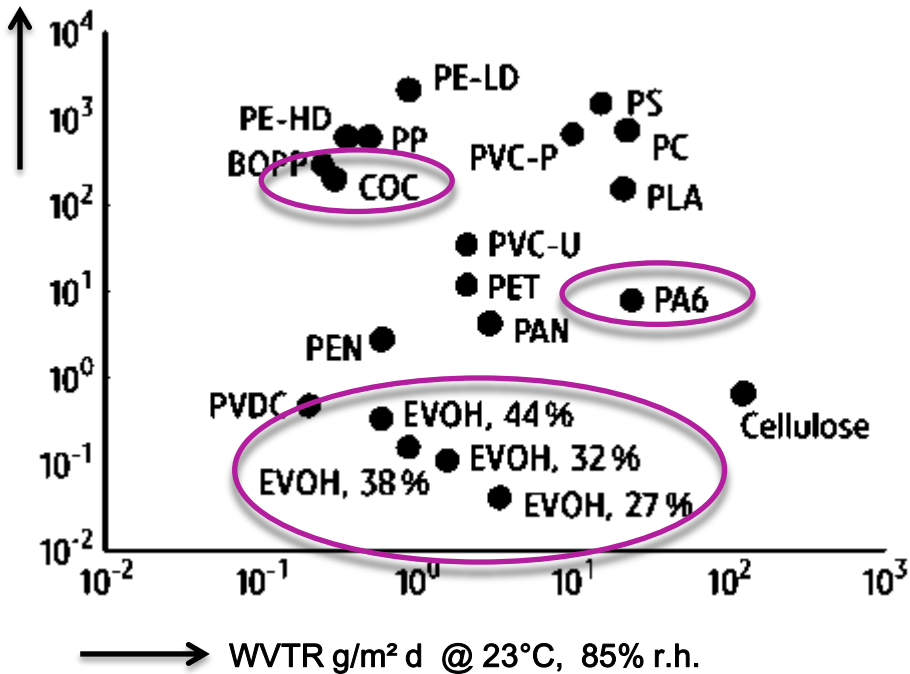
Also see Presentation by
Cornelia Lipperheide,
BfArM



“CoEx-BFS” allows improvement of container properties e.g. oxygen permeation.

Options Overview

OTR cm^3 (STP) / m^2 d bar



Materials:

- EVOH: very high oxygen & flavor barrier
- PA: high oxygen barrier & flavor barrier
- COP / COC: low adsorption & high water barrier

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



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Objective:

Easy, fast and sensitive R&D-method for overall-OTR of complete, filled, high barrier containers, i.e. reliable results within 10-20 days

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Two different ampule designs have been selected.

BFS-Container Designs



Ampoule 20ml Drawing: 3121J-A27B60



Test-Kit 10ml Drawing: 3123D-A25F70



-a- 20 ml twist-off ampule (automatically filled)

-b- BFS test-kit container (manually filled)

-c- 5 Layer design

-d- Materials & Layer thickness range

- inside LDPE-tie-EVOH-tie-LDPE-outside

- LDPE: Purell 3020D: 100 μm to 300 μm

- Tie: Mitsui admer NF408E: 20- 30 μm

- EVOH: Kuraray F171B 32 mol%: 50 to 125 μm

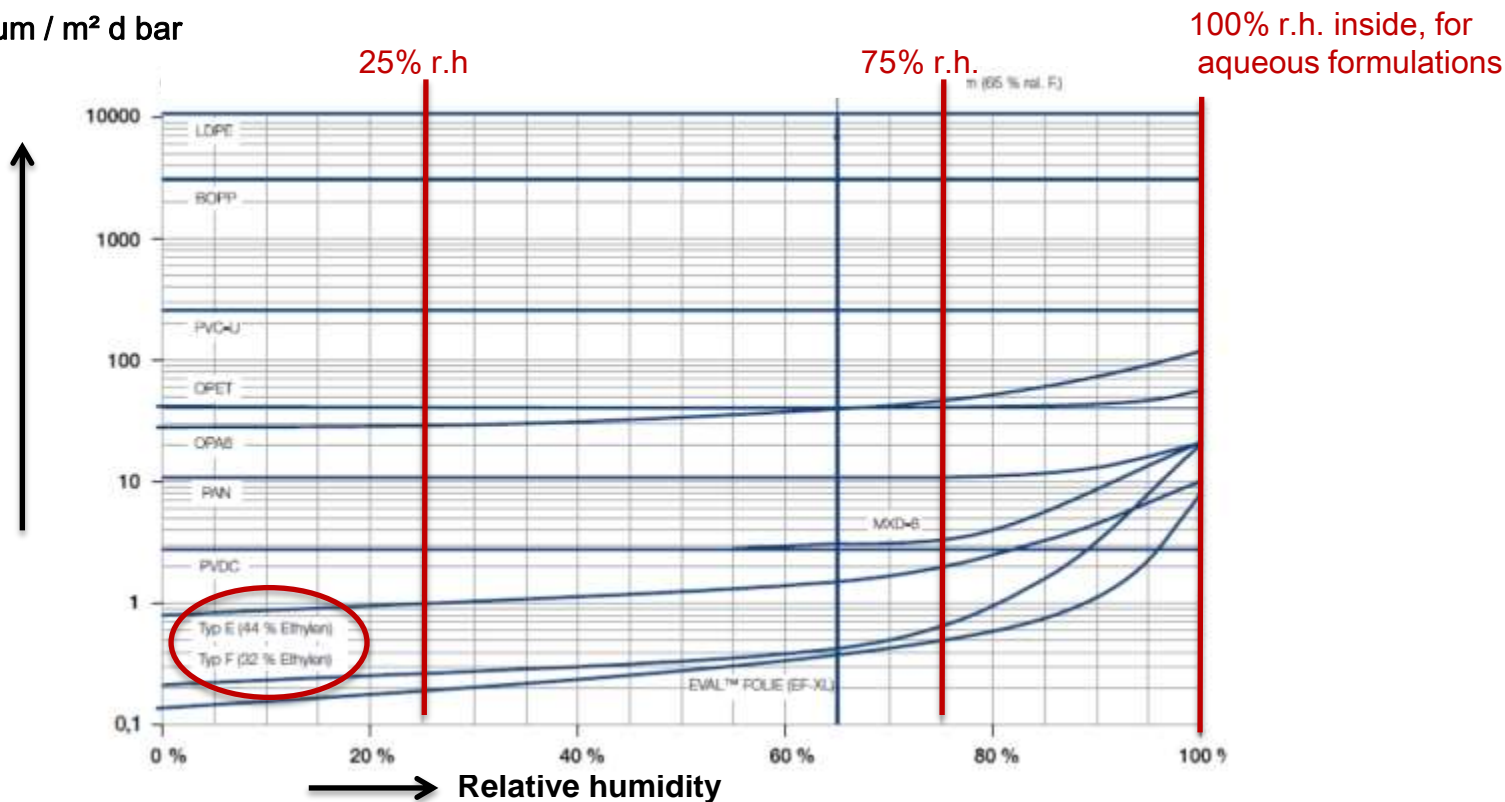
- No regrind.



EVOH has great barrier properties, however they depend on its water content.

Barrier Material Properties

OTR
 $\text{cm}^3 \cdot 20 \mu\text{m} / \text{m}^2 \cdot \text{d} \cdot \text{bar}$
at 20°C

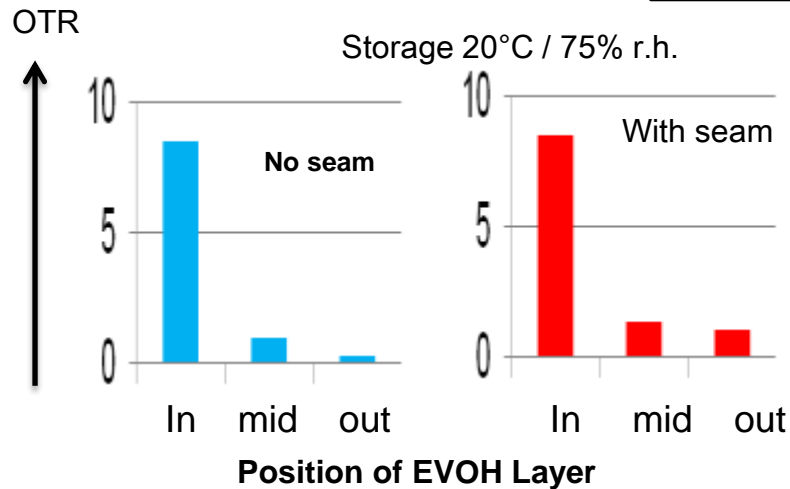


Z. Zhang et al. Permeation of oxygen and water vapor through EVOH films as influenced by relative humidity, J. Appl. Polymer Science Vol.82 (8), 1866–1872, Nov.2001



Mathematical modelling is used as a QbD element for container design.

The Model

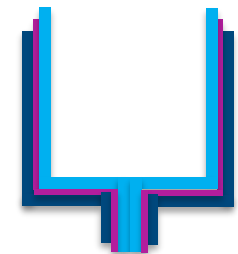
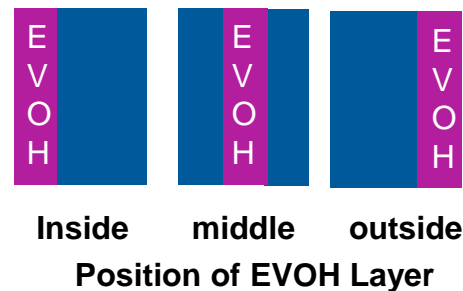
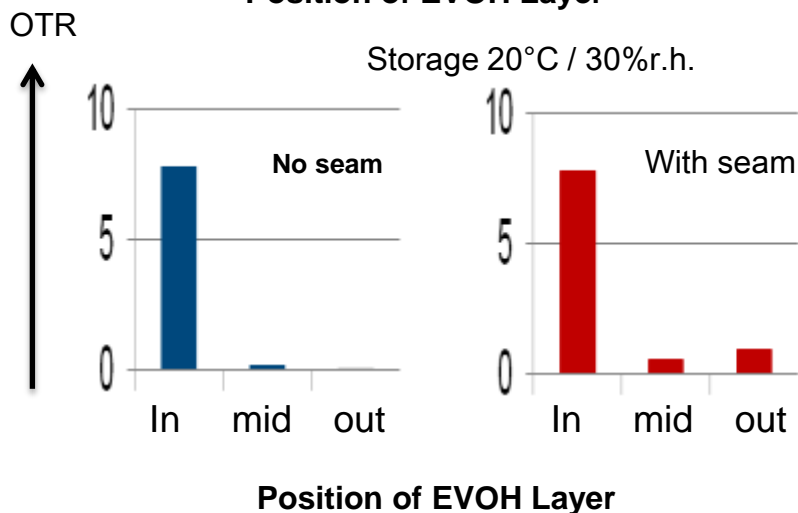


Parameters:

1. 3 layer designs (i.e. without simulation of tie)
2. OTR data from 3 materials
3. OTR as function of water content for EVOH
4. WVTR data from 3 materials
5. Equilibrium conditions
6. Container-design & layer position

Results:

1. Seam & storage conditions are important
2. Experimental verification of Model necessary

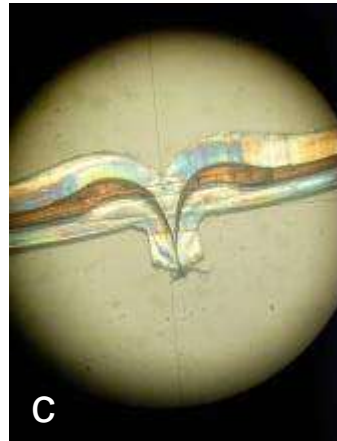
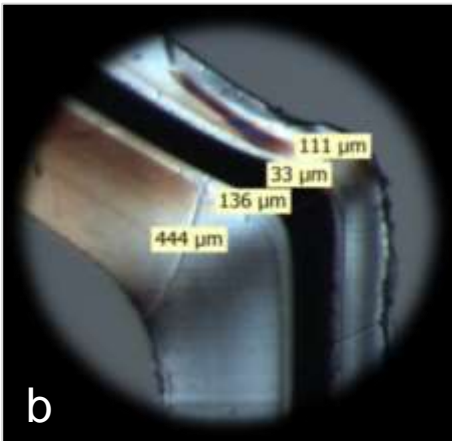
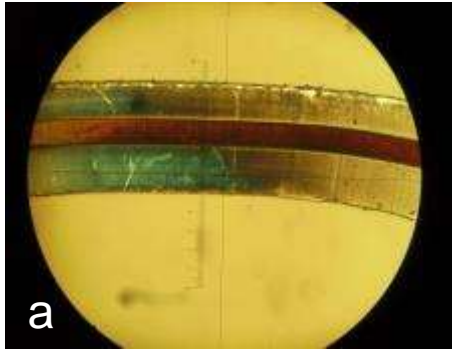


Seam-principle



Light microscopy shows layer presence & thickness distribution.

General Assessment



Basic assessments:

Light microscopy of cross section & iodine for

- Verification of barrier layer presence
- Measurement of thickness distribution
- Seam geometry assessment

Process (IPC methods):

- Extruder mass flow

Cross sections of 5 layer ampule in cylindrical (a), corner (b) and seam position (c) (EVOH layer colored using iodine)



Different methods have been screened for the assessment of Oxygen-Barrier performance.

Methods Overview

Objective:

Easy, fast and sensitive R&D-method for overall-OTR of complete, filled, high barrier containers, i.e. reliable results within 10-20 days

-1- Assay method

Degradation of O₂ sensitive formulation

-2- Redox indicator method

Monitoring of color change of indigocarmin redox indicator

-3- Surrogate method

H₂ gas permeation

-4- O₂ in headspace method

spectroscopic headspace analysis



An oxygen sensitive formulation was used as direct method to assess container performance.

Method -1-: Assay



Co-Extrusion Bottelpack: 321-079 GMP

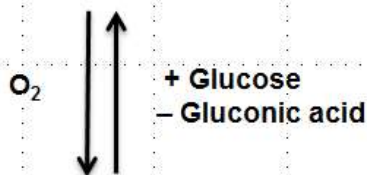
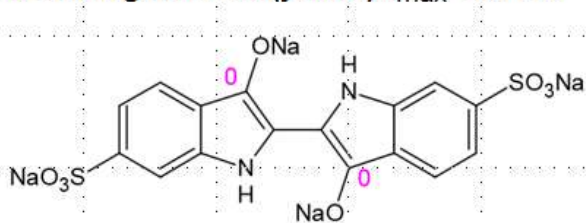
- Co-Extrusion Bottelpack: 321-079
- O₂ sensitive test solution
- Nitrogen flushing during processing
- Degassing of test solution prior to filling
- Storage at 40°C / 75% r.h. & 25°C / 60% r.h.
- USP-Iodometry analysis (J₂ & Na₂ S₂O₃).



An organic redox system was applied to continuously monitor oxygen ingress.

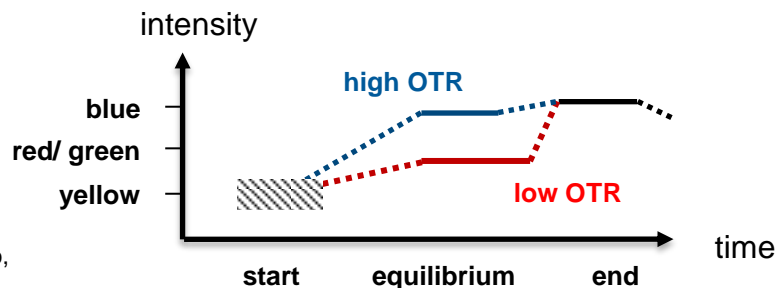
Method -2-: Redox Indicator

Leuco-Indigocarmine (yellow) $\lambda_{\max}^{\text{red}} = 407 \text{ nm}$



Indigocarmine (blue) $\lambda_{\max}^{\text{ox}} = 610 \text{ nm}$

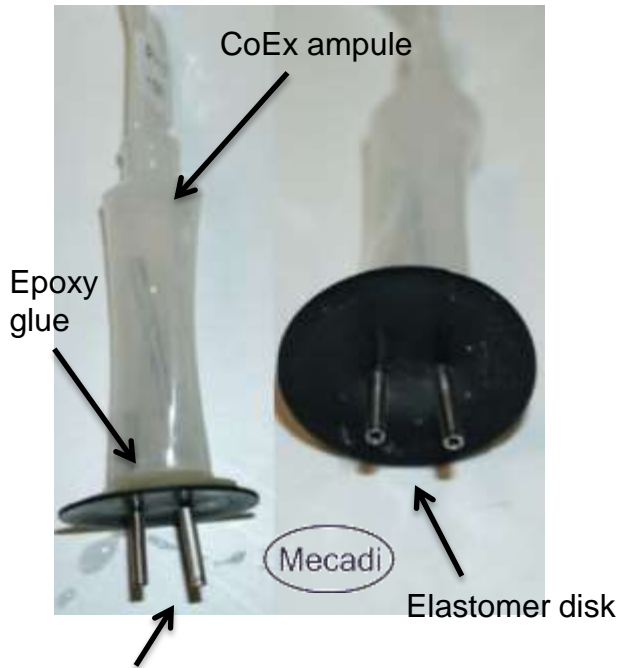
- Test-kit containers
- Manually filled with Indigodisulfonate solution with Glucose / NaOH, pH=7,4
- UV-VIS spectroscopy
- Color status (yellow-red/green-blue) reflects equilibrium of O_2 ingress & Glucose oxidation



P. G. Tratnyek, T. E. Reilkoff, A. W. Lemon, M. M. Scherer, B. A. Balko, L. M. Feik, B. D. Henegar, *Chem. Educator*, **2001**, 6, 172-179.
L. S. Buchoff, N. M. Ingber, J. H. Brady, *Analytical Chemistry* **1955**, 27, 1401-1404.

Hydrogen gas permeation was applied as fast, surrogate method.

Method -3-: H₂ Permeation



CoEx ampules: with and without side seam

Preconditioning

- a) 26d at 40°C: inside 100% r.h. / outside 75% r.h.
- b) 12d at 25°C / 0% r.h.

Measurement:

- Outside: 40°C / 75% r.h.: sweep gas (air)
- Inside 40°C / 100% r.h.: H₂ gas
- Electrochemical H₂ detection in sweep gas
- Sensistor H2000 Hydrogen for H₂ traces in ppm range

Steel capillaries

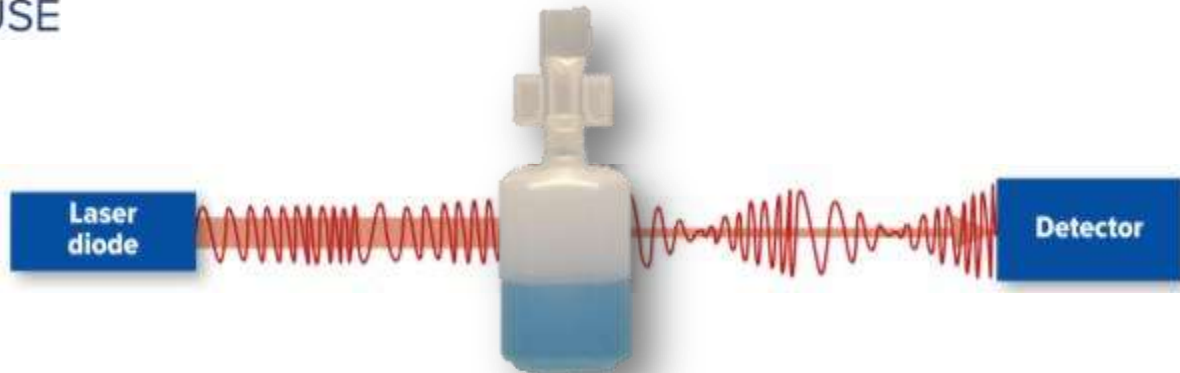
Partner: Mecadi, Bexbach, Dr. Andreas Konrad



Laser headspace spectroscopy offers non destructive testing.

Method -4-: O₂ in headspace

LIGHTHOUSE

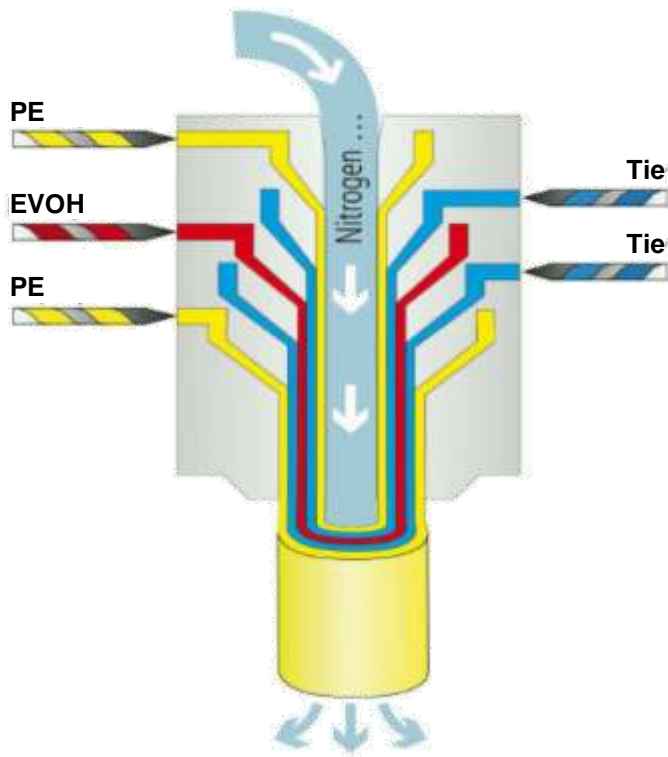


- Tunable Diode Laser Absorption Spectroscopy at 760 nm
- Test-kits filled with water
- Conditioning at 40°C for 4 weeks
- Storage at 40°C / 75% r.h. & 25°C / 60% r.h.

- 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

Overview

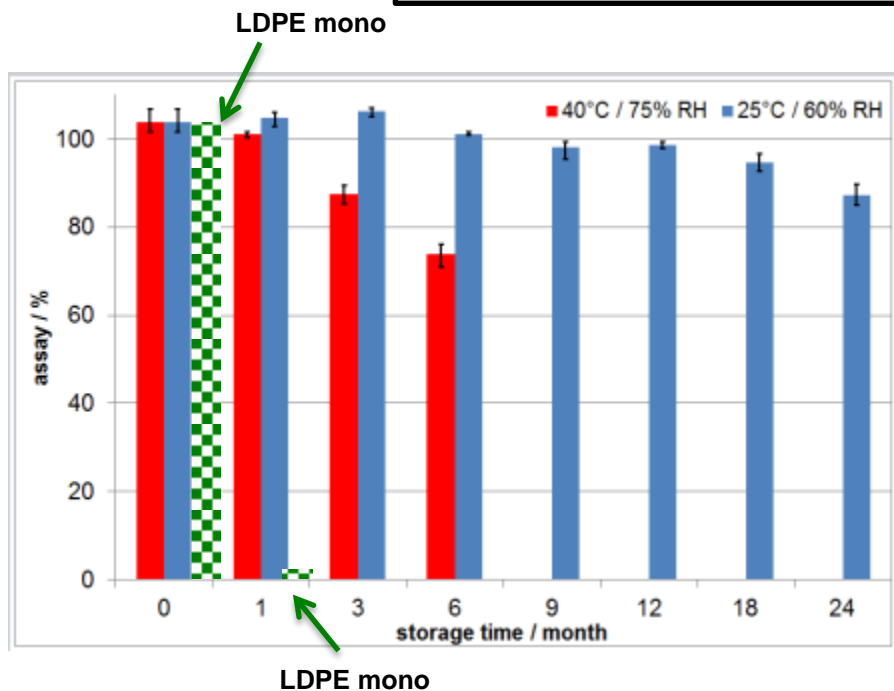


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Oxidative degradation / assay method is not suited for development of CCS and process.

Results: Assay-Method



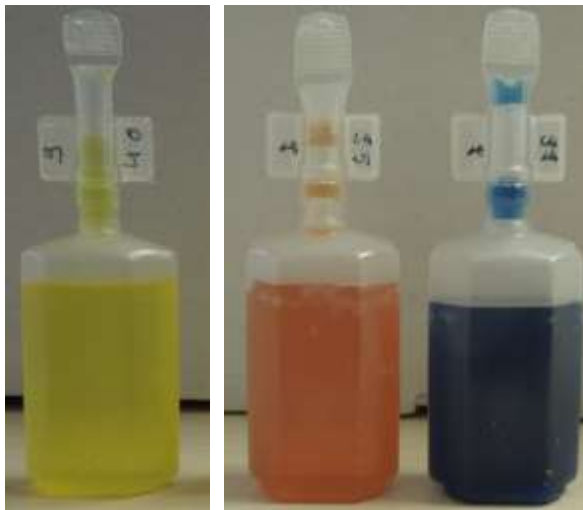
Example: CoEx ampoules with O₂ sensitive solution tested at 40°C / 75 %r.h. and 25°C / 60% r.h. over 6 and 24 months. Range indicated by error bars;

Summary

- 1- Significant improvement by EVOH layer compared to LDPE-mono
- 2- Strong dependence on start conditions
- 3- Limited sensitivity
- 4- No clear effect of barrier layer designs
- 5- Time consuming destructive testing

Redox-indicator method is not suited for development CCS and process.

Results: Redox-Indicator Method



CoEx test-kit ampoules at start (left) and after 117h at 23°C (middle) and 37°C (right)

Pros:

- Non destructive method
- Continuous monitoring
- Local effects visible

Cons:

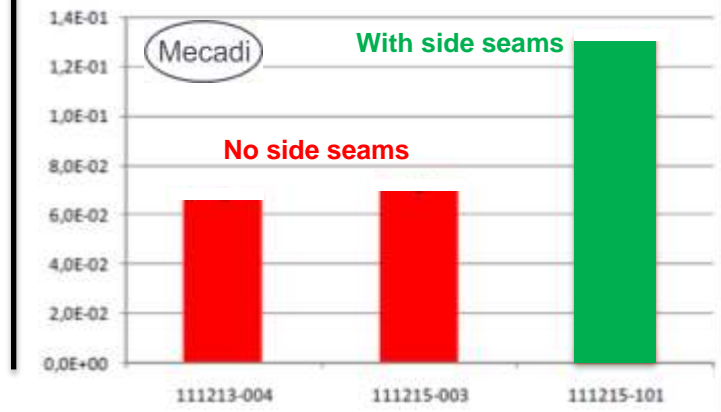
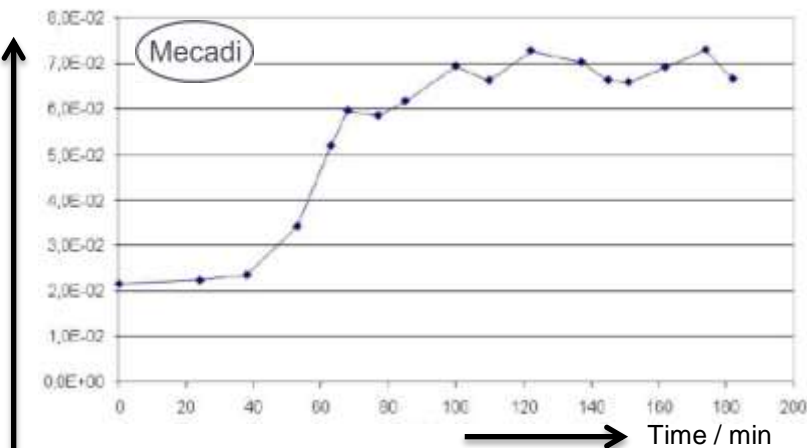
- Strong dependence on start conditions
- Dependence on filled volume
- Limited thermal stability / fading effects at $T > 50^{\circ}\text{C}$
- Complex preparation technique
- Spectrometry results accuracy limited



Hydrogen gas permeation results clearly show conditioning & seam effects.

Results: H₂ permeation at 40°C:
inside 100% r.h., outside 75% r.h.

Permeation P / Ncm³/d bar)



- 1- Break through point reached after ca. 50 min
- 2- Side seam increased permeation by factor of 2
- 3- Ampoules conditioned at 25°C / 0% r.h.
(compared to conditioned at 40°C / 75% r.h.):
 - a- Permeation reduced to 60%.
 - b- Reach same permeation after 9 days

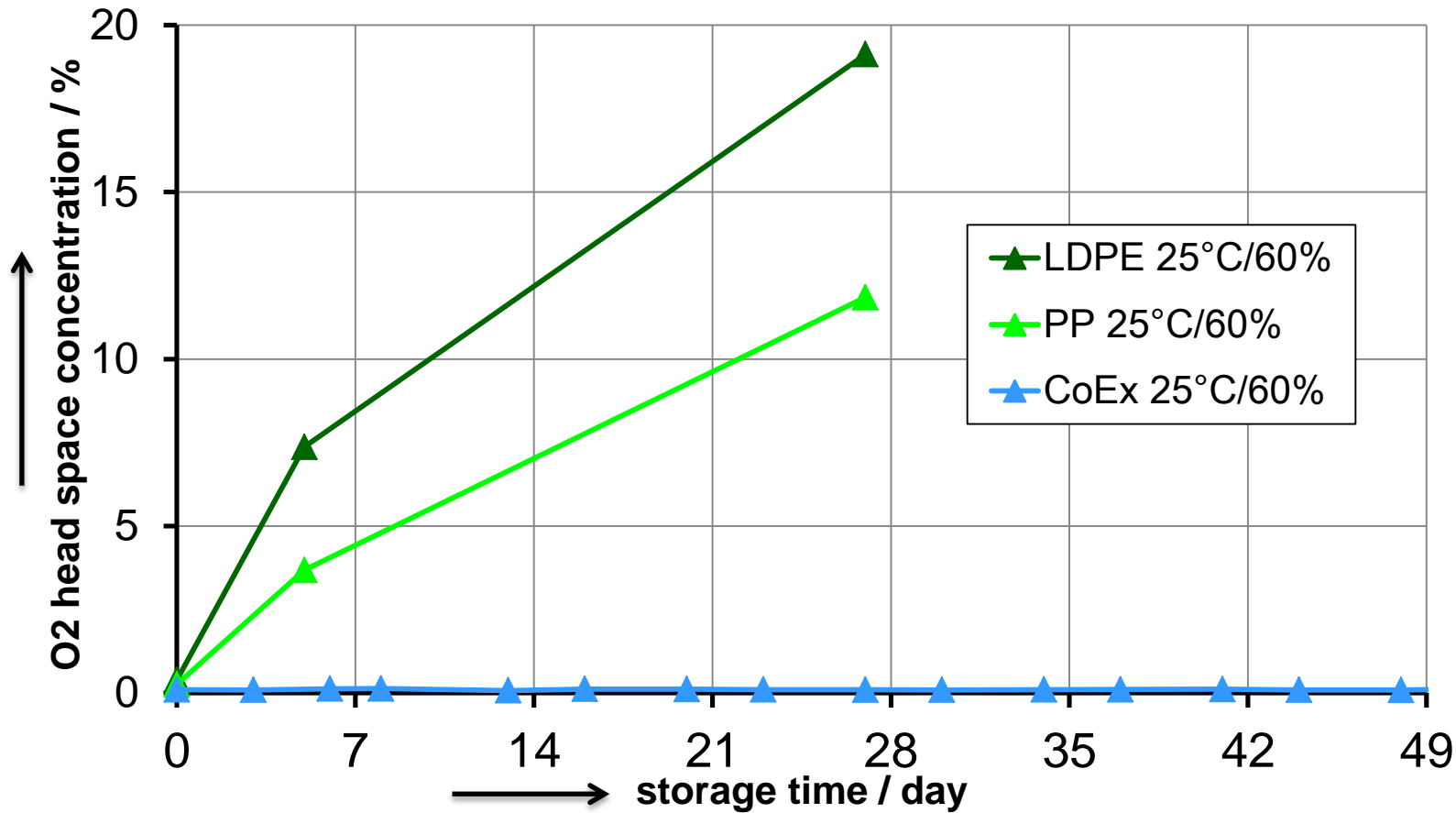
However:

- a- Destructive method
- b- Complex sample preparation



First O₂ head space data showed strong barrier effect of EVOH.

Results: Laser HSA

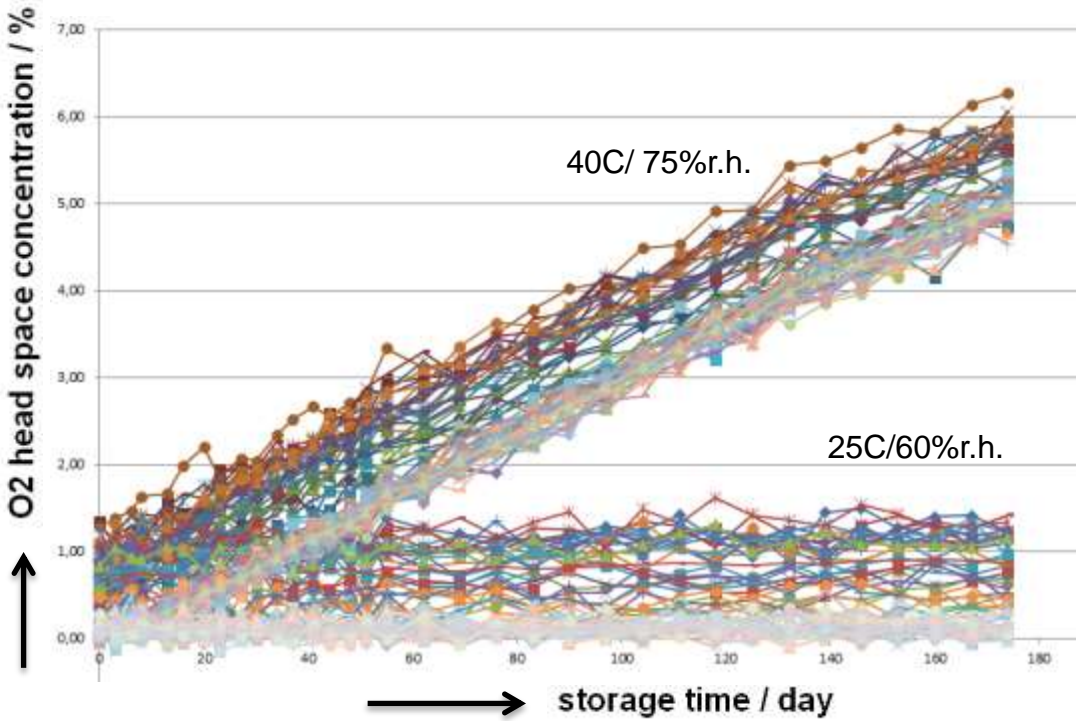


O₂ headspace concentration in different ampules over 7 weeks tested at 25°C / 60% r.h.



Laser headspace spectroscopy allows continuous testing of many samples.

Results: Laser HSA (Wilco-Data)



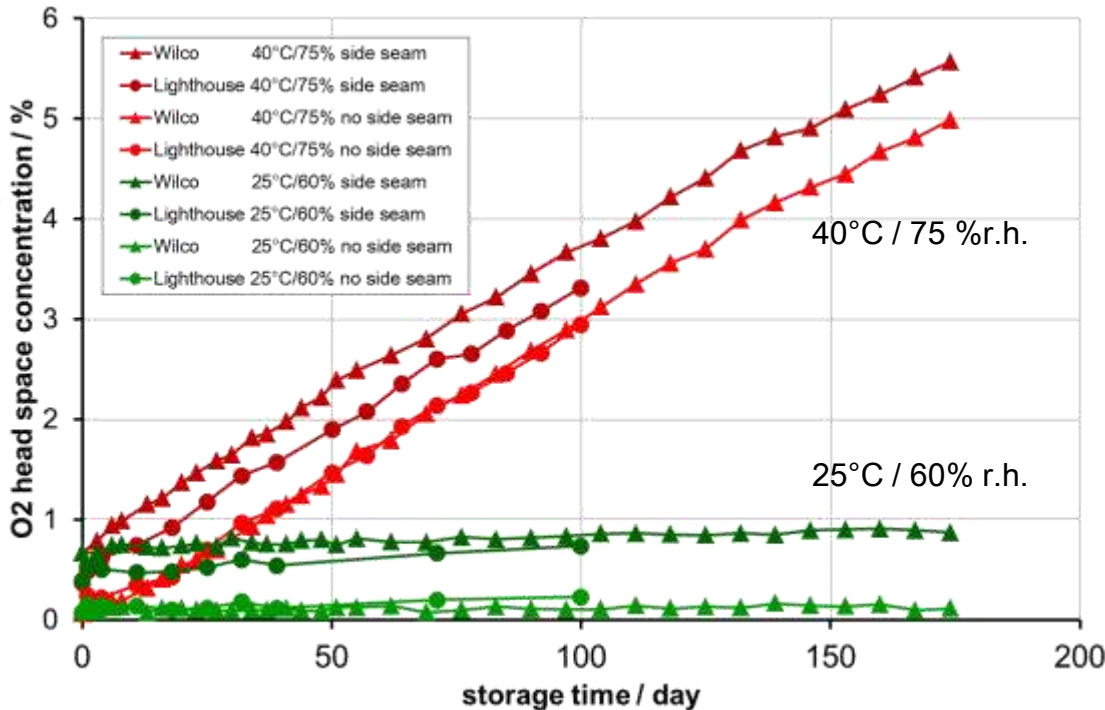
- N=120 ampules tested
- Total duration 174 days
- 34 measurements / ampule

O₂ headspace concentration of individual water filled CoEx ampules (N=120) over time tested at 40°C / 75% r.h. (upper curves) and 25°C / 60% r.h.(lower curves)



Laser HSA gave consistent results, seam effects need to be addressed in future work.

Method 4: Laser HSA



- 1- very consistent O₂ measurements
- 2- average rates
 - at 40°C / 75% r.h.: 28×10^{-3} % per day
 - at 25°C / 60% r.h.: $1-2 \times 10^{-3}$ % per day
- 3- no clear side seam effect visible

O₂ headspace concentration of water filled CoEx ampoules (average of N=30 each) over time tested at 40°C / 75% r.h. (upper curves) and 25°C / 60% r.h.(lower curves)



Summary: OTR- Characterization of Multilayer Blow-Fill-Seal Containers

Key Messages

Objective:

Easy, fast and sensitive R&D-method for overall-OTR of complete, filled, high barrier bfs-containers, i.e. reliable results within 10-20 days

- 1- Four different analytical methods for R&D have been screened:
Laser headspace spectroscopy using test kit containers is preferred, it allows:
 - easy handling and sample preparation
 - Fast & continuous measurement of large numbers of containers
 - Direct O₂-measurement also at higher temperatures and pressures

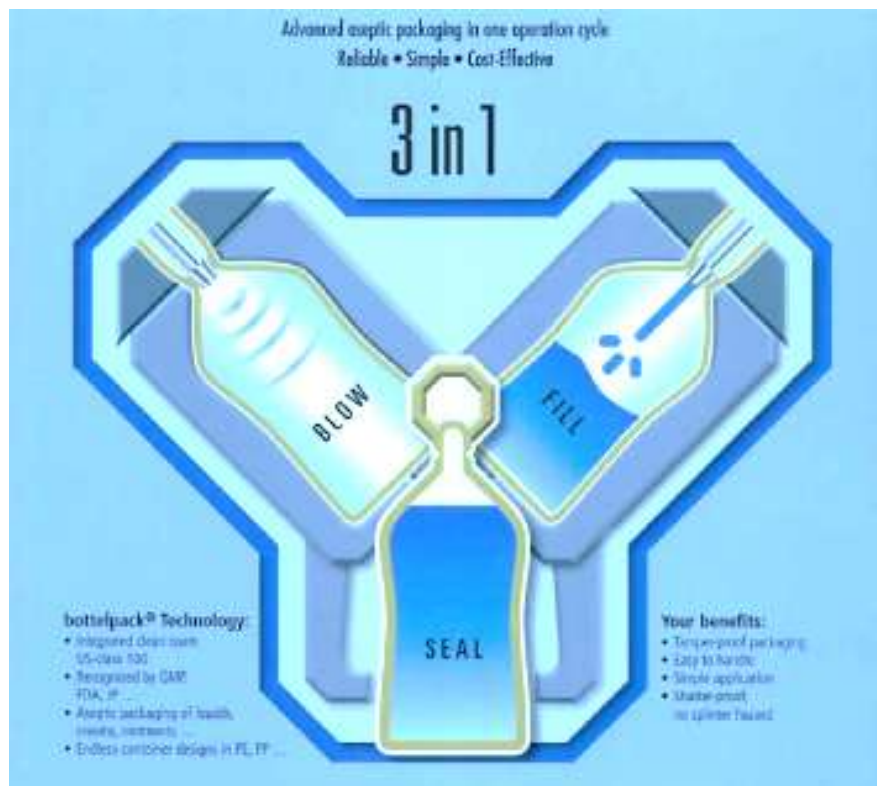
- 2- CoEx-bfs with EVOH provide significant improvements in OTR
- 3- EVOH moisture sensitivity is important

- 4- Seam effects are under further evaluation



Literature

rommelag®



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13. Wei Liu et al. *BioPharma International* Vol 24,(7), July 2011, pp 22-30
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