Dosage forms, designs and usability of BFS containers

- Ophthalmics
- Inhalation
- Parenterals / Terminal sterilization

User acceptance and usability

Optimized application of infusions / Easy empty containers

BFS standards include unit dose and multi dose systems e.g. for eye-care products.

<table>
<tr><td>unit dose ampoules</td><td colspan="4">multi dose ampoules</td></tr>
<tr><td></td><td></td><td colspan="3">with additional (inserted) components</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>KMT
2 piece tamper evident cap

Consistent drop size & no-jet dosing
</td><td>Tip & Cap</td><td>Novelia®
(Nemera)

Preservative free</td><td>Ophthalmic Squeeze Dispenser (Aptar)

Preservative free</td></tr>
</table>

BFS standards include unit dose and multi dose systems e.g. for eye-care products.

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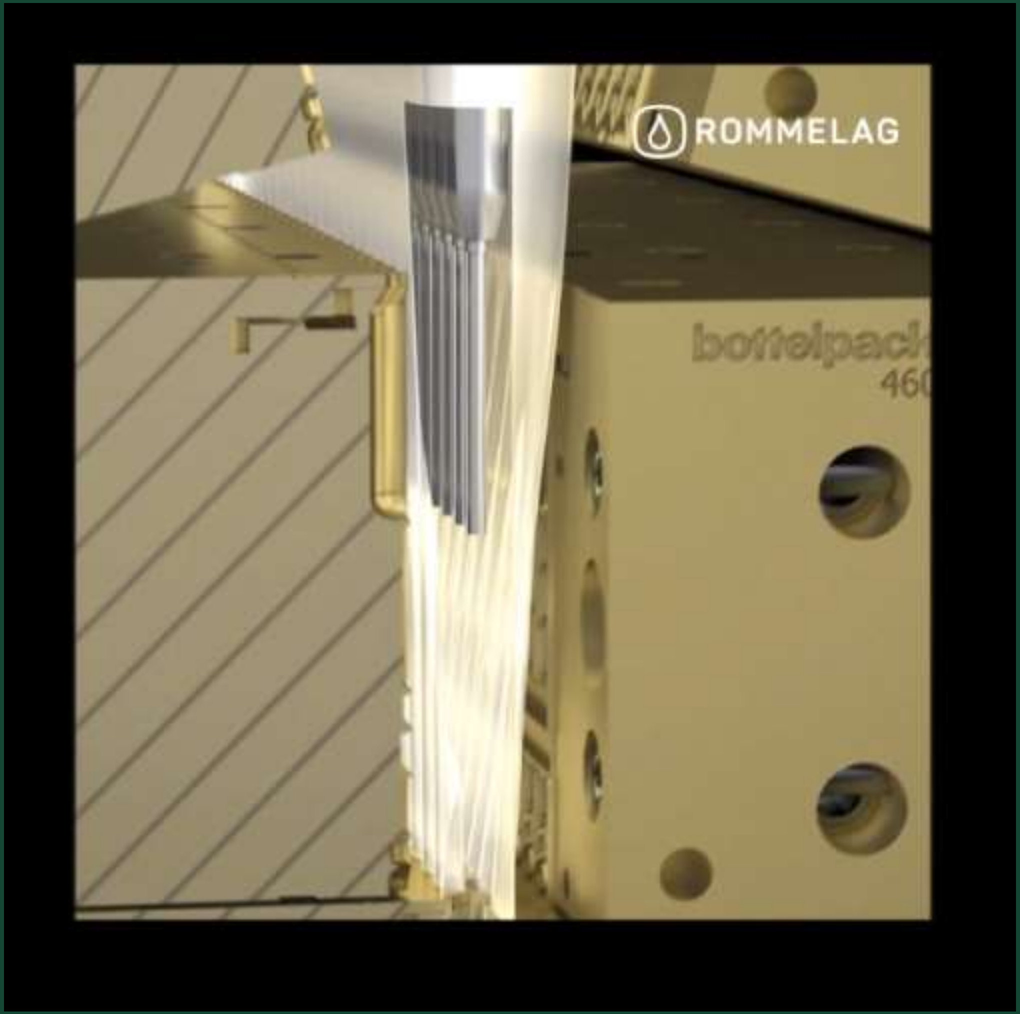
Video

3 seconds and five BFS-process steps from polyolefine granulates to closed containers: Inner details.

Video



From BFS to Blow-Fill-Insert-Seal (BFIS): Insertion of stoppers, connectors, needles ….

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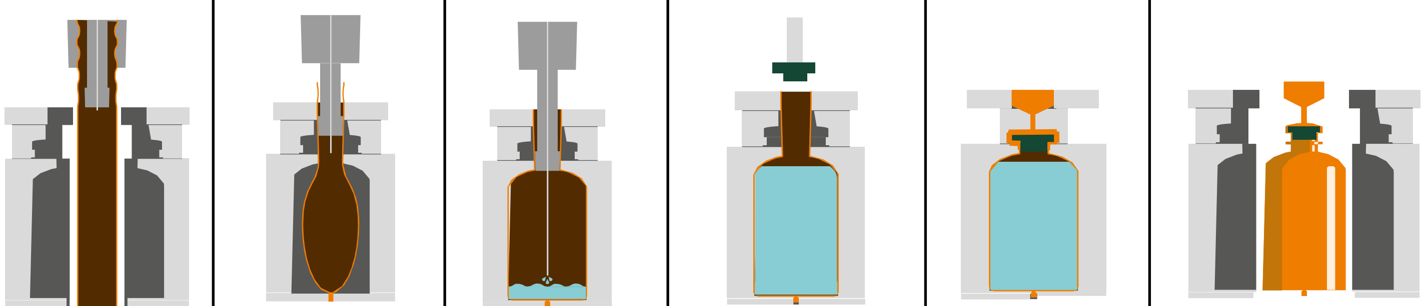
Blow-Fill-Insert- Seal (BFIS)-Process

15 sec



EXTRUSION	BLOWING	FILLING	INSERTION	SEALING	DEMOULDING
Polymer parison Extrusion	Bottles are blown into mould	Time-Pressure-Dosing system	Parts are inserted	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

BFS standards include unit dose and multi dose systems e.g. for eye-care products.

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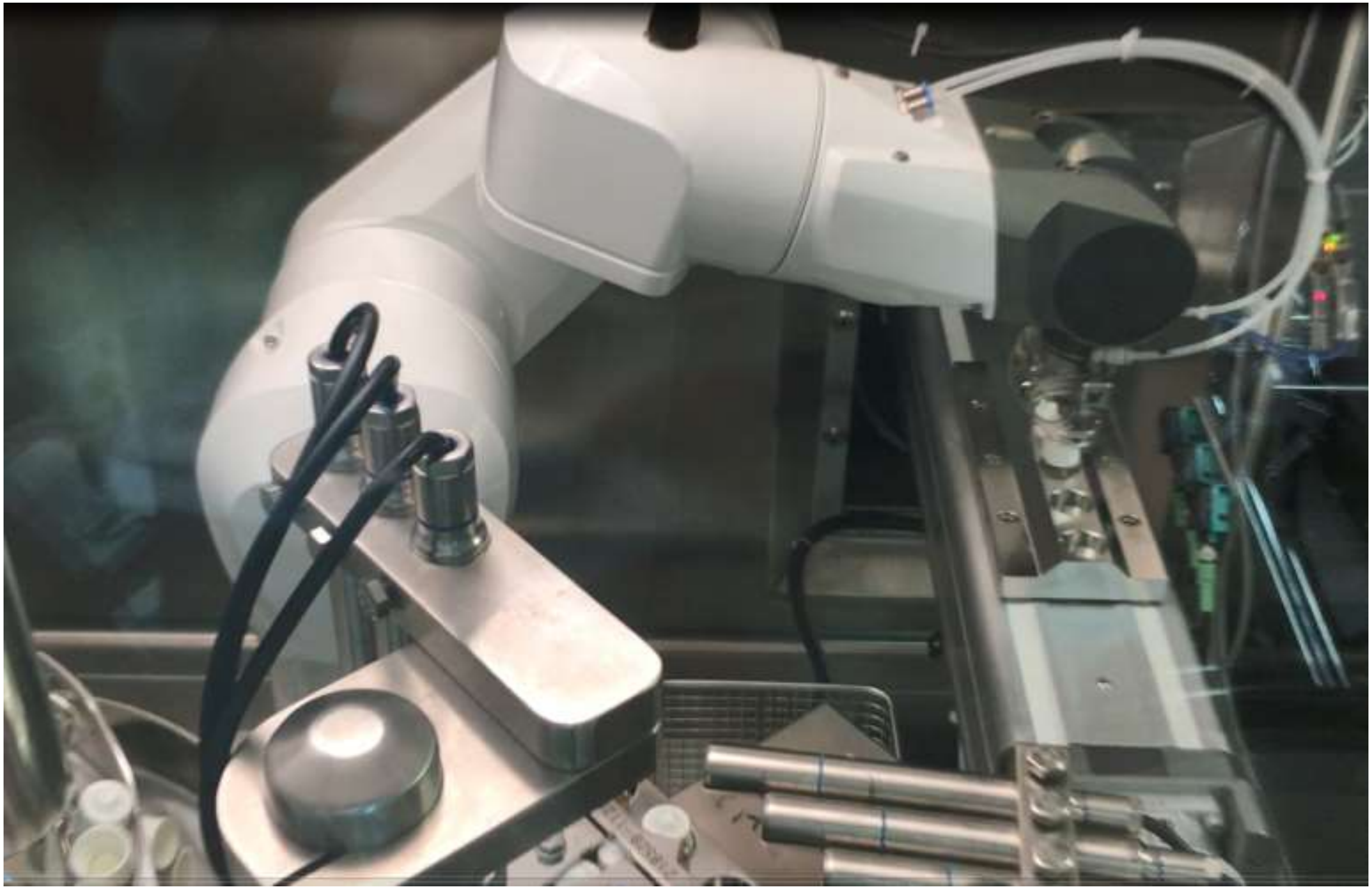
Video



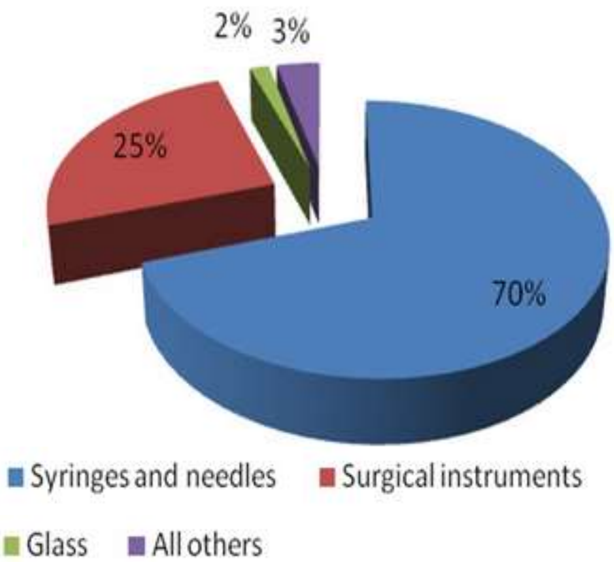
Blow-fill seal (BFS) Containers allow a wide range of applications & designs.

Examples of BFS containers

Small volume parenterals (SVP) have to cope with sharps protection.

Sharps injuries

Objects causing injuries



Hofmann F et al. Needle stick Injuries in Healthcare – Frequency, Causes & Preventative Strategies. Gesundheitswesen 2002;64(5):259-66

One Hundred Sixth Congress of the United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Monday, the twenty-fourth day of January, two thousand

An Act

To require changes in the bloodborne pathogens standard in effect under the Occupational Safety and Health Act of 1970.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Needlestick Safety and Prevention Act".

L 134/66 EN Official Journal of the European Union 1.6.2010

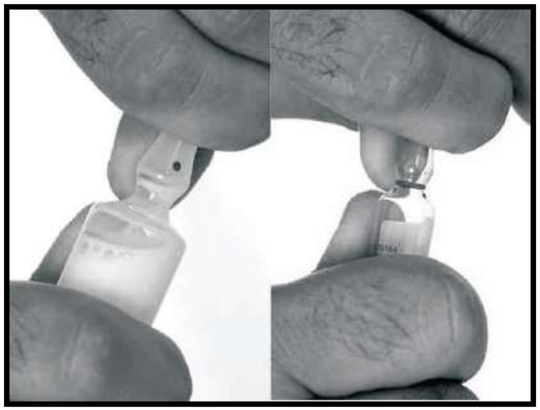
DIRECTIVES

COUNCIL DIRECTIVE 2010/32/EU

of 10 May 2010

implementing the Framework Agreement on prevention from sharp injuries in the hospital and healthcare sector concluded by HOSPEEM and EPSU

Ampoule handling



Antônio Roberto Carraretto, Erick Freitas Curi et al.
Glass Ampoules: Risks and Benefits
Rev Bras Anestesiol 2011; 61: 4: 513-521

Connector must securely fit to different designs.

Some key-targets

1. Easy twist-off opening
2. Safe fit to syringe designs worldwide
3. Intuitive connecting
4. Good tightness at Luer-Cone
5. Easy transfer into syringe

6. ISO 594 / ISO 80369-7 compliant
7. Suited for PP & LDPE
8. Including sterilization & aging effects

Michael W. Spallek, Johannes W. Geser Usability of Glass versus Polymer Ampoules: A Comparison PDA Parenteral Packaging, Rome, 2-2018

A closer look into details for polymer ampoules

Video

Video

The BFS-process allows to produce a large variety of bottle designs for Large Volume Parenterals (LVP).

Literature outline weakness of PP packaging.

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Literature

Pharmaceutical Development and Technology, 2010; 15(1): 6–34

Review of sterile packaging systems 23

Table 6. Comparative properties of major plastic polymers.[39,75,84]

Property	PVC (Polyvinyl chloride)	LDPE (Low density polyethylene)	HDPE (High density polyethylene)	PP (Polypropylene)	EVA (Ethylene vinyl acetate)
Compatibility with contained drug products	Poor	Good	Good	Good	Fair
Moisture permeation	Very poor	Good	Excellent	Good	Very poor
Heat sterilization	Fair	Poor	Good	Excellent	Very poor
Transparency characteristics	Good	Fair	Poor	Fair	Fair
Collapsibility characteristics	Excellent	Poor	Poor	Poor	Good
Disposability	Poor	Good	Good	Good	Fair

Research and Development, Baxter BioPharma Solutions, Bloomington, Indiana, USA

Infusion bottles use mostly LDPE & PP medical grade polymers.

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Typical BFS materials

HDPE PP LDPE PET

Soft PP

LDPE, HDPE & PP

from e.g. LyondellBasell (Purell®), Borealis (Bormed®), etc.

Autoclavable PE 106-115ºC; PP 121ºC

Extractables dossiers (approx. 40 pages) available for selected PE & PPs (by Toxikon)

Soft PPs new developments by Borealis (SB815MO)* & Sumitomo with low flex modulus (400-500 MPa) and modern additive packages

Martina Sandholzer, Joanne Belshaw: Development of a EP and USP compliant soft polypropylene for blow-fill-seal applications
PDA Parenteral Packaging Conference Venice April 13th, 2016
Michael W. Spallek et al.: Characterization of Multilayer Blow-Fill-Seal Containers for Pharmaceutical Packaging, PDA Parenteral Packaging, Bad Soden, March 5th, 2015
Isabelle Trocherie Advancing flexibility, softness and transparency with Polybutene-1 for parenteral applications PDA Parenteral Packaging, Rome, 2-2018

Cost effective PP bottles that empty well need an improved design.

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EasyEmpty - key development targets

NaCl 0.9 %, batch: 153618141, exp.: 7-2018

1. **Unvented administration (closed system)**
2. Easy empty, i.e. max. fill-ratio (fill volume / total volume)
3. Minimal air head space, i.e. minimal height / weight
4. Self standing BFS infusion bottle
5. Standard head design
6. Suited for PP (i.e. autoclaving 121°C, 20 min)
7. Benchmark: BBraun 500 ml - LDPE 3220D

Trend: closed system, i.e. unvented application /1-2/

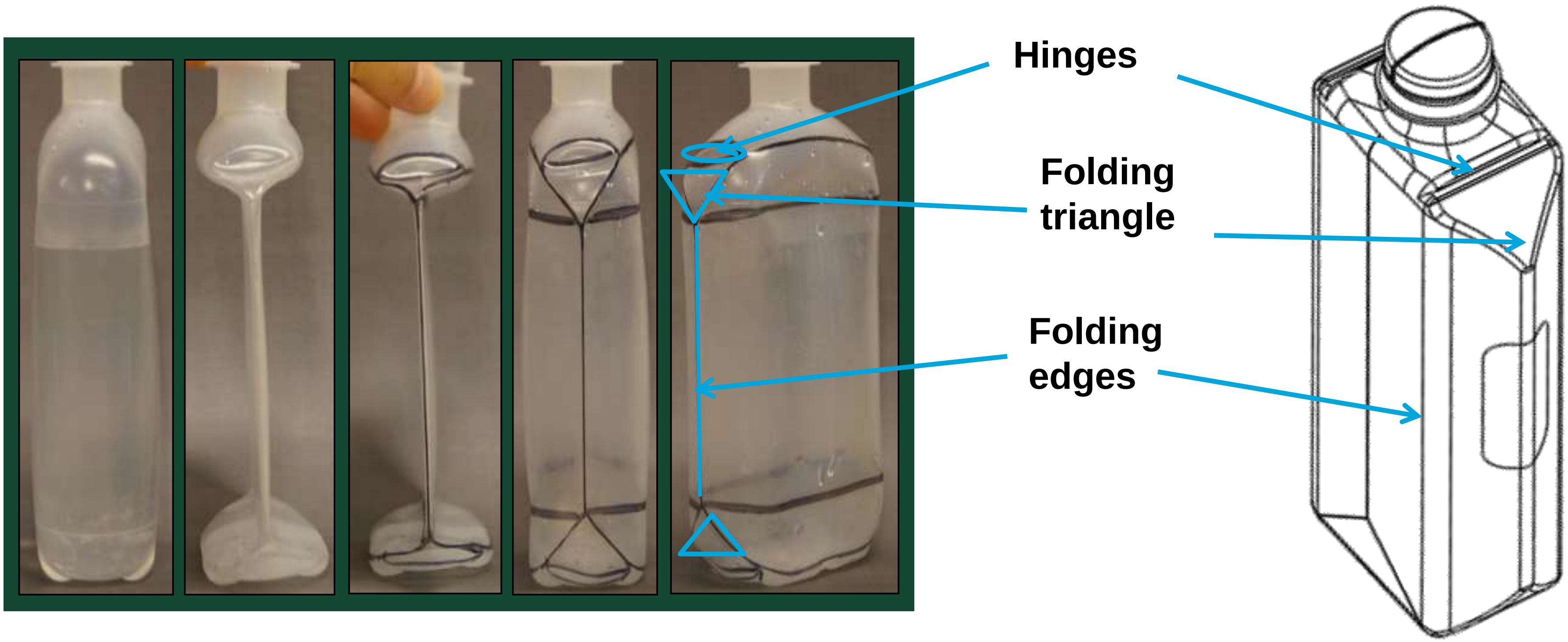
Tradition: open infusion

Figure 1 Open Infusion Container - Glass container with air filter.

/1/ Maki DG, Rosenthal VD, Salomao R,
Impact of switching from an open to a closed infusion system on rates of central line-associated bloodstream infection: a meta-analysis of time-sequence cohort studies in 4 countries.
Infect Control Hosp Epidemiol 2011;32:50–8

/2/ Graves N, Barnett AG, Rosenthal VD.
Open versus closed IV infusion systems: a state based model to predict risk of catheter associated blood stream infections.
BMJ Open 2011;**1**:e000188

Analysis of various “standard bottle designs” indicated likely design improvements.



(4308C-A42D40)

Christoph Kaschta Modelling the discharge behavior of blow-fill-seal infusion bottles by finite element analysis and experimental verification. PDA Parenteral Packaging, Barcelona/Spain, 14-15 March 20

FEM Simulation has been applied to support fast design development.

Example EE 100ml version 1

FEM grid

Collapsing over time

Approach:

1. X-Ray-CT-Scanning EE100v1 for real wall thicknesses
2. FEM modelling based on scan
3. Verification of simulation results by experiments
4. Simulation of different critical design attributes
5. Verification of best simulation results by experiments

Christoph Kaschta et al.(accepted for presentation)
Modelling the emptying behavior of blow-fill-seal infusion bottles by finite element method and experimental verification, PDA Parenteral Packaging Conference 3-2016, Barcelona

FEM simulation and lab results fit together well.

FEM Simulation

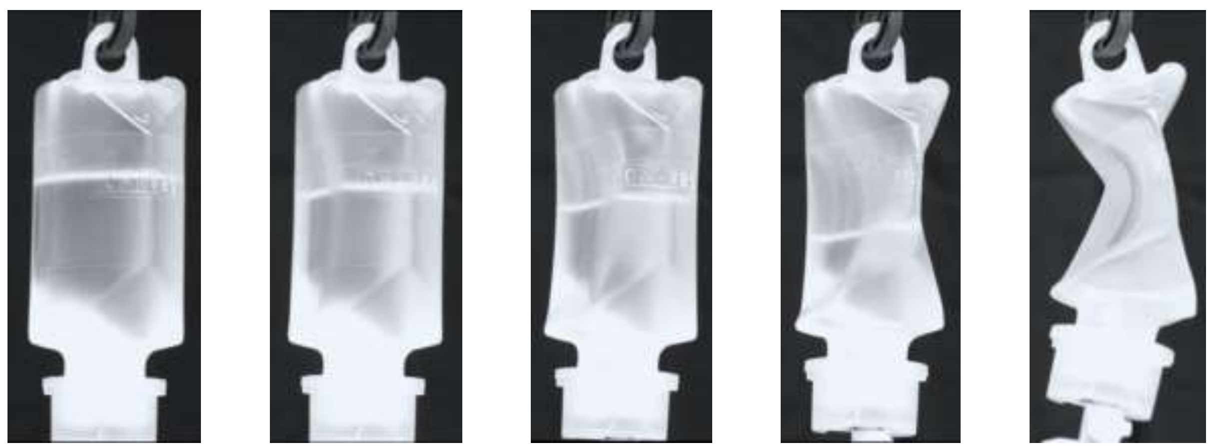
LS-Dyna

Input:
Young's modulus 425 MPa
CT wall thickness distribution
Smoothened edges

Lab experiment

Lab conditions:

Temp.: 22 ± 2°C
Needle: 23G / 0,6 x 30 mm
Demin. Water
H_{eff} 775 mm



t_0 Discharge time t_{end}

Christoph Kaschta Modelling the discharge behavior of blow-fill-seal infusion bottles by finite element analysis and experimental verification. PDA Parenteral Packaging, Barcelona/Spain, 14-15 March 20

The EasyEmpty PP container well compares favorably to the BBraun LDPE Reference.

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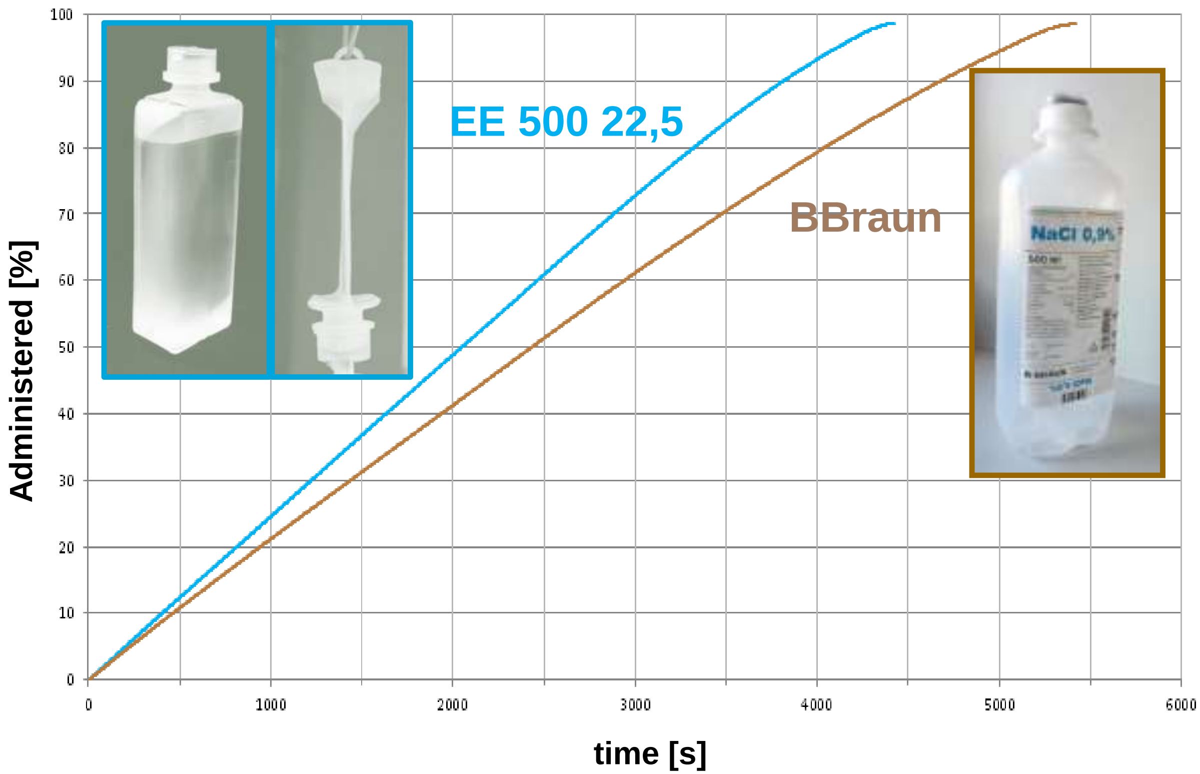
Comparison EE-22,5 g BBraun-Reference 27,5 g



fill-ratios:

BBraun: 524/677= 77 %

EE: 526/664= 79 %

Type:	EE 500 (4308C-A42D40)	BBraun
Total volume:	664ml	677ml
Fill volume:	526ml	524ml
Weight (empty):	22,5g	27,5g
Polymer:	SB 815 MO PP	3220D LDPE

FEM simulation was a valuable tool for the development of innovative infusion bottles.

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Key- Results

	Established LD-PE-bottle	Established PP-bottle	New bottle
Safety	+	+	+
Particulate matter	+	+	+
Extractables	+	0	+
Sterilization temperature	113°C	121°C	121°C
Sterilization time	≥ 75 min	≥ 20 min	≥ 20 min
Young´s modulus	Low (300 MPa)	High (950 MPa)	Low (425 MPa)*
Container size	Minimal headspace	Increased headspace	Minimal headspace
Discharge behavior	Good	Good, if…	Good

* Martina Sandholzer, Joanne Belshaw Development of a EP and USP compliant soft polypropylene for blow-fill-seal applications PDA Parenteral Packaging Conference Venice April 13th, 2016

