pda.org

Best Practices for Glass Primary Containers

PDA Training Course, Mainz, June 11th/12th 2024

Dr. Folker Steden,
Head of Product Mgt & Scientific Services
Senior Principal Expert, SCHOTT AG

PDA Parenteral Drug Association

CONNECTING PEOPLE SCIENCE AND REGULATION®

Glass primary packaging

Where we come from…

Drug Evolution, Tubing Applications, From Sand to Patient

Packaging development…where we come from…

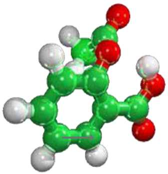
Ab 1928 maschinell produziert:
Splitterfreie Majole.

Sterilisierbar: Jenaer Spritzen
aus Präzisionsglasrohr.

Today trillions of high quality glass containers are in daily use to protect sensitive drug formulations.

Drug Evolution

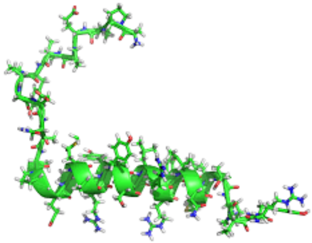
With increasing complexity of the molecules the requirements for the packaging material also increased



- 0.81 nm -

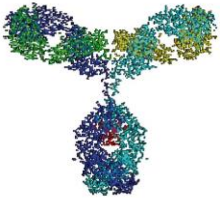
e.g. Aspirin

$C_9H_8O_4$



- ~10 nm -

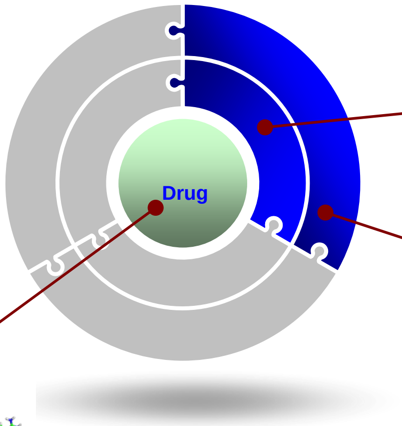
e.g. pancreatic polypetide

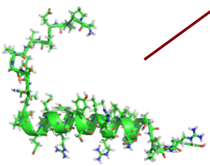


- ~20 nm -

e.g. Herceptin

Influence of packaging material on „new generation“ drugs





Formulation

Stablility system (pH – Buffer, Charge, Support of protein aktivity a.s.o.)

Primary Packaging

Container is part of formulation (in aspect of stability) because the container will have influence!

Tubing Applications

From Sand to Patient

History of Glass

The History of Glass

Moldavit

glass by meteor strike

Fulgurit

the fossil finger of god

Obsidian

glass vulcano

~ 15.000 B.C.

Neolithikum

Antique glass melting furnace

~ 3.500 B.C.

First glass made by humans (accidentally discovered during the firing of pottery and later purposefully used as glaze and jewelry)

The History of Glass

The oldest preserved glass vessel: Goblet of Pharaoh Thutmosis III.

1.500 B.C.

First production of hollow glassware

658 B.C.

First recipe for glass of the Assyrian king Ashurbanipal

"Take 60 parts sand, 180 parts ashes of sea plants, 5 parts chalk – and you obtain glass."

200 B.C.

Invention of the blowpipe in Syria

64 B.C.

By occupation of Syria by the Romans, the glassmaking spread throughout the Roman Empire

The History of Glass

476 A.D.

With the end of the Roman Empire a lot of knowledge is lost

15th century

Luxury glassmaking: Murano became Europe‘s elite glass-making center (Venetian Glass)

Production of tube glass: Pulling of glass tubes

1908

Production of tubes for pharmaceutical ampoules and vials

The History of Glass

1923

Introduction of continuous tube production from the melting tank using the Danner method

Ampoules machine

1928

First ampoule and syringe production

Today

Dedicated tubing for each container format

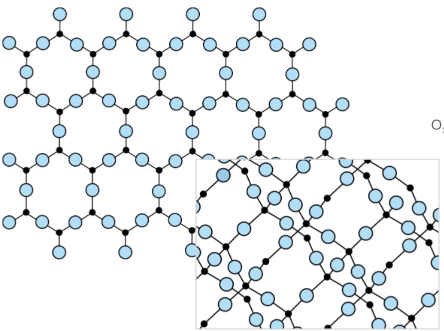
Sterile Containers

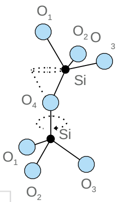
Glass Science

Glass Structure, Overview Glass Types, Glass Properties

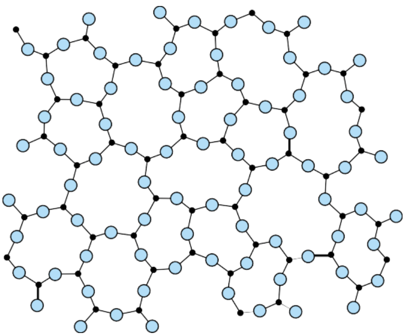
Glass Structure

crystalline quartz sand

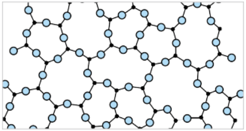
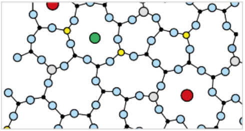
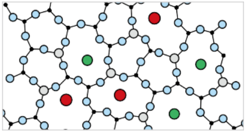
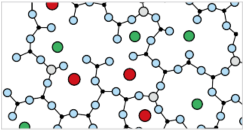




amorphous quartz glass



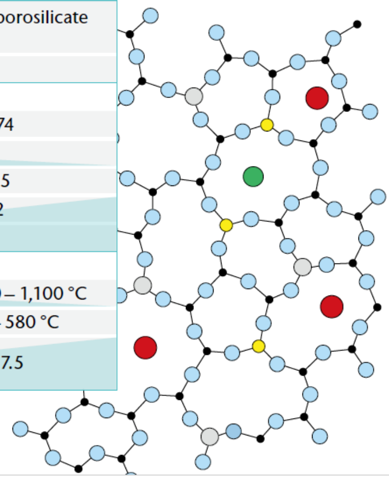
Overview Glass Types

Quartz	Borosilicate	Aluminosilicate	Soda-lime
			
	BORO-8330™ FIOLAX®		AR-GLAS®

- Oxygen, Silicon, Boron: Network formers
- Aluminum, Sodium, Calcium: Network modifiers

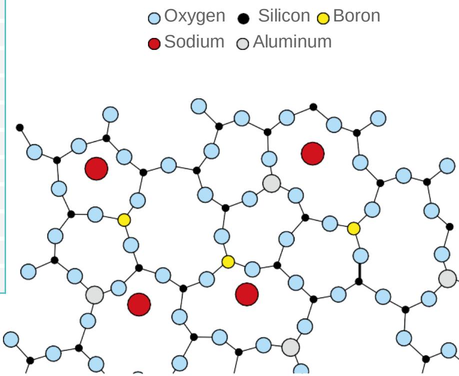
Overview Borosilicate Glasses

Glass Type	Borosilicate 3.3	Borosilicate 5.0	Borosilicate 7.0
Chinese Classification	High borosilicate glass	Middle borosilicate glass	Low borosilicate glass
Example SCHOTT	BORO-8330™	FIOLAX®	–
Composition			
SiO_2	80 – 82	72 – 75	70 – 74
B_2O_3	12 – 13	9 – 11	5 – 8
Al_2O_3	2	5 – 7	4 – 6.5
Na_2O/K_20	4	6 – 9	9 – 12
MgO/CaO/BaO	0	1 – 3	5 – 7
Physical Data			
Working Point	1,260 °C	1,145 – 1,170 °C	1,030 – 1,100 °C
Transformation Temperature (Tg)	525 °C	565 – 575 °C	550 – 580 °C
Mean Coefficient of Thermal Expansion (CTE)	3.3	4.9 – 5.5	6.3 – 7.5



Overview Composition of Glass Types

	Borosilicate			Soda-Lime	
	FIOLAX® clear 	FIOLAX®amber 	BORO-8330™ 	ILLAX® 	AR-GLAS® 
SiO_2	75	70	81	67	69
B_2O_3	10.50	7.50	13	5	1
Al_2O_3	5	6	2	7	4
Fe_2O_3	–	1	–	2	–
Na_2O	7	6.50	3.50	12	13
K_2O	–	1	0.50	1	3
BaO	–	2	–	< 0.50	2
CaO	1.50	< 1	–	1	5
TiO_2	–	5	–	–	–
MgO	–	–	–	–	3
MnO_2	–	–	–	5	–



Glass Properties

Overview Physical Properties


Viscosity


Melting


Shelf Life

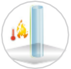

Electric Conductivity


Transparency

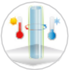

Light Protection

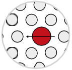

Strength


Stress


Thermal Expansion


Thermal Conductivity


Thermal Resistance

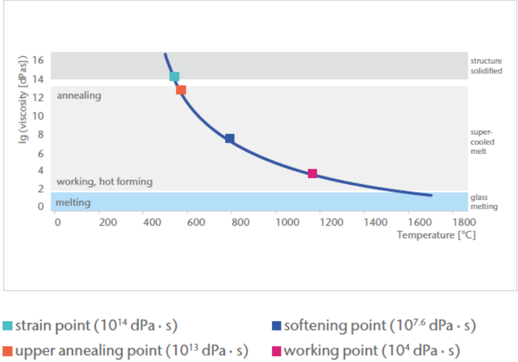

Permeability

Glass Properties

Viscosity

Viscosity

Viscosity is the resistance to flow. A liquid glass melt has a viscosity comparable to oil/honey. The higher the resistance to flow the higher the viscosity.

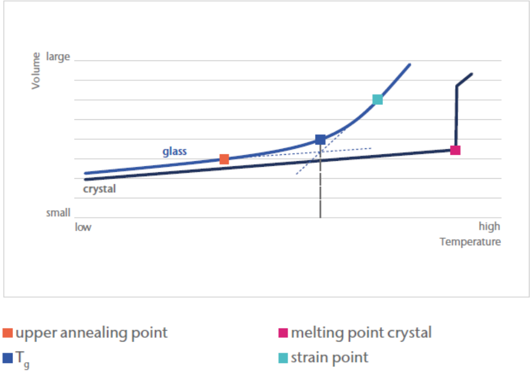


Glass Properties

Melting

Melting

Unlike many materials like e.g. water, glass gets solid without a distinct melting point. The transformation temperature T_g marks the transition from a hard and brittle state to a viscous state.

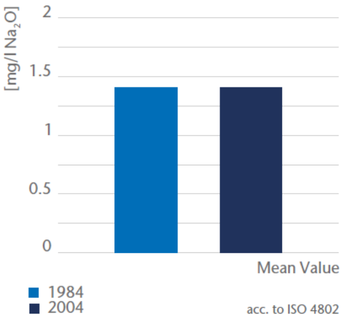


Glass Properties

Shelf Life

Shelf Life

The shelf life of glass is practically unlimited.

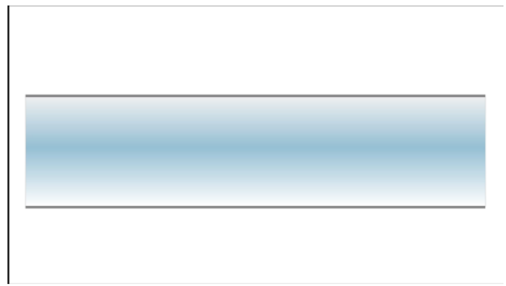


Glass Properties

Transparency

Transparency

Glass is a highly transparent material. The visual properties can be adjusted by the chemical composition. Due to its amorphous structure, visible light can pass through it easily.

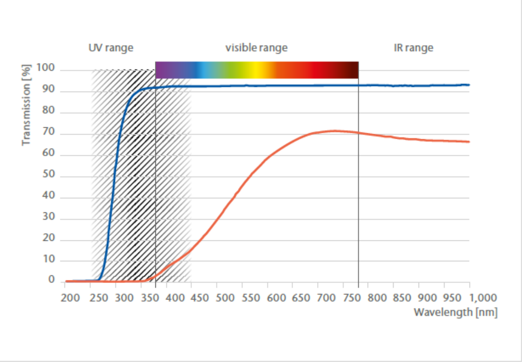


Glass Properties

Light Protection

Light Protection

Amber glasses provide protection against UV light for light-sensitive drugs. The coloration is achieved by adding iron, titanium and/or manganese to the glass composition.



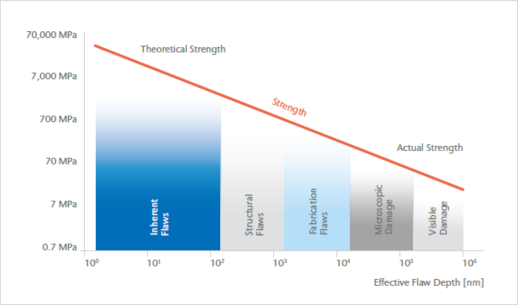
Glass Properties

Strength

Strength

Glass is a brittle material with a very high theoretical strength. Strength of glass is not a characteristic material value, but depends on the quality of the surface:

The more surface flaws and defects, the lower the practical strength.



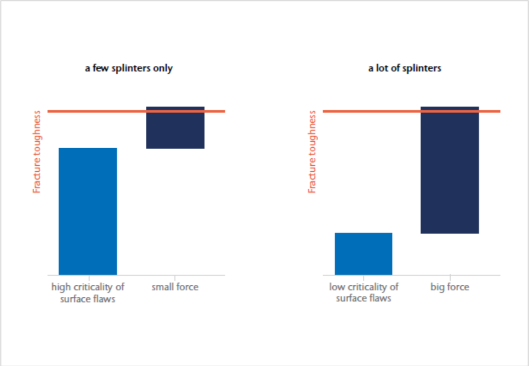
R.E. Mould, In: Fundamental Phenomena in the Materials Sciences, ed. LJ. Bonis, JJ. Duga and JJ. Gilman, 119 – 149 (1967). Modified and simplified view.

Glass Properties

Stress

Stress

Stress can be introduced into the glass by deforming the atomic structure, e.g. by mechanical load or through a heat treatment.

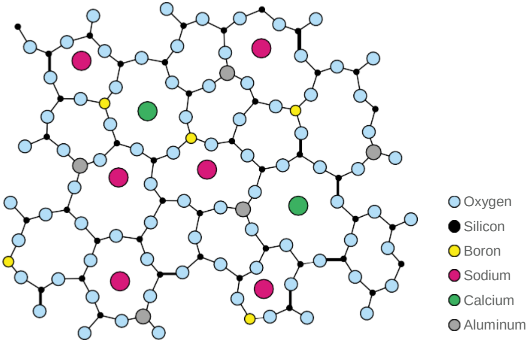


How to Create Stress in an Atomic Structure?

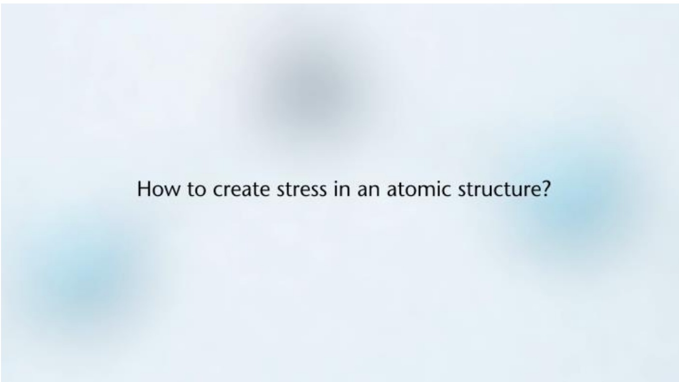
- Pharmaceutical glass is a three dimensional amorphous network build out of [SiO_4] tetrahedrons **“**filled**”** with different metall ions

---

- This system can be
  - *temporarily* stressed by mechanical load or by
  - *permanent* deforming of the atomic structure after a heat treatment (residual stress)



How to Create Stress in an Atomic Structure?



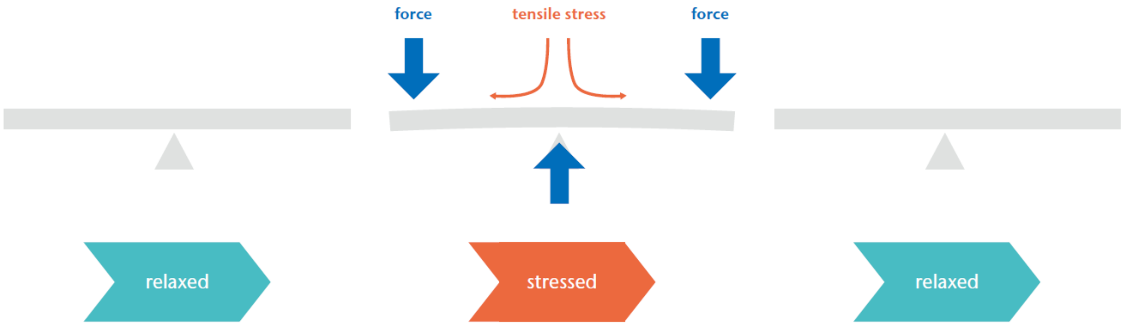
Inner Energy of the glass structure E_i depends on the level of relaxation in the molecular structure.

Temporary Induced Stress

Temporary Stress Caused by Applied Mechanical Load

Glass with a certain thickness is almost a non-elastic material.

But the solid body returns to its original shape after the mechanical load is removed.



Residual Stress

Residual Stress Caused by Thermal Shock

Stress caused by immediate thermal shock stays residual in the network structure. When liquid glass is cooled down rapidly below T_g (transformation point) the SiO_4 tetrahedrons cannot move back into their preferred positions. The energy stays inside the structure and will lead to higher breakage risk.

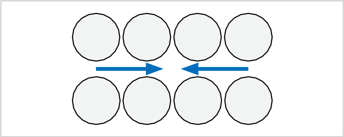
Residual stress in the tube ends of non annealed glass after closing (red = tensile stress, blue = compressive stress)

Residual stress in the vial after forming

"Good Stress" vs. "Bad Stress"

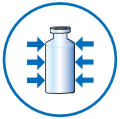
The Difference between Compressive and Tensile Stress

Compressive stress (the "good stress")

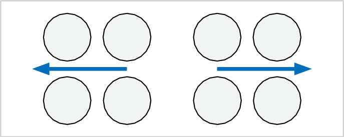


Glass can withstand compressive stress quite well. Defects and flaws on the surface are not supported to grow.

Example:

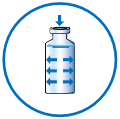


Tensile stress (the "bad stress")



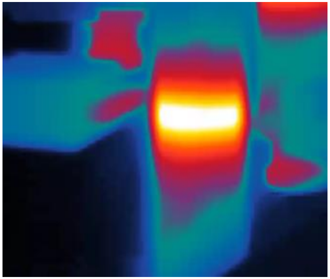
Glass is a metastable solid phase. If tensile force is applied every flaw and defect is supported to grow and can lead into a fatal error.

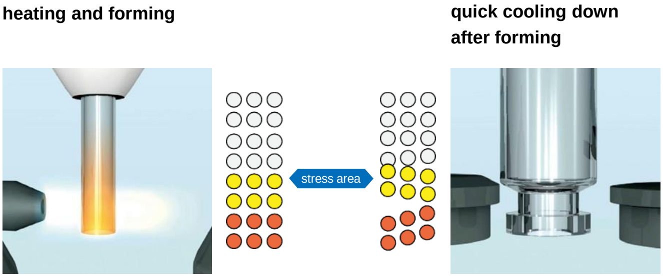
Example:



Creation of Stress during Container Formation

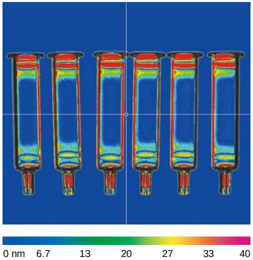
Local Heating and Quick Cooling Leads to Stress in Transition Zone





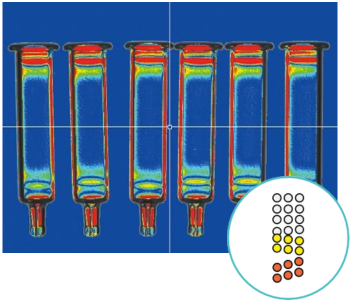
Creation of Stress during Container Formation

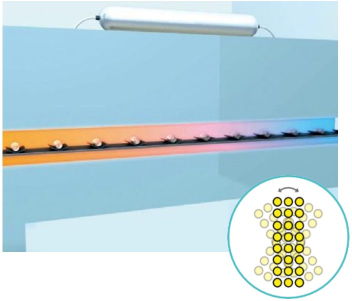
StrainScope

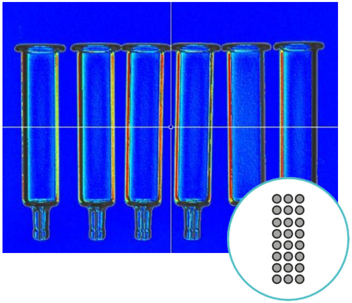


Release of Stress during Annealing

Permanent stress in glass is released by slow and uniform annealing above the transformation temperature of glass (T_g).



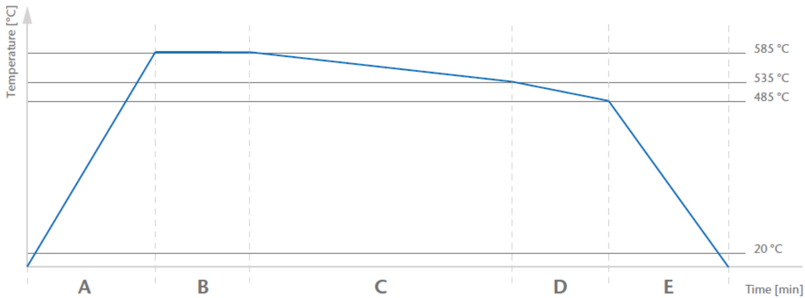




Release of Stress during Annealing

The optimal annealing curve depends on the glass composition and wall thickness

Annealing curve for FIOLAX® clear for a wall thickness of 1 mm



A	B	C	D	E	
Quick heating	Maintain temperature	Very slow annealing	Slow annealing	Quick annealing	Procedure
Maximum 2000 °C/min		Maximum 38 °C/min	Maximum 77 °C/min	Maximum 2000 °C/min	Condition
0.1	2	1.3	0.7	0.1	Time in minutes

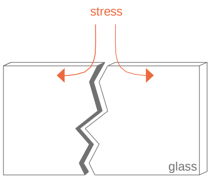
Stress and Breakage

Physical Background

Fracture toughness
(equation according to Griffith theory)

$$K = \sigma \cdot Y \sqrt{c}$$

K	stress intensity factor (critical stress intensity = fracture toughness)
σ	stress (induced by an applied force)
Y	geometrical factor (which considers the location of the defect among others)
$\sqrt{c}$	critical dimension (e.g. depth of defect)



- When a force is applied onto a glass surface, energy is lead into the glass.
- This energy needs to be relieved by wandering in the glass and splitting it.
- A critical value has to be overstepped to result in breakage.

Stress and Breakage

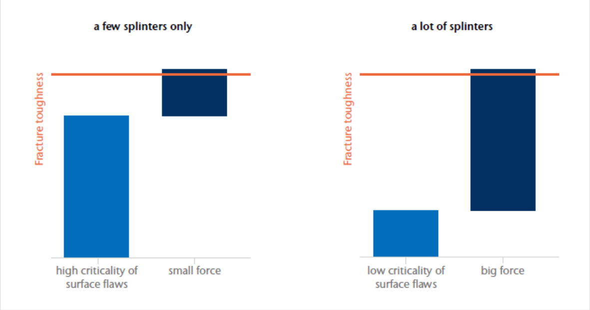
Physical Background

Fracture toughness
(equation according to Griffith theory)

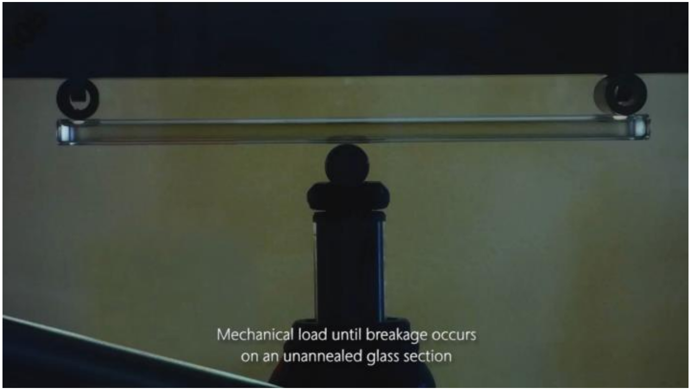
$$K = \sigma \cdot Y \sqrt{c}$$

K	stress intensity factor (critical stress intensity = fracture toughness)
σ	stress (induced by an applied force)
Y	geometrical factor (which considers the location of the defect among others)
$\sqrt{c}$	critical dimension (e.g. depth of defect)

The strength of glass is not a material constant.



Stress Distribution in Glass: Example #1



Mechanical load until breakage occurs on an unannealed glass section

Stress Distribution in Glass: Example #2

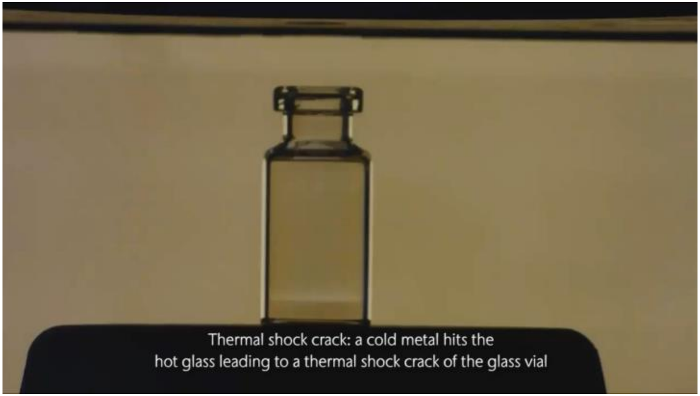
Mechanical load until breakage occurs on a glass section with scratches on the bottom side

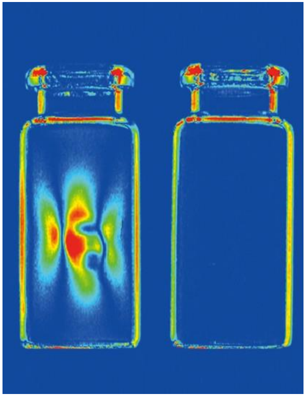
Stress Distribution in Glass: Example #3

Mechanical load until breakage occurs on a glass section with scratches on the upper side

Stress Distribution in Glass: Example #4

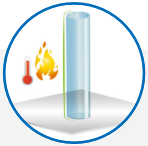
Thermal shock crack: a cold metal hits the hot glass leading to a thermal shock crack of the glass vial





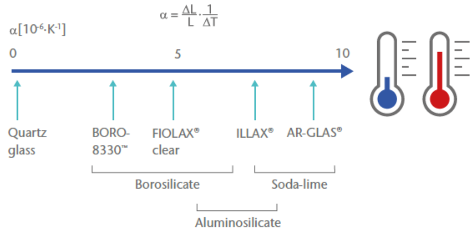
Glass Properties

Thermal Expansion



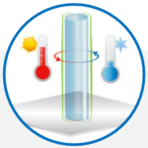
Thermal Expansion

Change in volume when a material is heated (expansion) or cooled down (shrinkage).



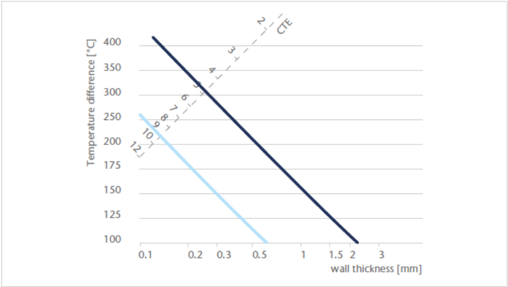
Glass Properties

Thermal Resistance



Thermal Resistance

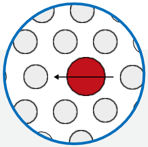
Stability when subjected to a sudden temperature change. It depends on the glass type as well as the wall thickness.



borosilicate glasses 5.0 (FIOLAX®)
soda lime glasses (AR-GLAS®)

Glass Properties

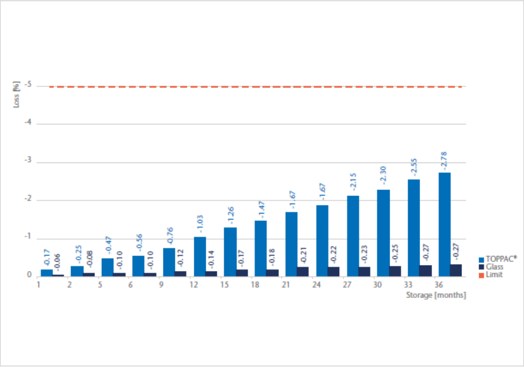
Permeability



Permeability

Glass is considered impermeable against gases,

e.g. water vapor or oxygen.



Glass Properties

Overview Chemical Properties


Hydrolytic Resistance


Acid Resistance


Alkali Resistance


Extractables


Elemental Impurities


Water Skin

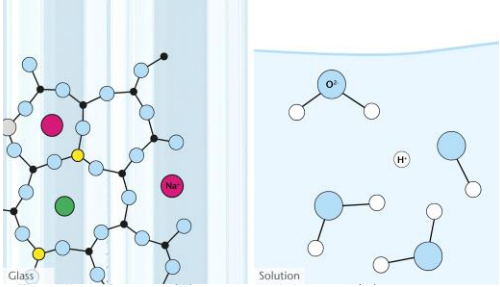
Glass Properties

Hydrolytic Resistance

Hydrolytic Resistance

Resistance to water attack. In contact with water, sodium ions from the glass can be exchanged with hydrogen ions from the solution.

Low level of extraction/high H. R. : Type I borosilicate glass High level of extraction/low H. R. : Type III soda-lime glass



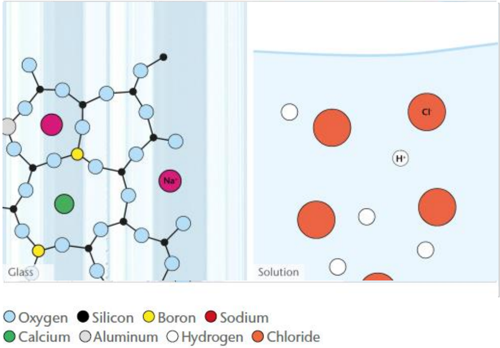
Oxygen Silicon Boron Sodium
Calcium Aluminum Hydrogen

Glass Properties

Acid Resistance

Acid Resistance

Resistance to acid attack. Similar to the ion-exchange mechanism of water attack, sodium ions from the glass can be exchanged with hydrogen ions from an acid.



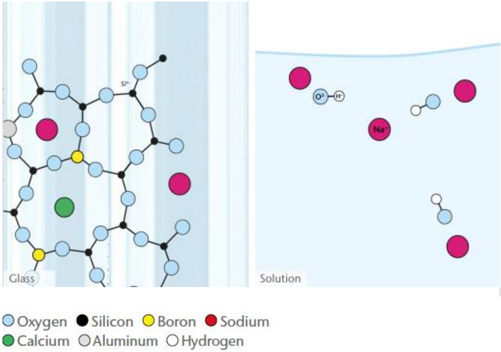
Glass Properties

Alkali Resistance

Alkali Resistance

Resistance to alkaline attack. In contact with base, hydroxide ions cause a dissolution/ corrosion of the glass network.

This attack/corrosion is continous and ~15 times stronger.

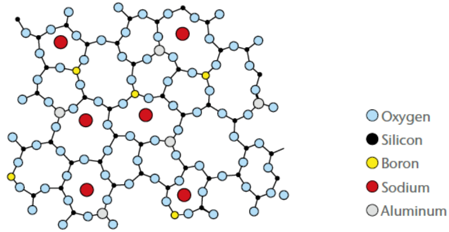


Glass Properties

Extractables

Extractables

All kind of elements that can be extracted from glass (under harsh conditions). These can be glass components, which are present in the composition as well as elemental impurities, which may derive from raw material impurities.

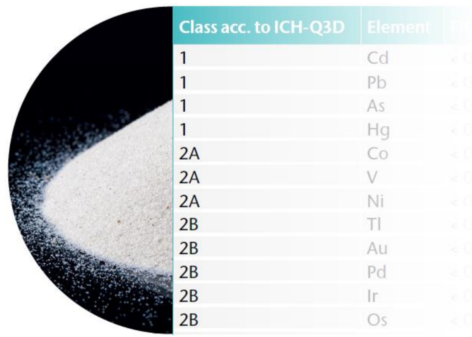


Glass Properties

Elemental Impurities

Elemental Impurities

Impurities, that may derive from raw materials,
e.g. iron from sand.



Class acc. to ICH-Q3D	Element
1	Cd
1	Pb
1	As
1	Hg
2A	Co
2A	V
2A	Ni
2B	Tl
2B	Au
2B	Pd
2B	Ir
2B	Os

Glass Composition & Properties

Overview

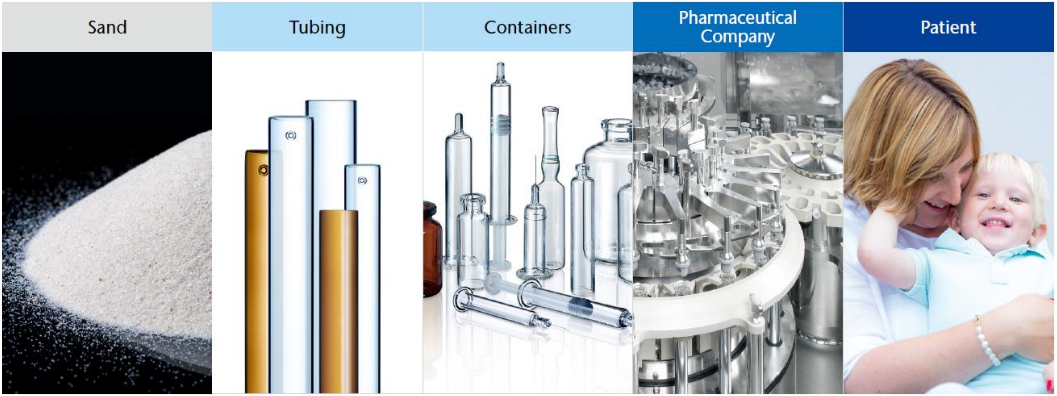
	BORO-8330™ 	FIOLAX® clear 	FIOLAX® amber 	ILLAX® 	AR-GLAS® 
Glass Type	Borosilicate	Borosilicate	Borosilicate	Soda-lime	Soda-lime
Hydrolytic Resistance	Type I	Type I	Type I	Type III	Type III
CTE	3.3	4.9	5.4	7.8	9.1
Drug suitability	All, esp. Parenterals	All, esp. Parenterals	All, esp. light-sensitive Parenterals	esp. light-sensitive non-parenterals	esp. non-parenterals
Color	clear	clear	amber	amber	clear
ChP Classification	high borosilicate glass (“3.3 glass”)	middle borosilicate glass (“5.0 glass”)	middle borosilicate glass (“5.0 glass”)	soda-lime glass	soda-lime glass

Tubing Production Process

Process Chain Pharma, Tubing Production, Tubing Quality

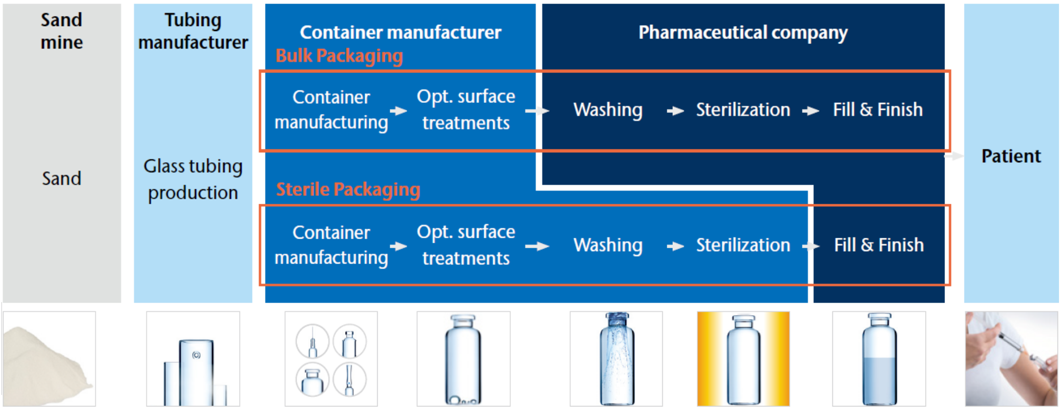
Process Chain Pharma

Bulk Packaging vs. Ready-To-Use Packaging



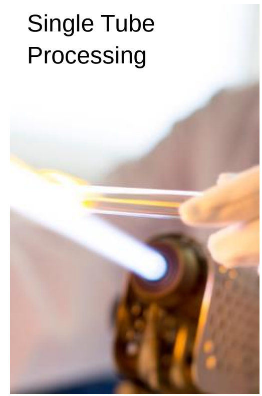
Process Chain Pharma

Bulk Packaging vs. Ready-To-Use Packaging



Tubing Production

Overview



Tubing Production
Raw Materials

Element in network	Raw materials	
Network formers		
Silicon (Si)	SiO_2	sand
Boron (B)	$Na_2B_4O_7$	borax
Network intermediates		
Aluminum (Al)	Al_2O_3	alumina
Network modifiers		
Sodium (Na)	Na_2CO_3	soda
Potassium (K)	K_2CO_3	potash
Calcium (Ca)	$CaCO_3$ $CaMg(CO_3)_2$	chalk, marble, limestone dolomit
Magnesium (Mg)	$MgCO_3$ $CaMg(CO_3)_2$	magnesite dolomit
Barium (Ba)	$BaCO_3$	witherite


Raw Materials


Sand Mine

Tubing Production

Sand Mine Processing


Open Cast Mining


Mechanical Drainage

Open Cast Mining → Washing → Flotation → Mechanical Drainage → Drying → Protective Sieving → Loading Shipping


Washing


Drying

Courtesy of Gebrüder Dorfner GmbH & Co.

Tubing Production

Risk Mitigation

- At least two qualified suppliers for each raw material
- Raw material supplier audits are done globally from Mitterteich
- Risk analysis by FMEA
- Certificate of acceptance upon arrival

Supplier Evaluation Sheet

- Quality Management System
- Raw Material Extraction
- Raw Material Impurities
- Raw Material Reworking
- Processing Chemicals
- Process control
- Documentation
- Certificates
- Specifications
- Traceability

Certificate of Acceptance

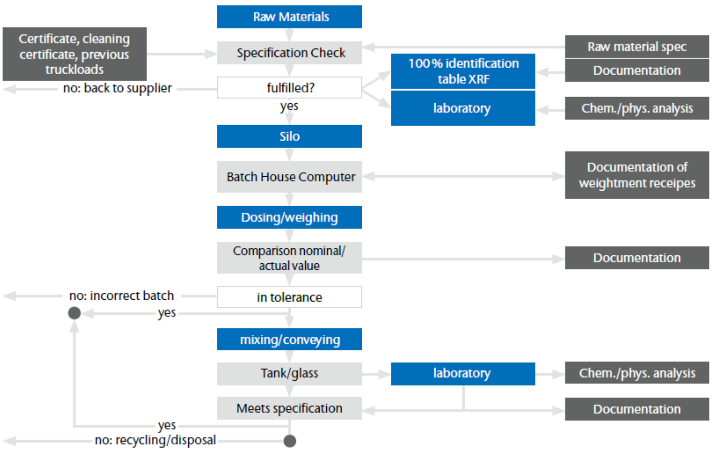
- Product Information
- Traceability Data
- Composition Analysis
- Impurity Profile
- Grain Size Distribution

Supplier Risk Analysis

- Mining
- Transportation
- Processing
- Warehouse Political
- structure

Tubing Production

Quality Inspection Flow Chart

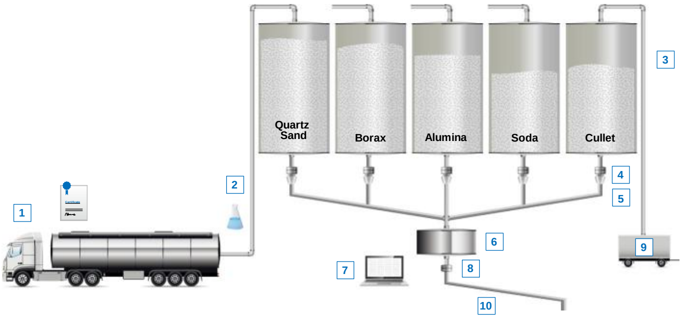


- 100 % Identification of Raw Materials by an energy dispersive X-ray fluorescence (EDXRF) benchtop spectrometer for a fast and reliable composition analysis
- Fingerprint: PASS/FAIL analysis for material type confirmation

PANalytical, Epsilon 4

Tubing Production

Raw Materials

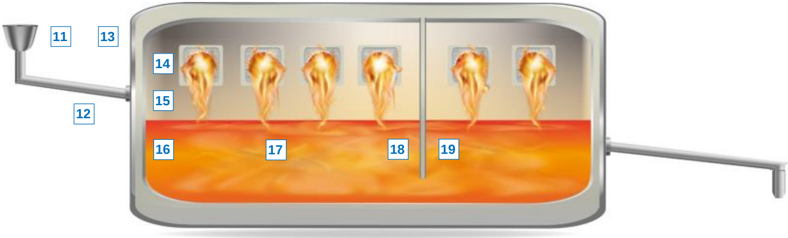


1. Raw Material Delivery
2. Raw Material Inspection
3. Storage Silos
4. Dosing Valve
5. Scales
6. Mixer
7. Process Control System
8. Pneumatic Vessel
9. Cullet Return
10. Batch Conveyor System

Tubing Production

Glass Melt

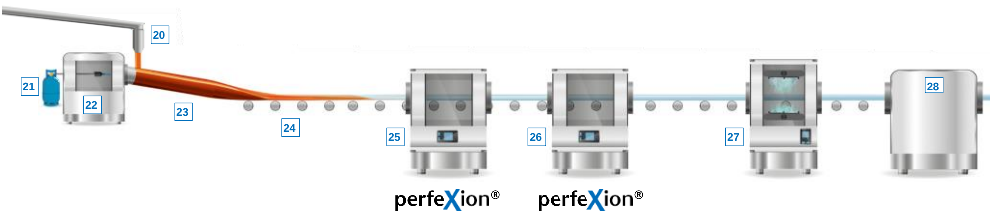
Melting Tank



- 11 Batch Silo
- 12 Feeder
- 13 Refractory Material
- 14 Burner
- 15 Combustion Chamber
- 16 Melting Tank
- 17 Glass Melt
- 18 Refining Tank
- 19 Working Tank

Tubing Production

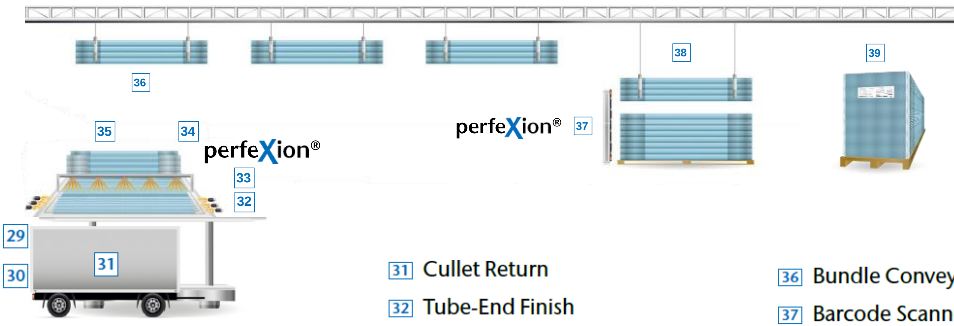
Tube Draw



20 Feeder
21 Air Supply
22 Mandrel Drive
23 Mandrel
24 Drawing Line
25 Inspection of Dimensional Features
26 Inspection of Visual Features
27 Anti-Scratch Coating
28 Drawing Machine

Tubing Production

Inspection and Packaging



- 29 Cutting Station
- 30 Sorting
- 31 Cullet Return
- 32 Tube-End Finish
- 33 Single Tube Inspection
- 34 Sorting
- 35 DENSOPACK® and Bundle Labeling
- 36 Bundle Conveyor System
- 37 Barcode Scanner
- 38 Palletizing
- 39 Pallet with Shrinking Foil and Pallet Label

Tubing Quality

Benefits for superior syringes and cartridges

The customizable **Inside Diameter Tolerance** down to ± 0.05 mm

- supports More consistant plunger gliding forces
- Higher dosage accuracy

The customizable **Outside Diameter Tolerance** in combination with the ID tolerance results in a highly accurate wall thickness which supports

- More precise cone forming
- More precise flange forming

Zero Defect on **Inside Open Airlines** supports

- High security on Container Closure Integrity

Tubing Quality

Benefits for superior vials

The customizable **Wall Thickness Tolerance** down to ± 0.03 mm

- supports Highly accurate crimp neck forming
- Highly accurate blow-back geometries
- Highly accurate bottom forming

The **100 % Cosmetic Quality inspection** supports

- Yield rates with camera inspected vial manufacturing
- (converting) Yield rates in camera inspected vial fill & finish process

Borate Evaporation

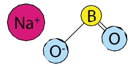
Alkali Borates from the Glass Composition, Alkali Borate Evaporation during Hot Forming

What Are Alkali Borates?

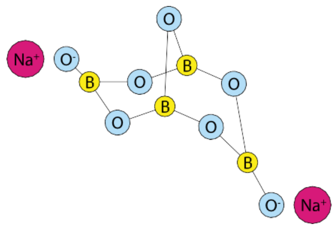
- Colorless salts, which contain boron and alkali ions (e.g. sodium)
- Crystals usually contain a certain amount of water (decahydrate, pentahydrate)
- Are highly water soluble

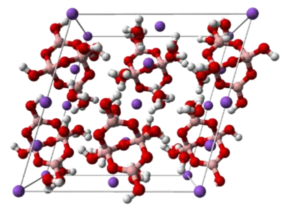
The two most common structures are

- Sodium borate $NaBO_2$



- Sodium tetraborate $Na_2B_4O_7$





Alkali Borates from the Glass Composition

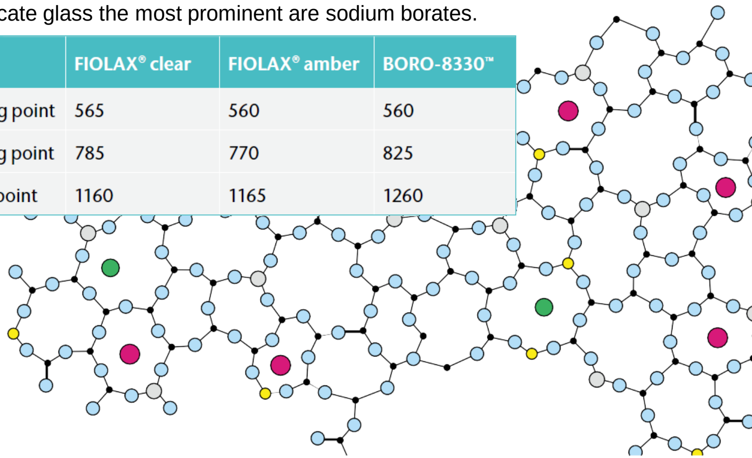
At temperatures above the working point e.g. during forming, compounds start to evaporate from the glass – for borosilicate glass the most prominent are sodium borates.

		FIOLAX® clear	FIOLAX® amber	BORO-8330™
Temperature T [°C] of glass at viscosity η [dPa · s]	10^{13} Annealing point	565	560	560
	$10^{7.6}$ Softening point	785	770	825
	10^{4} Working point	1160	1165	1260

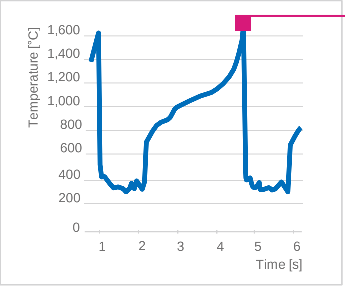
Boiling temp. [°C]

- $NaBO_2$ 1434
- $Na_2B_4O_7$ 1575
- NaOH 1388
- NaCl 1465

Oxygen, Silicon, Boron, Sodium, Calcium, Aluminum



Temperatures during Hot Forming

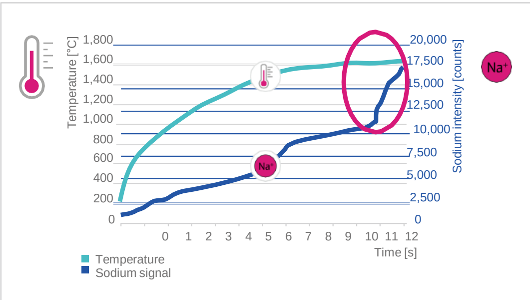


Especially the bottom forming process of a vial or ampoule requires **high temperatures up to 1,600°C**

Boiling temp. [°C]

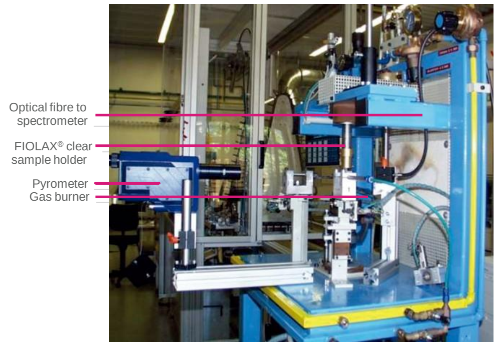
- $NaBO_2$ 1434
- $Na_2B_4O_7$ 1575
- NaOH 1388
- NaCl 1465

Alkali Borate Evaporation during Hot Forming



- Maximum temperature is achieved after 8 seconds (for the power set)
- Over-proportional increase of the sodium signal after 11 seconds

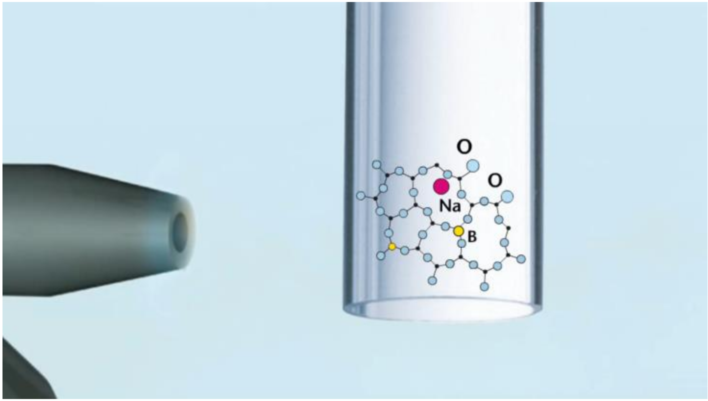
Experimental setup



Measurement of the alkali evaporation with a spectrometer

Alkali Borate Evaporation and Precipitation

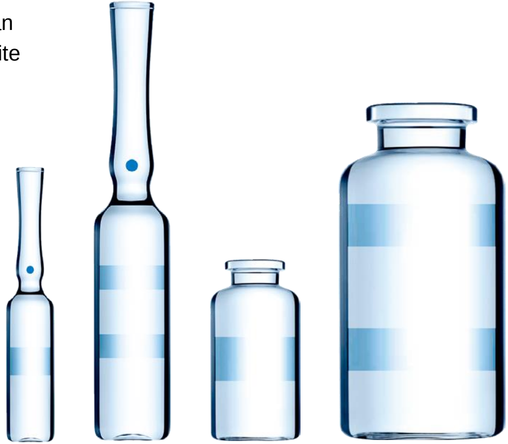
Alkali borates are released during hot forming, these can condensate at cooler areas.



Alkali Borate Evaporation and Precipitation

- Alkali borates are released during hot forming, these can condensate at cooler areas and may be visible as a white fog.
- Pronounced areas are at the body or a few mm above the bottom and below the shoulder, respectively.





Molded Vials

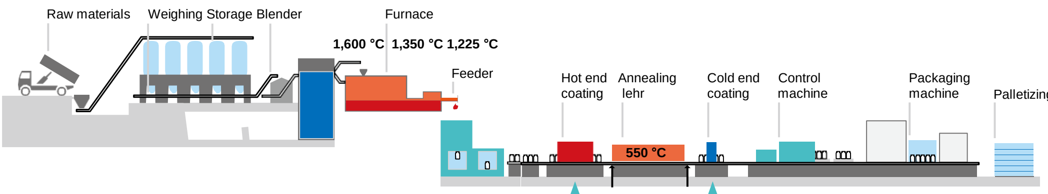
Tubular and Molded Glass Vials

Tubular Vials

Molded Vials

Molded Vials

Production Process: Overview



e.g. polyethylene derivatives,

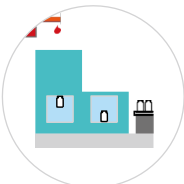
- Increase machine runability

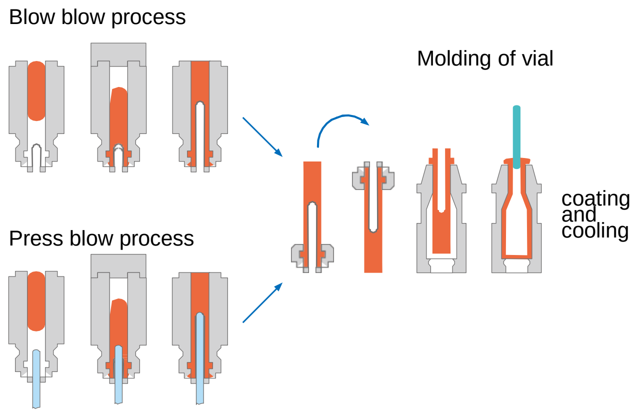
e.g. tin tetra chloride coating

- Increase strength of container
- Primer for cold end coating

Molded Vials

Production Process: Molding

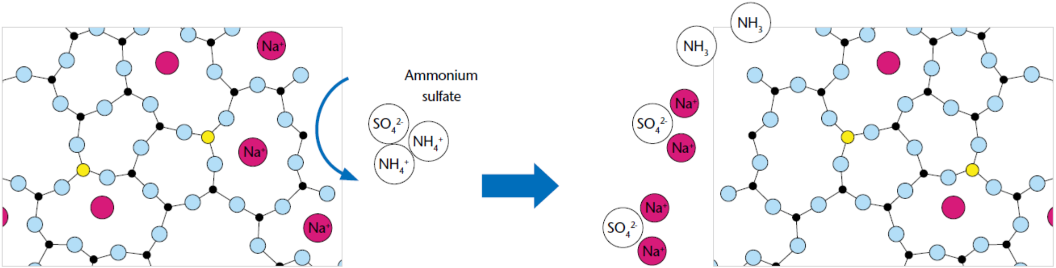




Molded Vials

Production Process: Ammonium Sulfate Treatment

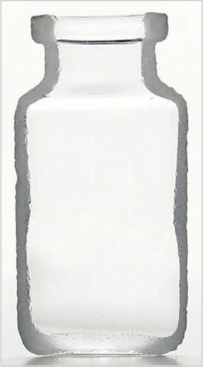
- Ammonium sulfate leads to the extraction of surface-near sodium ions
- This treatment can be applied
  - on a type III glass, which is then designated as type II glass
  - on a type I glass, which is then designated as surface-treated type I glass



Molded Vials

Dimensional Aspects

Molded Vial



52 g

Tubular Vial

40 g

Benefits of tubular vials:

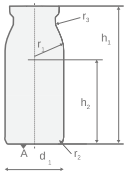
- Lower weight
- Tighter tolerances
- Consistent bottom and body thickness/inside diameter
- Formation of blowbacks possible

Molded Vials

Dimensional Aspects

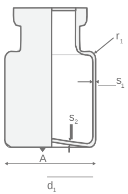
Molded: Insulin ISO 8362-4 (There is no tolerance for wall thickness defined)

Size	Capacity [ml]	a	d		h_1		h_2	r_1	r_2	r_3	t
2 l	2.5	1	18	± 0.5	30.6	± 0.6	17.6	7.9	1.6	2.5	0.4
5 l	7.2	1.4	19	± 0.6	52.8		36.5	12.7	1.5	1.5	1
10 l	13.1	1.6	23	± 0.6	58.9		42	10.3		2.5	1.5



Tubular: ISO 8362-1

Size	Capacity [ml]		a	d_1		d_2	d_3	d_4	h_1		h_2	h_3		r_1	r_2	s_1		s_2	t	mass [g]
2R	4	± 0.5	1	16	± 0.15	13	10.5	7	35	± 0.5	22	8	± 0.5	2.5	1.5	1	± 0.04	0.6	0.7	5
4R	6								45		32									6.1
6R	10		1.2	22	± 0.2	20	16.5	12.6	40		26	8.5		3.5	2			0.7		8.3
8R	11.5								45		31									9.4
10R	13.5	± 1		24					45		30	9		4.0						10.2
15R	19								60		45									12.8



Sizes and tolerances are given in [mm].

Molded Vials

Visual Aspects

Molded **Tubing**

- The transmission of light is comparable for tubular and molded vials
- Due to the dimensional fluctuations in molded vials, the transparency is lower

→ a high degree of transparency is especially important for (online) visual inspection

Tubular and Molded Glass Vials

Overview

	Tubular container	Molded container
Application	Small vials (~ 0.5 to 100 ml)	Large bottles/vials (~ 10 to 1,000 ml)
Production process	Two-step process (Glass Tubing – Glass Converting)	One-step process
	Small lot production possible	Large quantity production
	Flexibility for changes (time, cost)	Less flexible for changes (time, cost)
Dimensional Aspects	Lower weight	Higher weight
	Tighter tolerances	Lower/no tolerances
	Consistent bottom and body thickness/inside diameter	More distinct fluctuations, less uniform
Visual Aspects	High degree of transparency	Lower degree of transparency
	On-line visual inspection for particles etc. established	Difficulties for visual inspection
Cost	Often higher	Often lower