GLASS 101

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES

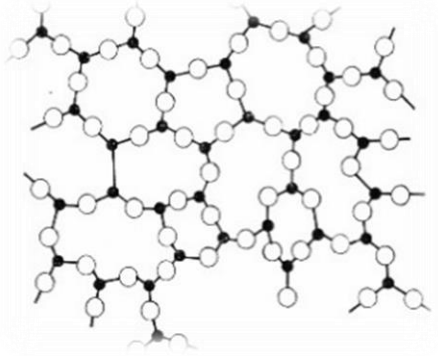
BASEL
27 – 28 FEBRUARY, 2020

Dr. Piet Christiaens

GLASS 101

What is Glass?

An inorganic fused substance that has been cooled to a rigid condition without crystallization (e.g. Supercooled amorphous substance)



Why Glass as packaging material?

- Well-known material
- Transparent
- Heat resistant
- Good barrier properties: gas & vapour tight
- Chemically and physically (quite) inert.

J. Zuercher, ECA Course E/L, Prague 2010

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Glass in Pharmaceutical Packaging

- Ampoules
- Injection Vials
- Infusion Bottles
- Syringes
- Carpules
- Bottles for oral drug products
- Bottles for solid preparations

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Composition of Glass – Function of Ingredients

- SiO_2 : Backbone structure
- CaO : Increasing hardness & Chemical resistance
- Al_2O_3 : Increasing Chemical Resistance
- Na_2O & B_2O_3 : Lowering the melting point
- Fe_2O_3, TiO_2 : Amber Glass
- CuO : Blue Glass
- Mn^{3+} : Violet Glass

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Glass Types

Glass Type	General Description	Uses
I	High resistant Borosilicate	Parenteral Preparations
II	Treated Soda-Lime	Acidic and Neutral Parenteral Preparations
III	Soda Lime	Not for Parenteral Preparations
NP	Soda-Lime	Oral / Topical

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Glass Composition for different Glass Types:

Component	Type I (Borosilicate)	Type II, III, NP (Soda-Lime)
SiO_2	70 - 73%	69 - 73%
B_2O_3	10%	0 - 1%
Na_2O	2 - 9%	13 - 14%
Al_2O_3	6 - 7%	2 - 4%
BaO	0,1 - 2,0%	0 - 2%
K_2O	1 - 2%	0 - 3%
CaO	0,7 - 1,0%	5 - 7%
MgO	0 - 0,5%	3 - 4%
ZnO	0 - 0,5%	-

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Metal Profile of a Type I - Clear Glass Vial (ICP-MS)

Main Metals	Amount (%)	**Trace Metals (> 1µg/g)**	Amount (µg/g)
Si	>30%	Mg	61
Al	2%	Ba	21
Na	2,40%	Ce	8,8
B	5,50%	Ti	6,7
K	0,1%	Hf	6
Ca	0,036%	Mo	4,8
Fe	0,7 - 1,0%	Y	2,8
Zr	0 - 0,5%	La	2,5
		Sr	1,7
		Pd	1,6
		Ga	1,2
		Pb	1

Zuccarello et. Al., PDA, J Parm Sci technol 63, 339-352, 2009

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Examples for Extractables / Leachables

- **High heating** during molding process leads to an **increasing release of alkali ions** from the glass surface => Delamination
- During the process, **components of the heated glass vaporize and deposit** on the surface
- **Heating promotes migration of alkali oxides** within the silica matrix to the glass surface
- Relevant for **glass containers** made from **tubular glass**
- **Small volume** containers are **more impacted** than larger containers

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Parameters, impacting the Glass Leachables

- **Filling Volume**: *smaller filling volumes show higher leachable concentrations*
- **Storage time**: *leachable concentrations increase over time*
- **Sterilization / Sterilization time**: *longer autoclaving cycles, higher concentrations*
- **Sterilization Temperature**: *higher temperatures, higher concentrations*
- **Type of contact solution**:

  [Si]: Lactic acid < acetic acid < ascorbic acid < malic acid < tartaric acid < oxalic acid < citric acid

  ***Complexing agents**, such as EDTA may also impact the metal release from Glass*

- **Impact of pH**: *higher pH, higher [Si] release.*

  In general, more metals are leaching out of glass at pH>9

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Risk of Glass Leachables

- **Most observed Metal Leachables from Glass:**
  Si and **Na** as MAJOR leachables, **K, B, Ca & Al** as MINOR LEA, **Fe**: traces
- **Alkali release:** pH shift of unbuffered solutions
- **Silicon (Si) release**:increased particle load, delamination!
- **Aluminum release**:
  Aluminum can accumulate in patients with reduced renal function, causing e.g. neurological diseases
- Potential **Arsenic (As) release**:
  glass can contain arsenic oxide (III) as a fining agent to improve glass tranparency. Arsenic is toxic!
- **Release of metals**, causing precipitation with some salts, present in the DP
  Ba => $BaSO_4$, Al => $Al(OH)_3$

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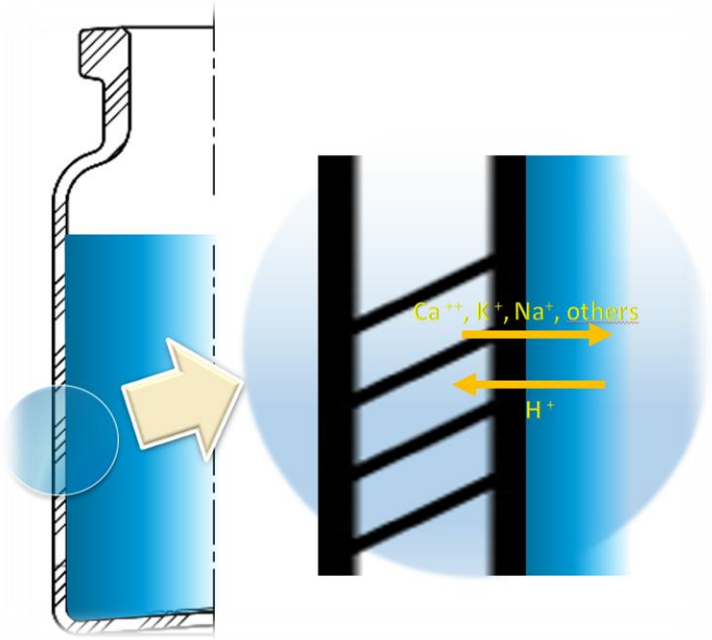
How to (try to) prevent Glass Leaching

1. Chemical surface treatment

$(NH_4)SO_4$ is injected before annealing

$(NH_4)SO_4 \rightarrow (NH_4)HSO_4 + NH_3$

$2Na^+ + (NH_4)HSO_4 \rightarrow Na_2SO_4 + NH_3 + 2H^+$



Afterwards, rinsing with Water to remove soluble $NaSO_4$

Result: lower pH shift because lower amounts of Na will leach

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How to (try to) prevent Glass Leaching

2. Put a Coating on the Glass

Deposition of SiO_x layer as an inert glass layer

e.g. Schott Type I Plus

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How to (try to) prevent Glass Leaching

3. Siliconization

Siliconized surfaces are hydrophobic, **reducing the wettability** of the container surface

Thus siliconized glass surfaces are **reducing the potential of interactions** with aqueous fillings

The **release of alkali ions is reduced**, compared to non-siliconized containers

However, Siliconized surface may then release organic compounds!
(e.g. Siloxanes)

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Questions?