SGD Pharmacy Division

Glass Primary packaging for healthcare

Flaconnage Pharmaceutique

GDR Verres: Altération des verres industriels

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PHARMA

Summary

- Overview of pharma glass packaging
- Drug product shelf life: Impact of initial hydrolytic resistance of Type II Glass
- Comparison study between molded and tubing type I glass
- Extractable and leachable evaluation from USP <1660> Chapter
- Conclusion
- Acknowledgment

Overview of pharma glass packaging

Pharmaceutical Glass: Presentation

- 3 types of pharmaceutical glass:
  - Type I : Borosilicate glass, ≈ 10% borax, B_2O_3
  - Type II : Silica soda lime glass with passivated inner surface
  - Type III : Silica soda lime glass

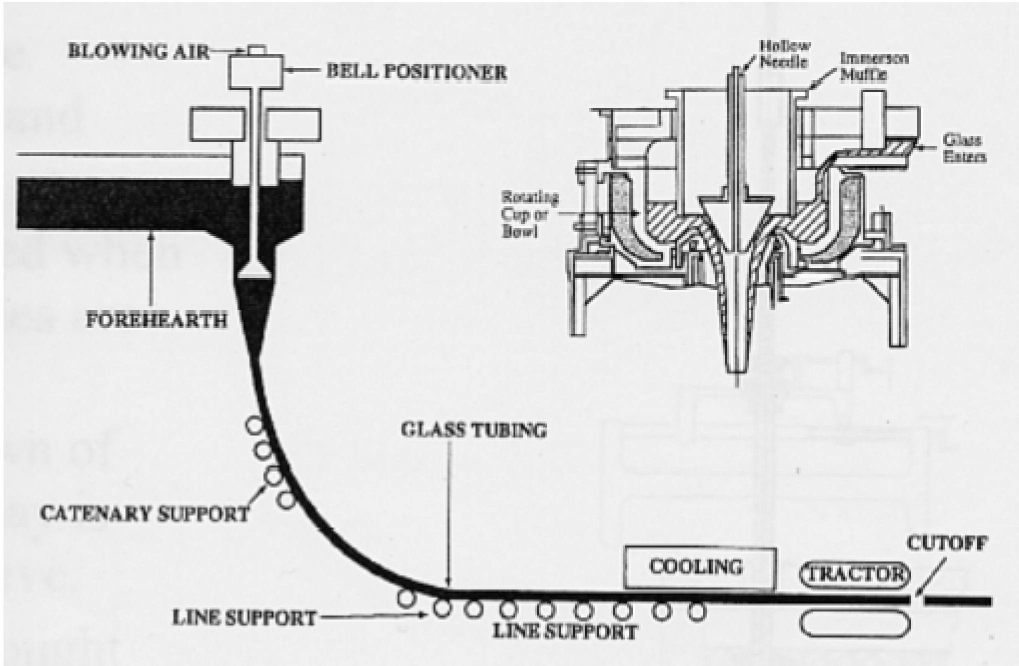
- Silica soda lime glass is the most usual glass used for manufacturing many kinds of glass products

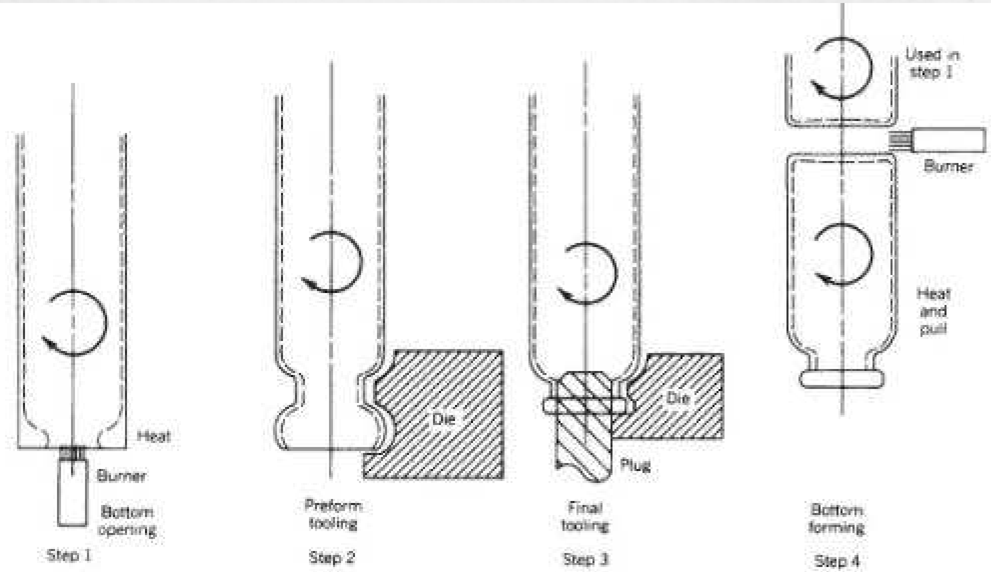
- Borosilicate glass is called Neutral Glass, used for most sensitive molecules and drug products

Tubing Glass:
2 step process

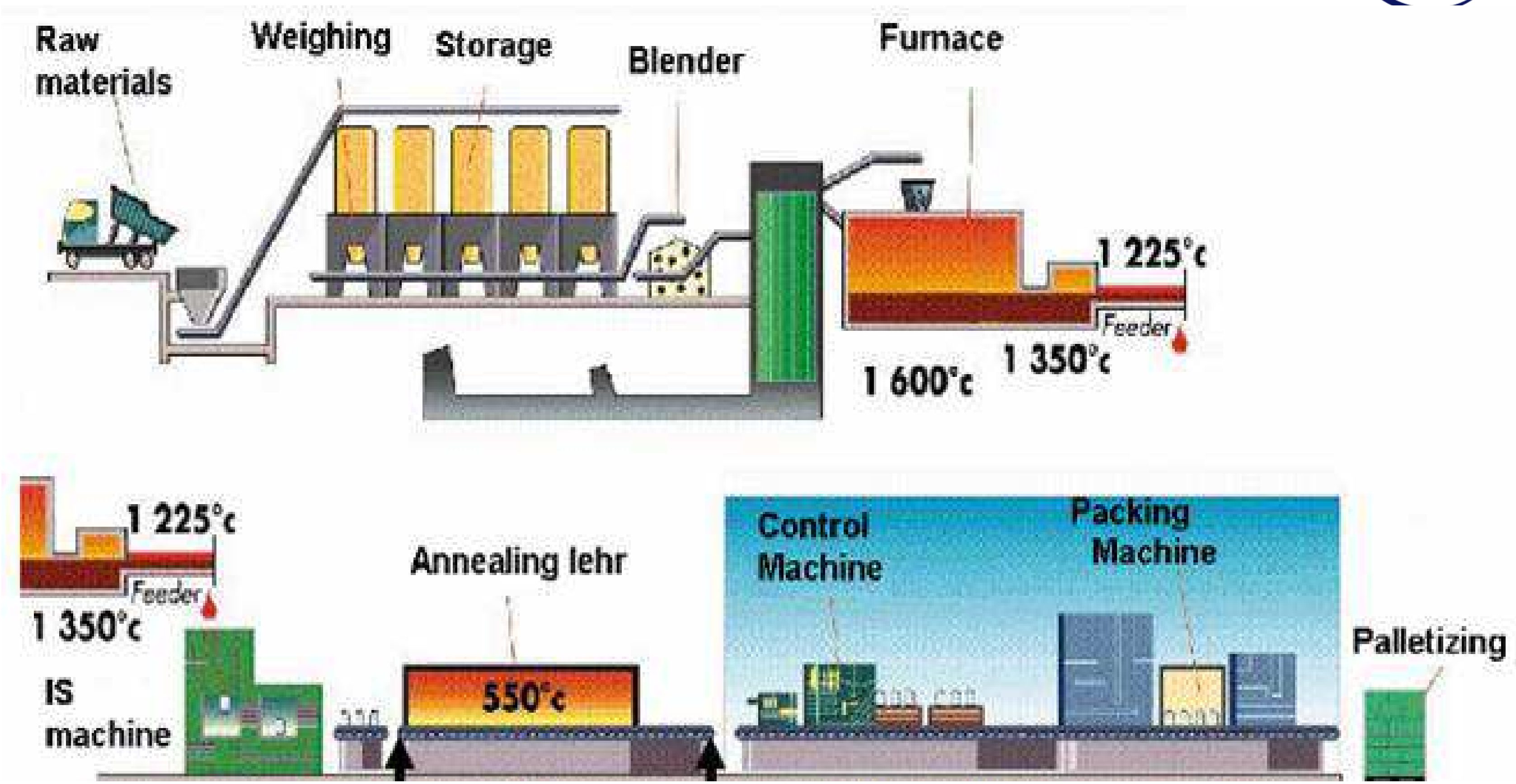
- 2 step process:
  - Cane manufacturing
  - Converting

- Capabilities:
  - Vials
  - Cartridges
  - Syringes





Molded Glass: 1 step process



SGD capabilities: Vials and Intravenous bottles from 3 ml to 1 L

- Neck finish 20 mm and higher
- Can also produce non round vials and bottles

Hydrolytic Resistance: Glass-Water reaction

$$SiO_3–O^- Na^+ + H^+–OH^- \rightarrow SiO_3–OH + Na^+–OH^-$$

- Diffusion Process : Superficial desalkalized layer

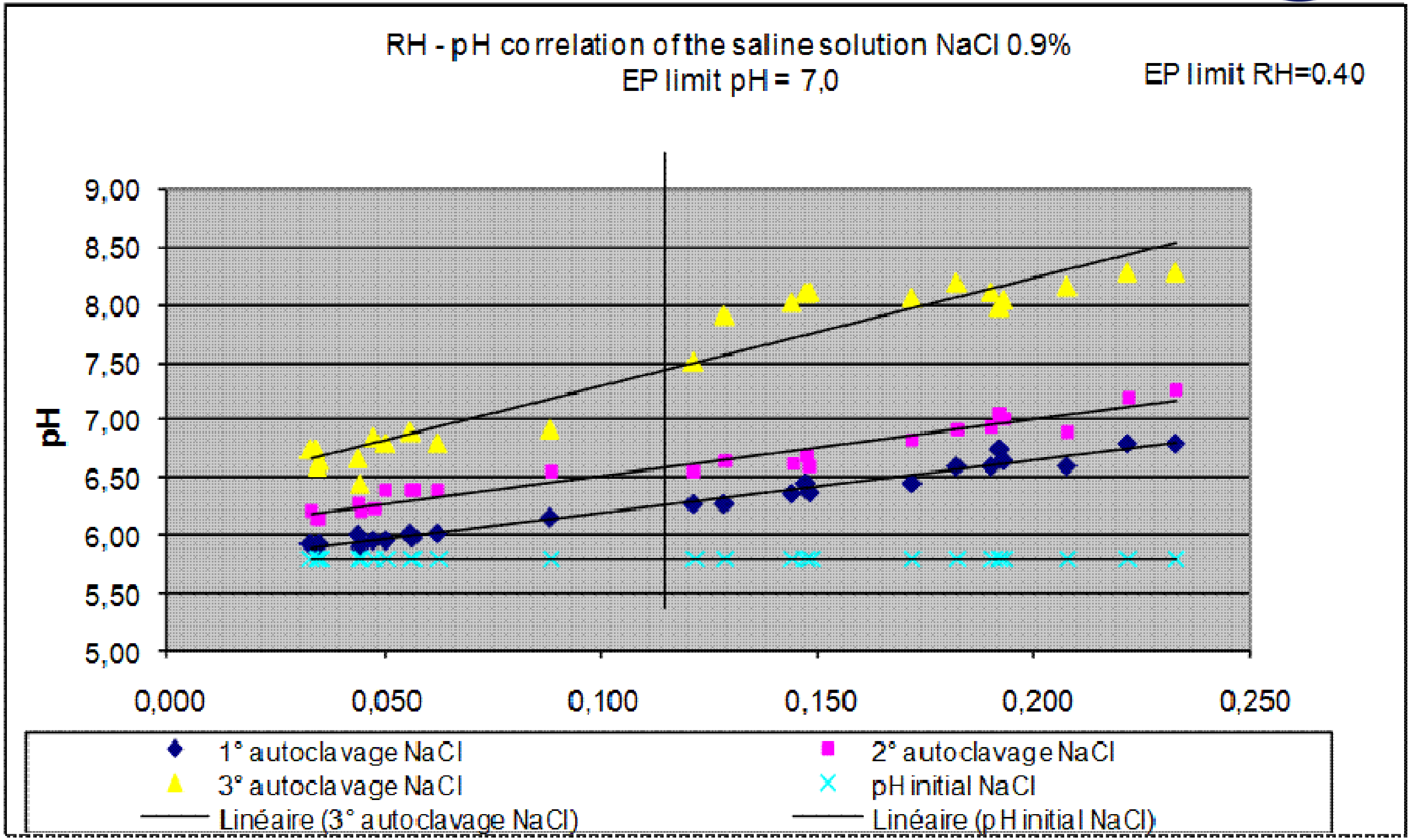
  Extracted Sodium=$a+bt^{1/2}$

- Ion-exchange H^+_{water} Na^+_{glass} liberates OH^- ions in the solution : ↗ pH

  Function of:
  - \- Ratio glass surface/volume of solution
  - \- Temperature
  - \- Time of contact

Drug product shelf life: Impact of initial hydrolytic resistance of Type II Glass

pH increase, function of the initial HR



pH increase, function of the initial HR

For NaCl 0,9% in 100ml vial Type II glass

- Autoclaving 1h – 121°C is equivalent to 2 years – 25°C
- Autoclaving 20 min – 121°C is equivalent to 1 year – 25°C
- Shelf life
    - 0< HR < 0,125 years pH< 7,0 (depending on the stopper)
    - 0,13< HR < 0,20 3 years pH< 7,0
    - 0,21< HR < 0,25 2 years pH< 7,0
    - 0,26< HR < 0,40 < 2 years

Comparison study between molded and tubing type I glass

Mass Composition Analysis

Method: X-Ray Fluorescence Spectrometry

- Vials are cut in pieces
- Surface is polished
- X-Ray Fluorescence: FX S8 TIGER BRUKER

Type I glass composition

- NEUTRAL GLASS : alkaline borosilicate glass with main components of (typical molded glass composition):

- Network Formers :	SiO_2+Al_2O_3	-	73%
	B_2O_3	-	12%
- Network Modifiers:	Na_2O; K_2O	-	10%
	CaO; BaO; ZnO	-	5%

- NEUTRAL GLASS may be composed of 2 primary phases
  - Silica-rich phase with low alkaline content
  - Boron-rich phase with most alkaline elements of the glass; it may be separated into micro-droplets within the silica rich matrix, depending on the composition

Composition by X-Ray Fluorescence

	Molded	Tubing 1	Tubing 2
Network Formers	85.7	90.2	91.1
Network Modifiers	14.2	9.6	8.7

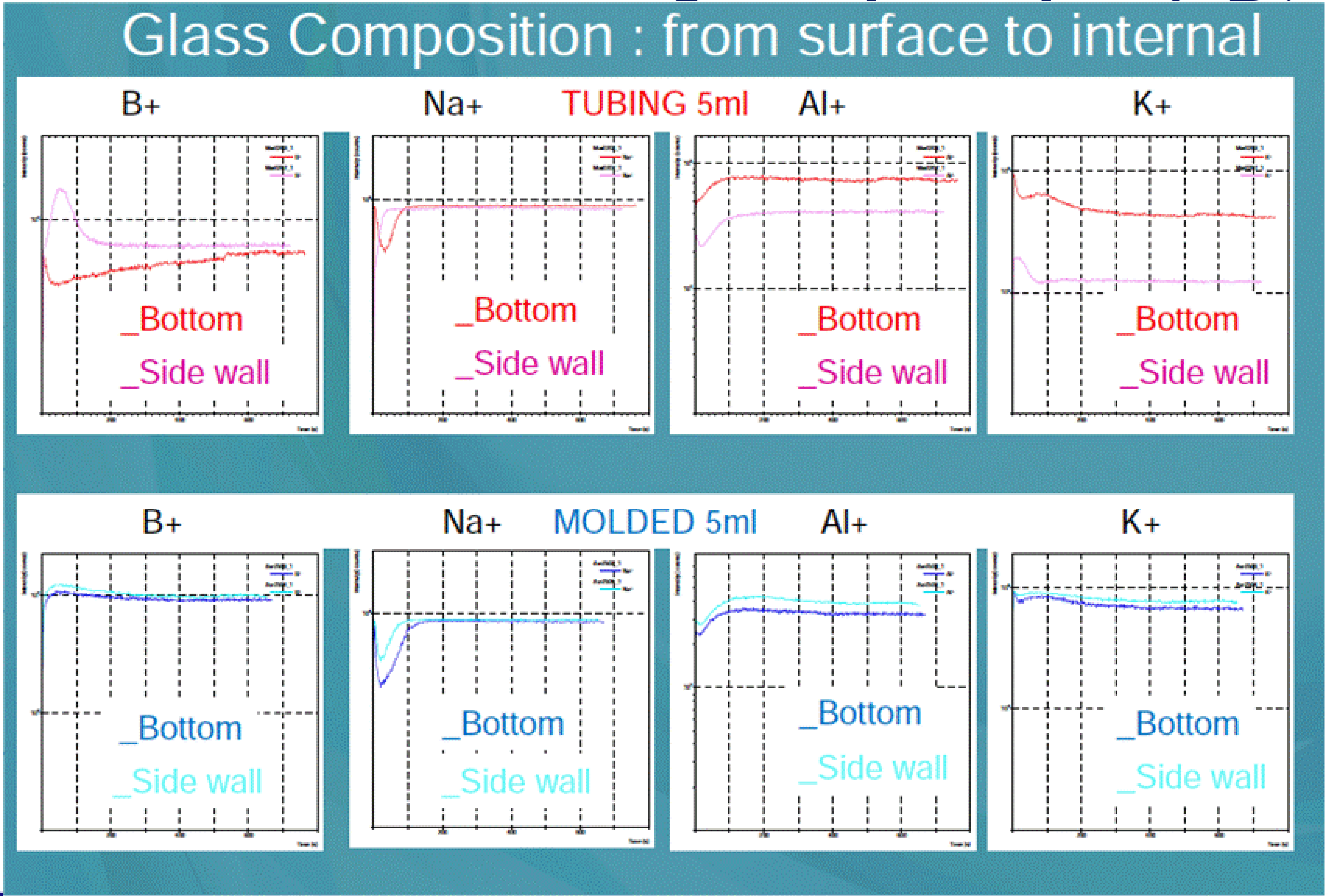
- Stronger network for bulk tubing glass, less modifiers
- Network modifiers needed to soften the glass to shape the vials for molded glass

Main elements (%)	Moulded Flint	5ml Tubing 1	10ml Tubing 2
SiO_2	69,1	70,8	74,3
Na_2O	6,1	7,1	7,2
K_2O	3,1	1,2	0,0
CaO	1,1	1,2	1,5
MgO	0,0	0,2	0,0
Al_2O_3	4,0	7,3	5,6
Fe_2O_3	0,02	0,03	0,02
B_2O_3	12,6	12,1	11,2
BaO	2,8	0,1	0,0
TiO_2	0,02	0,01	0,03
ZnO	1,1	0,0	0,0

Surface Composition Analysis: SIMS

- Surface SIMS analysis by Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS) **(ToF-SIMS)**
  - **4 glass vial samples : 2 molded and 2 tubing vials**
  - ToF-SIMS Profile by alternating analysis and abrasion cycles
  - **Analysis:**
    - Primary Ions Bi_1^+ 25 keV, I =1pA
    - Surface analyzed 100 x 100 µm², 128x128pixel
    - Positive Secondary Ions analyzed
  - **Abrasion:**
    - Primary Ions O_2^+ 500eV, I = 100nA
    - Surface : 300 x 300 µm²
  - **Cycle**
    - Analysis : acquisition of 1 scan (time of vol max = 100 µs)
    - Abrasion : 1.6s, Pause : 1s

Glass Composition : from internal surface to inside the glass (SIMS)



Surface Composition differences

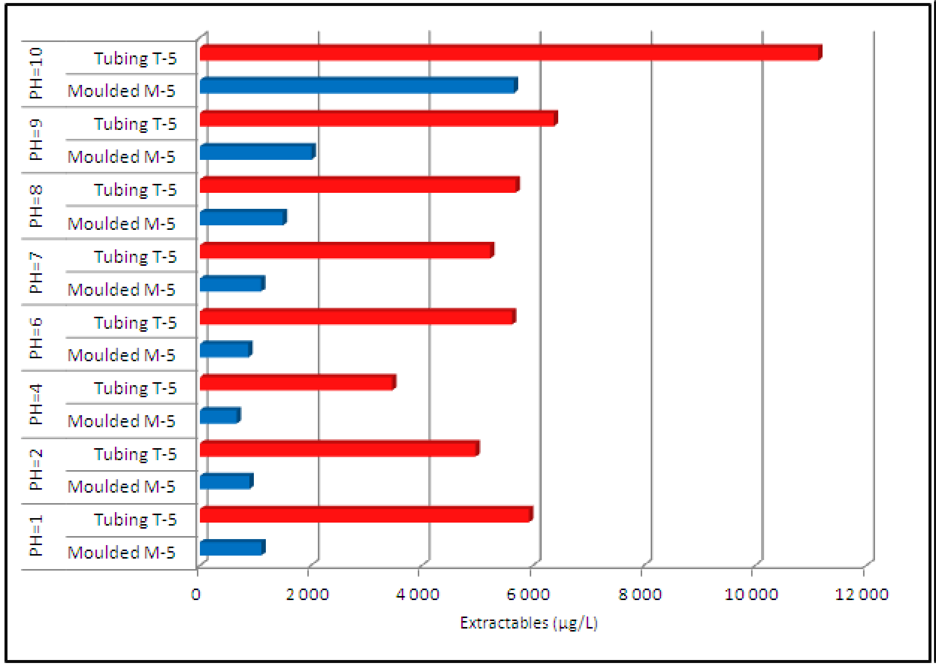
- All samples show a different surface composition from the bulk
- Small and curved samples may explain different bulk compositions between the bottom and the side wall
- More surface composition differences between side wall and bottom for tubing vials
- Sodium depletion at internal surface of vials for tubing and molded glass, resulted of process parameters

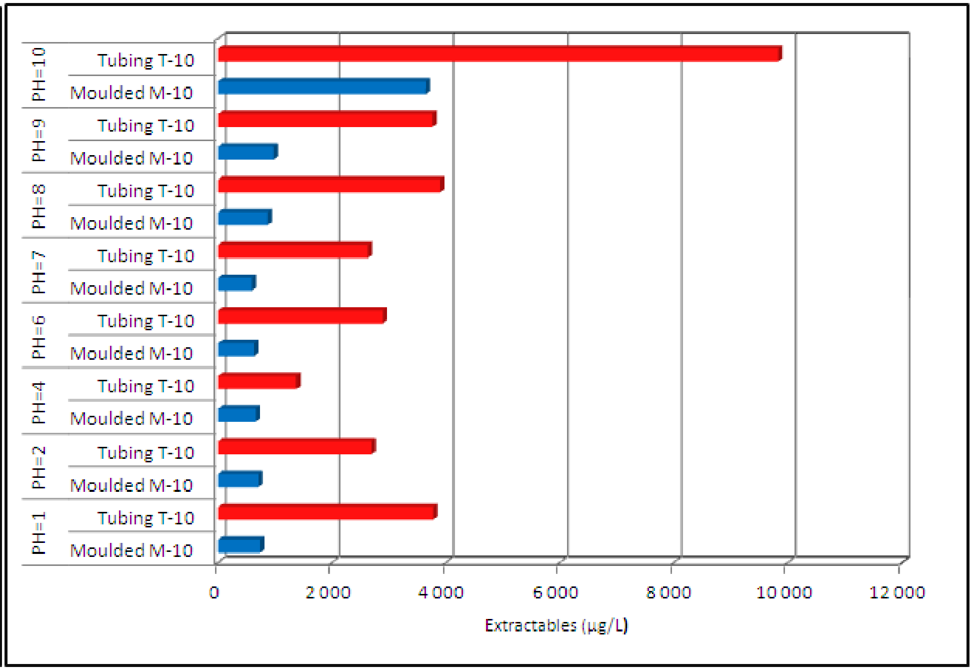
Extractable evaluation

Autoclave solution analysis with ICP

- **Solution Preparation**
  - Ultrapure water (18 MΩ.cm^{-1} resistivity) pH adjusted :
    - with HCl for acid pH
    - with NaOH for basic pH
- **Vials Extraction**
  - Filled at nominal capacity with the solution
  - Vials in autoclave at 121°C for 1h, Eur. Pharma. HR cycle , 3 to 5 measures for each pH
- **ICP Preparation**
  - Acidification HNO_3 Suprapur 2% before ICP measurements
  - Equipment Calibration with certified PE multielements solution
- **Results**
  - Equipment : Emission Spectrometry ICP (Perkin Elmer Optima 7300 DV)
  - Blank solution is analyzed and subtracted from autoclaved solutions.

Vial comparison : Total Extractables by ICP after 1h at 121℃ – 5 & 10ml





- Higher pH (10 or more) cause higher level of extraction
- Less elements extracted for Molded vials, at all pH
- Less extraction in volume for bigger vials (lower surface / volume ratio)

Extractable Analysis by element 5ml vial

	PH=1		PH=2		PH=4		PH=6		PH=7		PH=8		PH=9		PH=10	
Extracted Elements (µg/L)	Moulded M-5	Tubing T-5	Moulded M-5	Tubing T-5	Moulded M-5	Tubing T-5	Moulded M-5	Tubing T-5	Moulded M-5	Tubing T-5	Moulded M-5	Tubing T-5	Moulded M-5	Tubing T-5	Moulded M-5	Tubing T-5
Si	241	1632	203	1320	188	1118	368	3216	640	3443	818	3253	1079	3447	3481	6315
Na	272	1913	246	1647	185	1162	137	883	146	800	158	881	209	1026	471	1735
K	126	213	111	190	75	119	65	111	78	99	87	127	109	135	334	250
Ca	136	326	74	281	60	122	94	218	93	199	131	263	143	381	229	606
Mg	6	7	2	7	2	4	3	6	4	6	3	9	5	10	5	15
Al	58	771	54	541	34	221	62	509	4	84	87	511	140	630	339	1068
Fe	20	5	-	4	-	2	8	3	0	0	7	3	13	10	10	14
B	123	1058	99	939	51	691	62	639	73	585	99	578	158	675	421	1075
Ba	64	4	52	22	34	15	39	21	32	9	68	47	89	42	228	34
Ti	1	1	1	1	0	0	1	0	0	0	0	0	1	2	2	2
Zn	58	3	45	15	34	7	37	14	34	4	35	15	69	21	130	25
Extractables Total (µg/L)	1 105	5 931	887	4 967	663	3 459	872	5 618	1 101	5 227	1 491	5 684	2 012	6 377	5 648	11 137

- No visible attack of the glass, no flakes (methylene blue test shows nothing)
- Different local / surface glass compositions with tubing may cause higher extractions
- ICP detection limit on the blank solution 3σ<4µg/L (σ calculated on 10 measurements of the blank solution), Vial to vial variation +/- 10%

Extractable and leachable evaluation from USP <1660> Chapter

Molded Type I Glass

Extractables - Testing Plan

- **3 Solutions for New USP 1660 Chapter** to evaluate glass containers
  - KCl 0.9% pH 8.0 Autoclave for 2H at 121℃ (2 1h autocl ave cycles)
  - 3% Citric Acid at pH 8.0 for 24h at 80℃
  - 20 mM (1.5g/L) Glycine at pH 10.0 for 24h at 50℃
- NaOH (contains K) used to adjust pH →No measurements of Na, K in extracted solutions
- Autoclave samples closed with borosilicate beakers, other with aluminum foil
- **Glass Samples** : 100ml Type I molded vials from different glass makers
- **ICP Preparation**
  - Acidification HNO_3 Suprapur 2% before ICP-OES measurement
  - Equipment Calibration with certified PE multielements solution
- **Results**
  - Equipment : Emission Spectrometry ICP (Perkin Elmer Optima 7300 DV)
  - Blank solution is analyzed and subtracted from autoclaved solutions

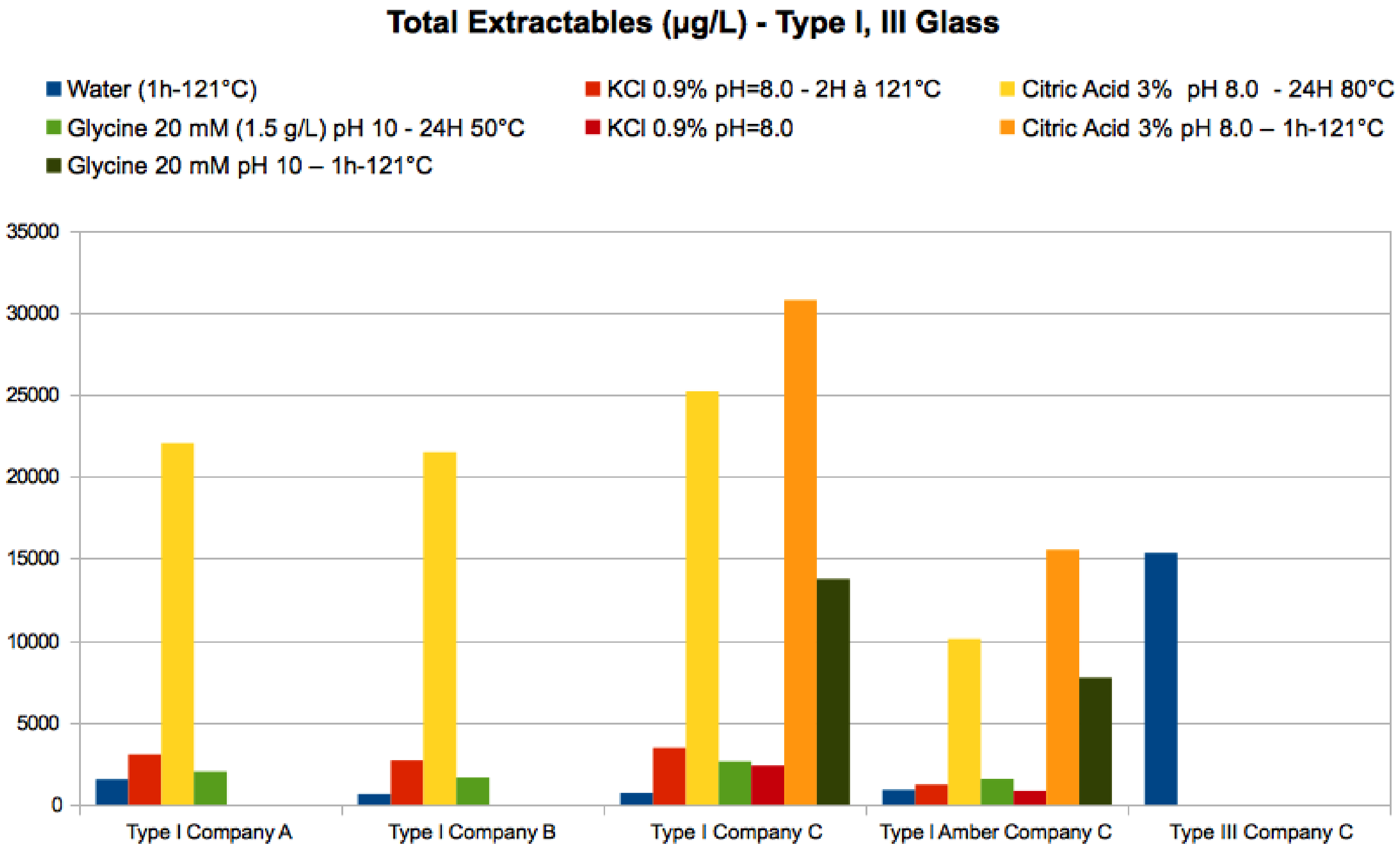
Results with Flint Glass SGD Type I

Extracted Elements (µg/L)	USP <1660> Methods: Water (1h-121°C)	KCl 0.9% pH=8.0 - 2H à 121°C	Citric Acid 3% pH 8.0 - 24H 80°C	Glycin 20 mM (1.5 g/L) pH 10 - 24H 50°C
Si	335	2,404	15,342	1,269
Na	126			
K	66			888
Ca	20	75	676	40
Mg	1	0	5	1
Al	41	258	2,146	106
Fe	1	2	19	0
B	70	419	4,197	182
Ba	44	214	2,012	102
Ti	0	1	13	0
Zn	18	87	796	39
Extractibles Total (µg/L)	**722**	**3,460**	**25,207**	**2,627**

Extracted Elements (µg/L)	1h 121°C Autoclave: Water (1h-121°C)	KCl 0.9% pH=8.0	Citric Acid 3% pH 8.0	Glycin 20 mM (1.5 g/L) pH 10
Si	335	1,649	18,379	9,218
Na	126			
K	66			2,002
Ca	20	50	847	172
Mg	1	0	7	2
Al	41	179	2,599	606
Fe	1	2	24	3
B	70	281	5,127	1,035
Ba	44	150	2,764	514
Ti	0	0	16	3
Zn	18	59	989	201
Extractibles Total (µg/L)	**722**	**2,371**	**30,752**	**13,754**
X vs water		**3**	**43**	**19**

- Citric acid extraction is quite extensive : modifiers and network formers
- The 3 solutions are more aggressive than water
- 1h-121℃ testing extracts more with Citric acid and Glyci n than couples temperature-time indicated in USP <1660>

Results



- Citric Acid at pH=8 is more aggressive than other solutions
- Flint glass extractables are similar with same chemical solution and testing procedures
- Extractions depend on : solution, glass composition and extraction conditions

Leachable Testing Conditions

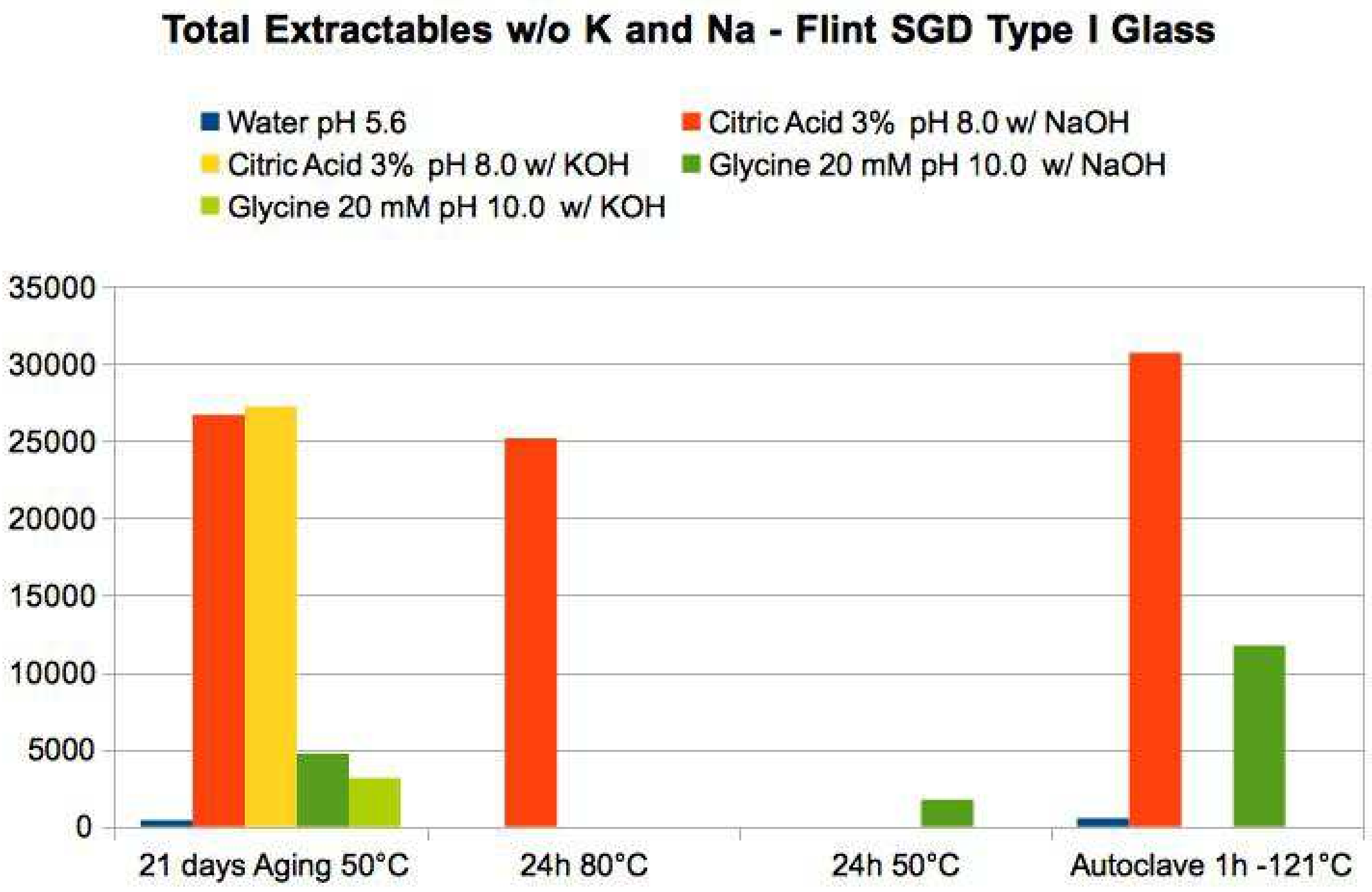
- **Same 1660 Solutions** as previous part, with pH adjusted 2 ways
  - Demineralized water at pH 5.6
  - 3% Citric Acid at pH 8.0, pH adjusted with NaOH
  - 3% Citric Acid at pH 8.0, pH adjusted with KOH
  - 20 mM (1.5g/L) Glycine at pH 10.0, pH adjusted with NaOH
  - 20 mM (1.5g/L) Glycine at pH 10.0, pH adjusted with KOH

- **Glass Samples** : 100ml Type I molded Flint SGD vials

All containers closed with Omniflex Helvoet stoppers

- **21 days aging at 50℃**

Results



- All results with Citric Acid are similar, higher than Glycin and water
- Adjusting the pH with KOH or NaOH gives similar results

Conclusion

Conclusion

- Interaction product/vial depends on composition and manufacturing process
- Process difference: 1 step forming process of molded vials seems to extract less glass formers than 2 step tubing process
- Tubing glass starts off better at cane stage but chemical robustness is impacted by converting step, which can differ from 1 supplier to another
- Due to its chemical robustness, molded can be considered as an alternative in aggressive extraction conditions
- Not all vials are equal for chemical resistance : depends on process, glass composition, solution in contact and storage conditions

Choice of a vial for pharmaceutical drug products is a complex decision depending on several parameters including extractables and leachables and chemical resistance

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