Glass Surface Technology

Extractables & Leachables 2013
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Influence of aggressive screening conditions and glass composition on the extractables and leachables from glass containers

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In partnership with SGD

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Agenda

- Background: Overview of pharma glass packaging options
- Comparison study between molded glass and tubing glass
- Extractables evaluation from USP <1660> Chapter
- Leachables
- Conclusion

Glass Surface Technology & SGD

Glass Surface Technology

- Technical Expertise in glass packaging and technology to solve packaging challenges
- Design and analysis of accelerated aging tests and extractions
- Design of solutions and coatings to improve inner durability and product contact

SGD

- Independent Glass Producer (formerly Saint-Gobain Desjonquères)
- Dedicated Pharmaceutical glass operations in France and Germany
- R&D lab is located in Mers-Les-Bains Facility, France, where Type I glass is produced

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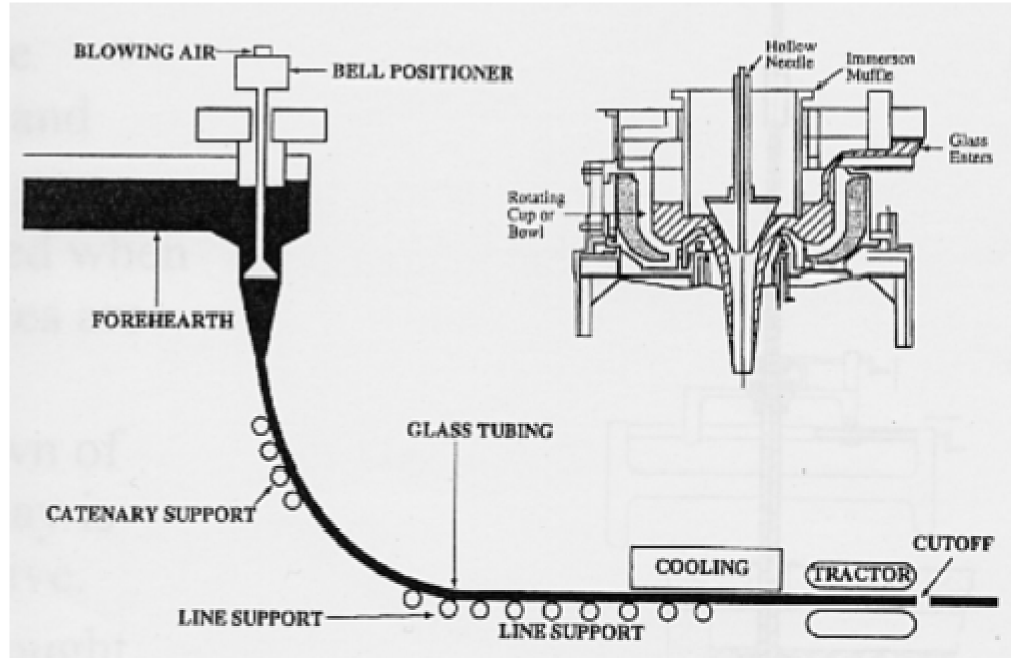
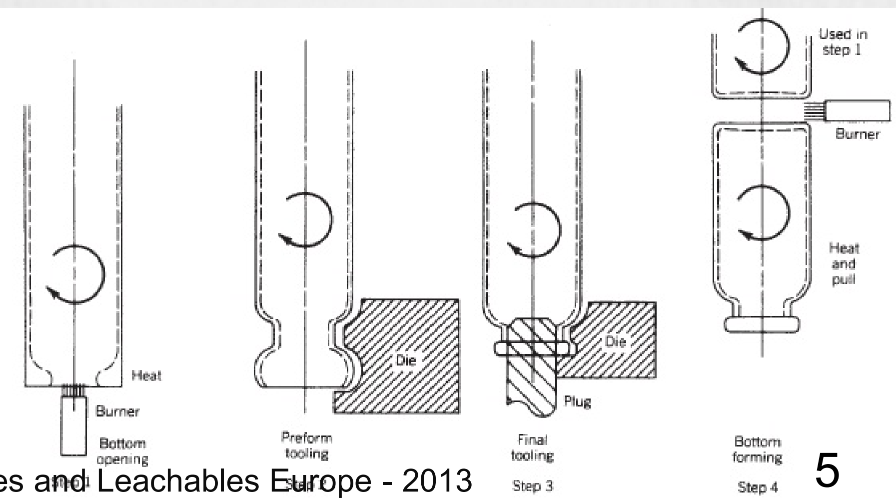
Tubing Glass

- 2 step process:
  - Cane manufacturing
  - Converting
- Capabilities:
  - Vials
  - Cartridges
  - Syringes





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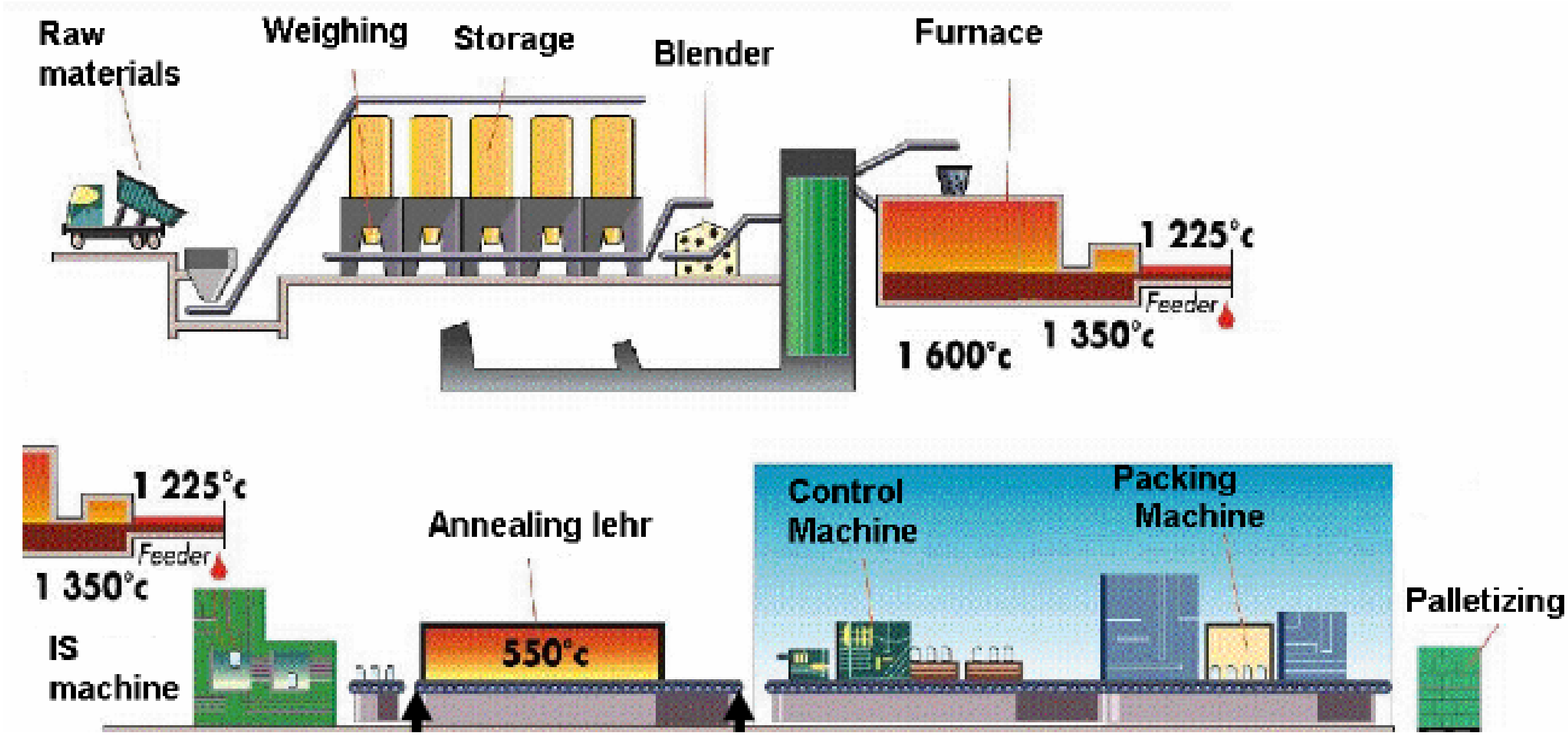
Molded Glass 1 step process



SGD Capabilities: Vials and IV bottles from 3 ml to 1 L.

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

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Mass Composition Analysis

<u>Method: X-Ray Fluorescence Spectrometry</u>

- Vials are cut in pieces
- Samples flattened at 750°C
- Surface is polished
- X-Ray Fluorescence on 34mm diameter samples
- FX S8 TIGER BRUKER

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Type I glass composition

- NEUTRAL GLASS is an alkaline borosilicate glass with main components of (typical moulded 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

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Composition by X-Ray Fluorescence Spectrometry

(%)	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

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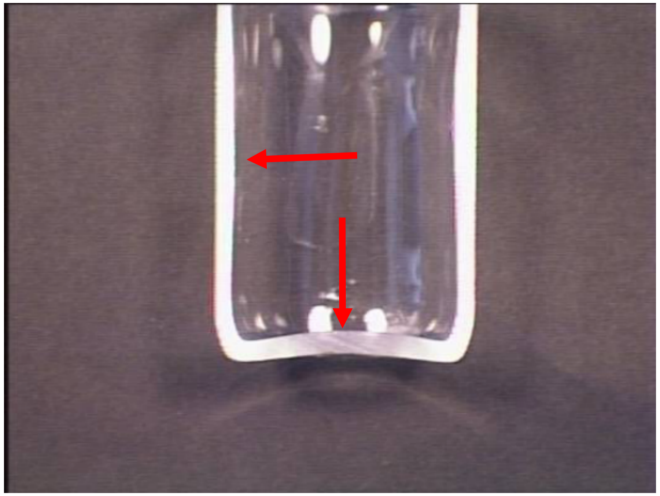
Surface Composition Analysis - SIMS

- Surface SIMS analysis by Time-of-Flight Secondary Ion Mass Spectrometry **(ToF-SIMS)**
  - **4 glass vial samples : 2 molded and 2 tubing vials**
  - ToF SIMS Profile by alternating analysis and abrasion cycles
  - **Analysis:**
    - Primary Ions Bi1+ 25 keV, I =1pA
    - Surface analyzed 100 x 100 µm², 128x128pixel
    - Positive Secondary Ions analyzed
  - **Abrasion:**
    - Primary Ions O2+ 500eV, I = 100nA
    - Surface : 300 x 300 µm²
  - **Cycle**
    - Analysis : acquisition of 1 scan
    - (time of max flight = 100 µs)
    - Abrasion : 1.6s, Pause : 1s



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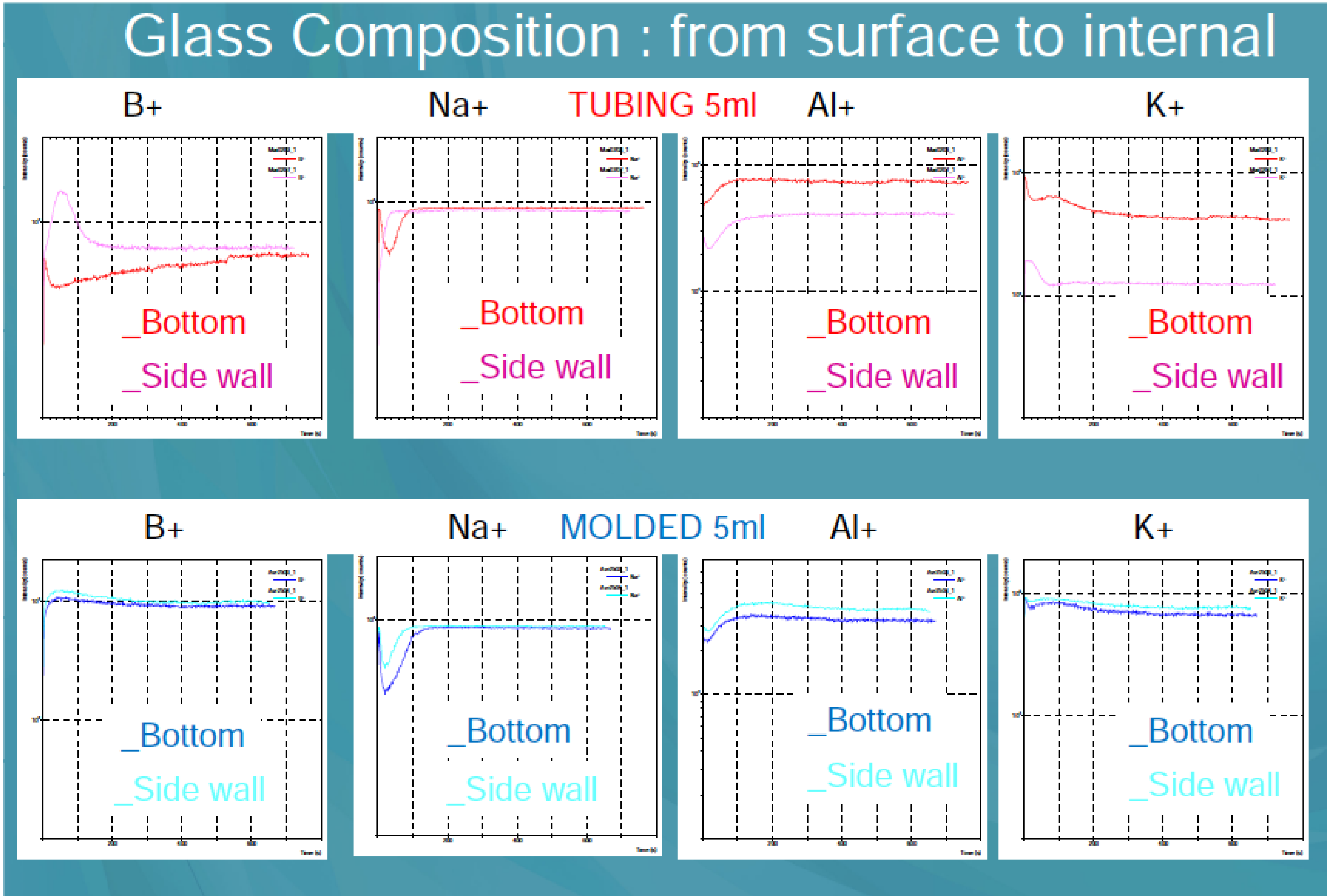
Glass Composition : from internal surface to inside the glass (SIMS)



Surface Composition differences

- All samples show a different composition at the surface 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 surface on the vial bottom for tubing, Boron-rich at the surface on side wall from Vial Forming
- Sodium depletion during forming for Asolvex Type I glass, both on bottom and on side walls (blowing effect)

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Hydrolytic Resistance Testing

- Standard test for Pharma Glass - Hydrolytic stability, expressed by the resistance to the release of soluble mineral substances into water under the prescribed conditions of contact between :
  - the inner surface of the container (Test A, surface test according to European Pharmacopeia, 3.2.1)
  - glass grains (Test B, glass grain test according to European Pharmacopeia, 3.2.1)

- The hydrolytic resistance is evaluated by titrating released alkali.

- The glass grain test is performed on crushed glass pieces, so represents the chemical resistance of the bulk glass

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Hydrolytic Resistance Comparison in (ml) HCl N/100

	Type I Molded	Tubing T-5
Grain Hydrolytic Resistance (ml)	0.53	0.43

- Better grain resistance for Tubing than molded because more network formers and less modifiers, Type I Limit 1 ml

	Type I Molded M-5	Tubing T-5	Type I Molded M-10	Tubing T-10
Vol 90% (ml)	8.1	8.3	12.25	12.4
Type I Limit	1	1	0.8	0.8
Surface Hydrolytic Resistance (ml)	0.15	0.50	0.17	0.41

- More critical for product interaction
- All vials are lower than type I surface limit, as required
- Better surface Hydrolytic resistance for molded vials

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Extractables evaluation

- Autoclave solution analysis with ICP
- **Solution Preparation**
  - Deionized water pH (18 MΩ.cm resistivity) adjusted :
  - with HCl for acid pH
  - with NaOH for base 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 for each pH
- **ICP Preparation**
  - Acidification HNO3 Suprapur 2% before ICP measurement
  - Equipment Calibration with certified PE multielements solution and acidification HNO3 Suprapur 2%
- **Results**
  - Equipment : Emission Spectrometry ICP (Perkin Elmer Optima 7300 DV)
  - The blank solution is analyzed and subtracted from the autoclaved solutions.

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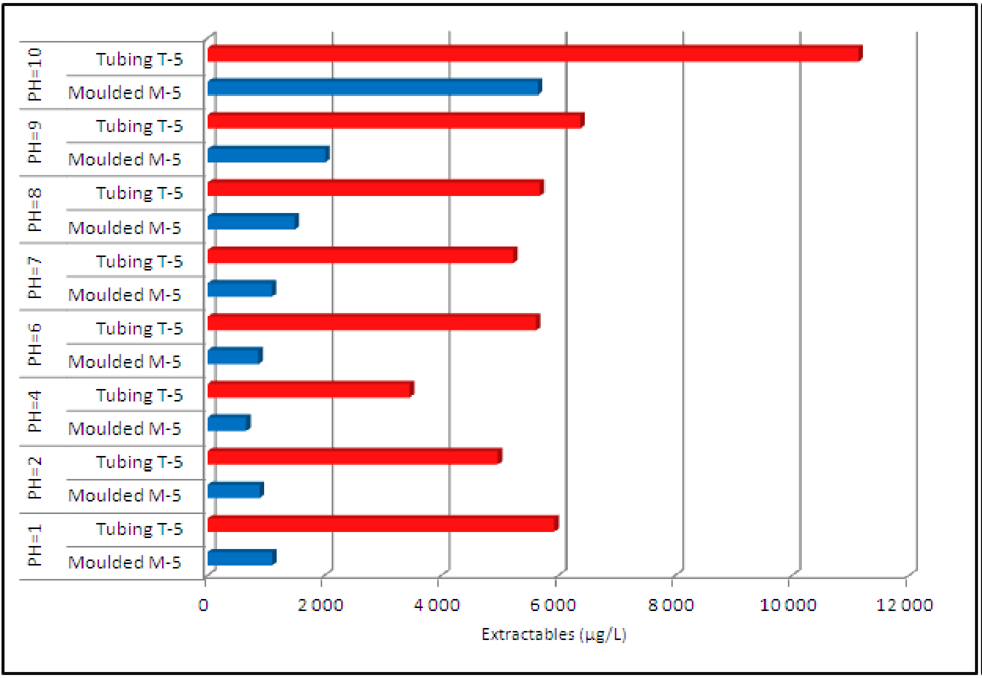
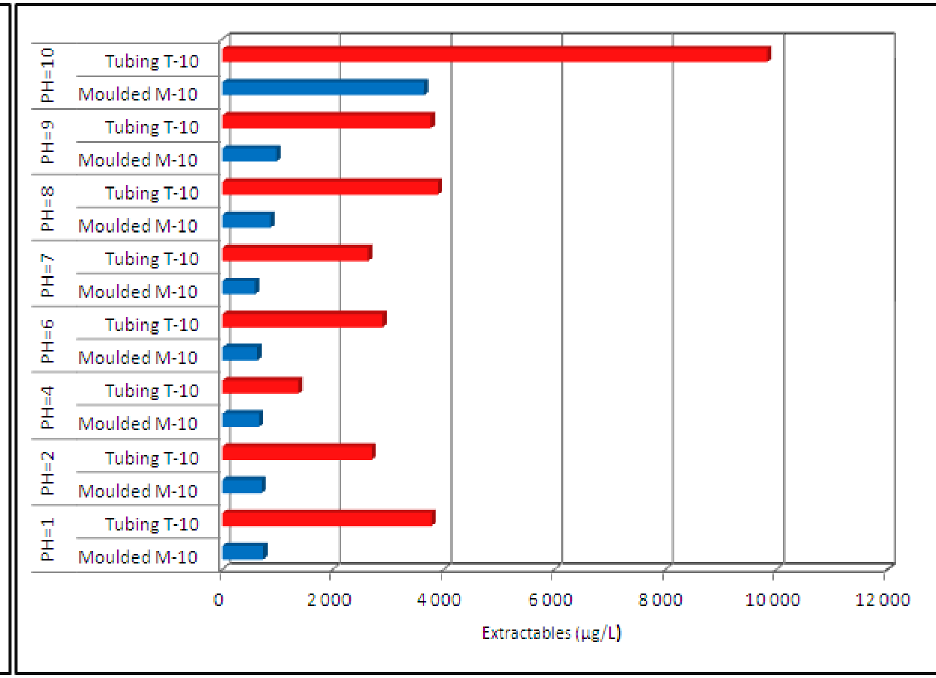
Vial comparison : Total Extractables by ICP after 1h at 121°C – 5 &10ml





- Less elements extracted with Molded vials, for all pH
- Higher pH (10 or more) causes higher extractions
- Less extraction in volume for bigger vials, surface/volume ratio lower

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Extractables Analysis by element– 5ml

	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 flake (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%

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Comments on Extractables

- **Tubing** : more Na and Ca extracted, but also Al, Si and B which are the glass network formers
- **Molded** : more K (not in the tubing 10ml glass composition) and Ba (traces in the tubing glass composition), which are mainly glass modifiers and less impacting the glass chemical robustness
- Bulk hydrolytic resistance is good for tubing, but surface resistance is not at the same level
- Local changes in glass compositions (processing effect) may explain some of the increased extraction

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Testing Plan

- **3 Solutions for New USP 1660 Chapter** to evaluate glass containers

- KCl 0.9% pH 8.0 Autoclave for 2H at 121°C (2 1h autoclave cycles)
- 3% Citric Acid at pH 8.0 for 24h at 80°C
- 20 mM (1.5g/L) Glycine at pH 10.0 for 24h at 50°C

- NaOH (contains K) added to bring pH to the right level, so Na and K not measured in extracted solutions
- Autoclave samples closed with borosilicate lab glass, Other vials closed with aluminum foil
- **Glass Samples** : 100ml Type I moulded vials from different glass makers
- **ICP Preparation**
  - Acidification HNO3 Suprapur 2% before ICP-OES measurement
  - Equipment Calibration with certified PE multielements solution and acidification HNO3 Suprapur 2%
- **Results**
  - Equipment : Emission Spectrometry ICP (Perkin Elmer Optima 7300 DV)
  - The blank solution is analyzed and subtracted from the autoclaved solutions

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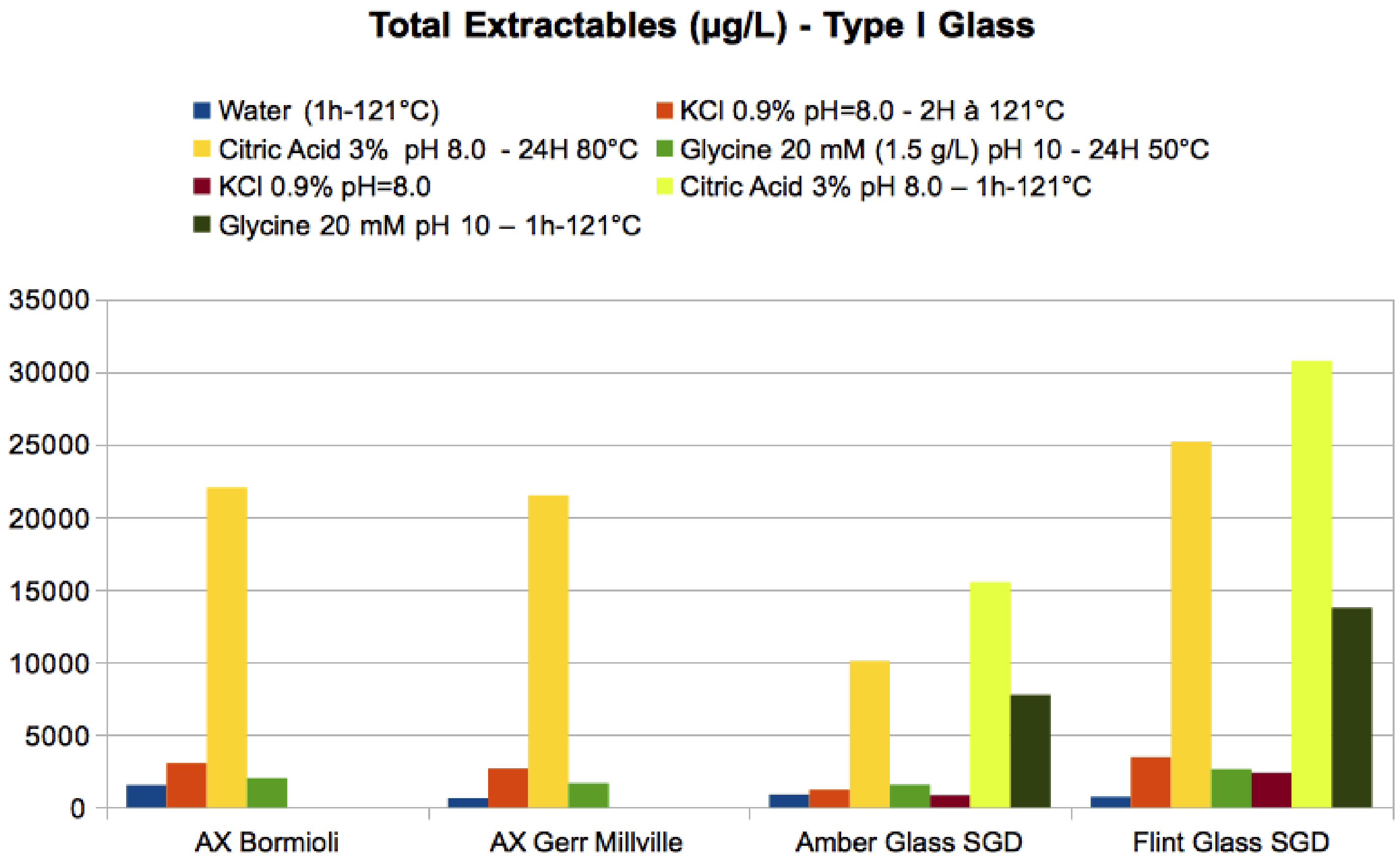
Results with Flint Glass SGD Type I

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 agressive than water
1h 121°C testing extracts more with Citric acid and Glycin than 24H at 80 and 50°C

Results



Citric Acid at pH 8 is more agressive than the other solutions
All Flint Glass are similar with same chemical solution and testing procedure
Extractions depend on : solution, glass composition and extraction conditions

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Results

Glass Composition				
(%)	Flint SGD	Amber SGD	Flint Gerresheimer Millville Wheaton (ref 1500)	Flint Bormioli (ref 1500)
SiO_2	69.1	65.4	66.3	67.4
Na_2O	6.1	7.3	9.6	8.3
K_2O	3.1	2.2	1.1	1.9
CaO	1.1	0.5	0.8	1.3
MgO	0.0	0.0	0.5	0.3
Al_2O_3	4.0	6.6	5.5	5.6
Fe_2O_3	0.02	0.86	0.06	0.03
B_2O_3	12.6	11.6	12.8	12.0
BaO	2.8	2.0	2.7	2.7
TiO_2	0.02	2.70	0.02	0.05
ZnO	1.1	0.7	0.6	0.4

All glass are type I glass (Hydrolytic Resistance better than limit)

Composition differences (Flint vs. Amber) may impact chemical resistance

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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 moulded Flint SGD vials

All containers closed with Omniflex Helvoet stoppers

21 days aging at 50°C

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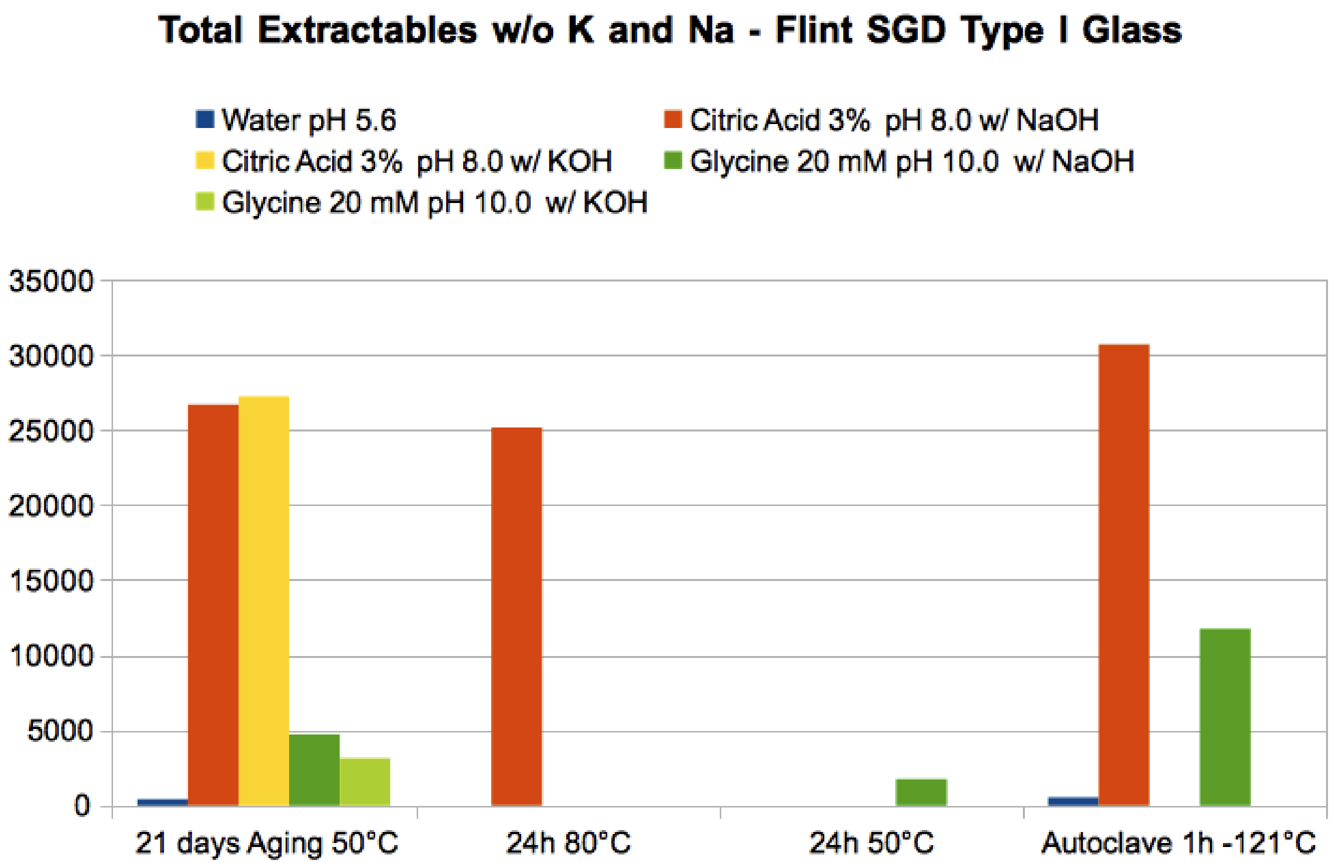
Results



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

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Conclusions

- Choice of a vial is a complete decision depending on several parameters, including Extractables and Leachables and chemical resistance :
  - Product interaction with the vial depends on 1) composition 2) how it was formed
  - 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 : it depends on process, glass and solution composition, as well as storage conditions

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