Review of corrosion principles that determine E&L concentrations of glass containers

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Session 3: Glass

Glass is the ideal material for parenteral packaging

Glass Attributes	Parenteral Needs
Chemically durable	• Acid, Base, and Neutral solutions
Hermeticity	• Gas impermeable
High elastic modulus	• Survive high stresses
Transparency	• Ability to view/inspect drug
Low expansion	• Survive rapid thermal cycles
Thermal stability	• Enable depyrogenation
Viscous phase transitions	• Formable into complex shapes
Sterilizable	• Able to be sterilized by many methods

Pharma measures Extractables & Leachables as signals of quality and chemical durability

- Extractables refer to components of materials used in the manufacturing, packaging, or delivery that may enter the product under accelerated conditions
- Leachables refer to components of those contact materials that enter the product under usual manufacturing, delivery and use conditions
- These might include:
  - Si, Al, B, Na, K, Mg, Ca, etc. from the glass
  - Silicones applied to glass surfaces as lubricants for plungers
  - Zn, Al, P from elastomeric closures
  - Organic species from materials used to fill and deliver the drug product
- For glasses, extractables and leachables generally originate in topmost <100nm

Despite current high-level understanding, observations seem to contradict established corrosion trends

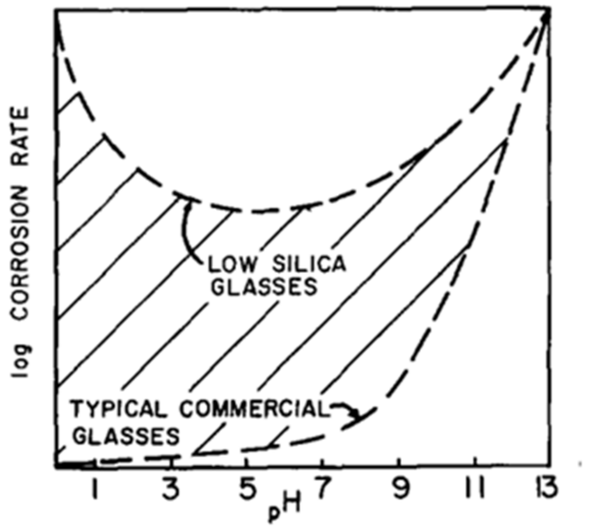
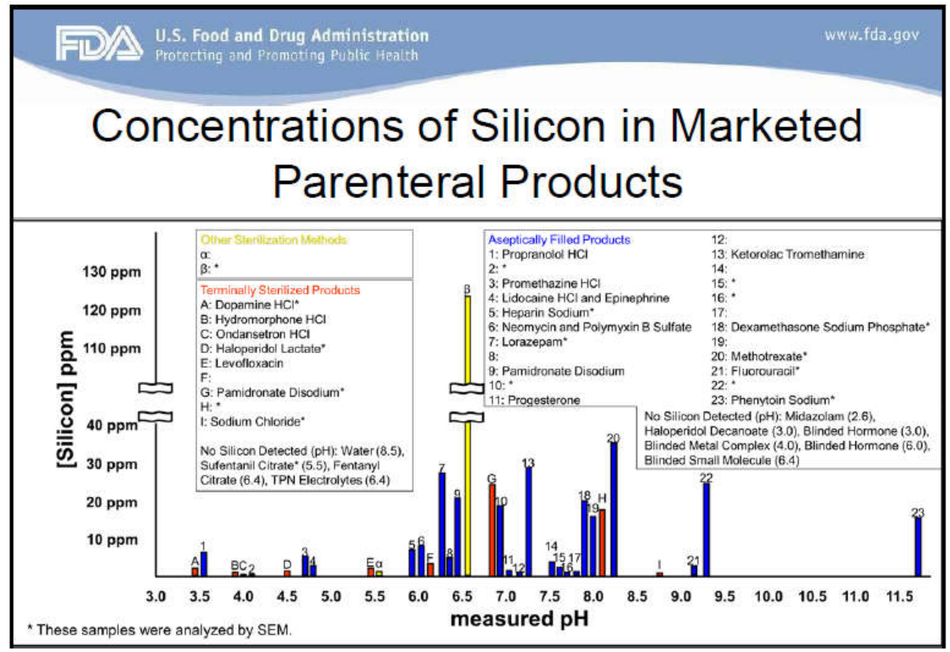


Fig. 11. Relationship between pH and corrosion rate for a variety of glasses.

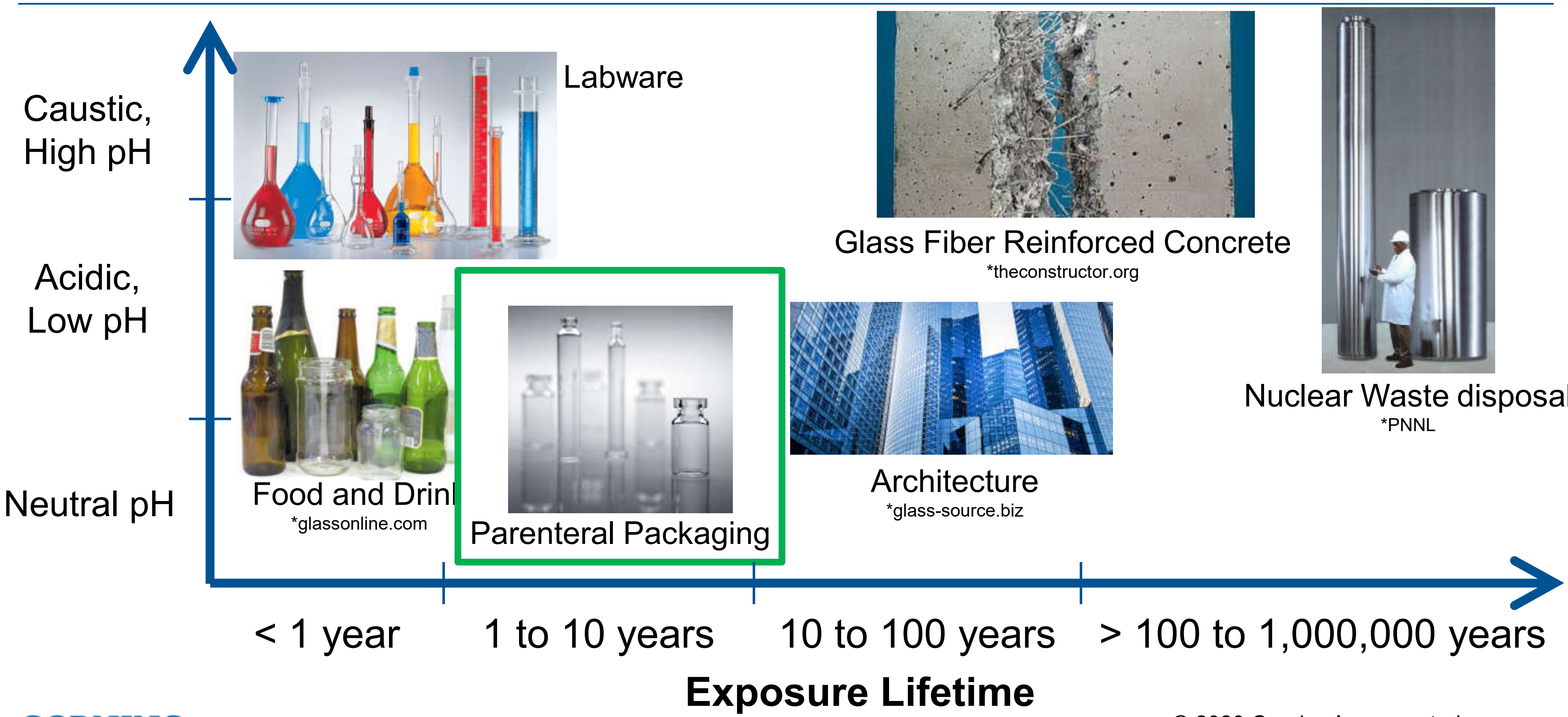
Adams, P. B., *J Non-Crystalline Solids* **1984,** *67* (1–3), 193-205.



Stephens, O., *PDA Packaging Conference.* Washington, DC, **2014.**

A linkage between glass corrosion mechanisms and observed extractables trends is needed.

Deep understanding of corrosion mechanisms is possible for prediction of long lifetimes of many glass products



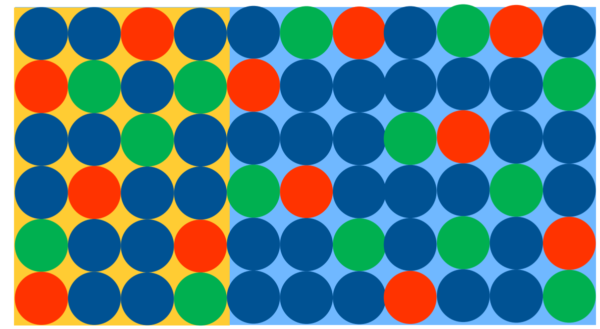
GOAL: Connect glass corrosion mechanisms to trends in measurable E&L concentrations

Outline:

- Review individual mechanisms, relationship to pH, and glass surface response
- Illustrate kinetic- and thermodynamic- relationships while applying Transition State Theory (TST)
- Key assumptions to enable modeling (across t, T, pH, SA/V, solution chemistry)
- Finally, compare the E&L behavior of aluminosilicate containers to conventional aluminoborosilicate containers

Corrosion by aqueous solutions: Acids and Neutral

- Neutral & acidic solutions corrode glass through hydration / exchange reactions



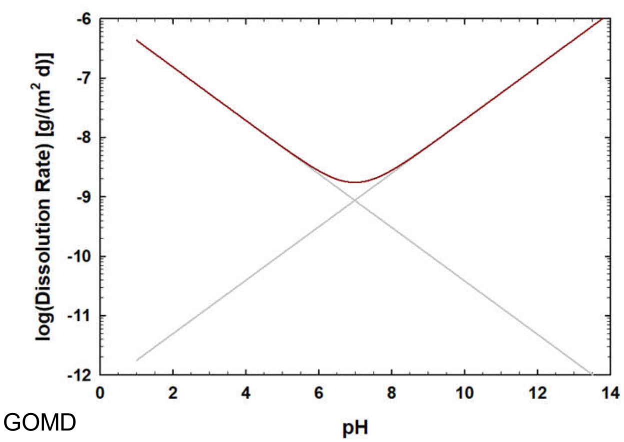
$$\equiv Si \quad O \cdot Na \; + \; H_2O \rightarrow \equiv Si \quad OH + Na^+_{solution} + OH^-$$

$$\equiv Si \quad O \cdot Na \; + \; H_3O^+ \rightarrow \equiv Si \quad OH + Na^+_{solution} + H_2O$$

$$\equiv Si \quad O \cdot Na \; + \; H^+ \rightarrow \equiv Si \quad OH + Na^+_{solution}$$

Slower corrosion rates, lower extract concentrations, passivating surface layers

- Corrosion rates increase with increasing reactant concentrations (H^+, H_3O^+; decreasing pH)



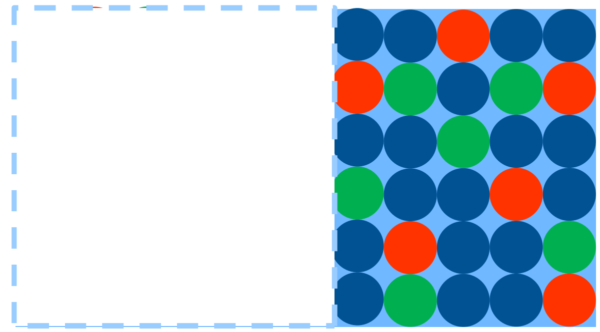
D. Strachan, '*Glass Dissolution as a function of pH: Mechanisms and Future Experiments*' 2018, ACerS GOMD

Corrosion by aqueous solutions: Bases

- Caustic (or basic) solutions corrode glass through network hydrolysis reactions

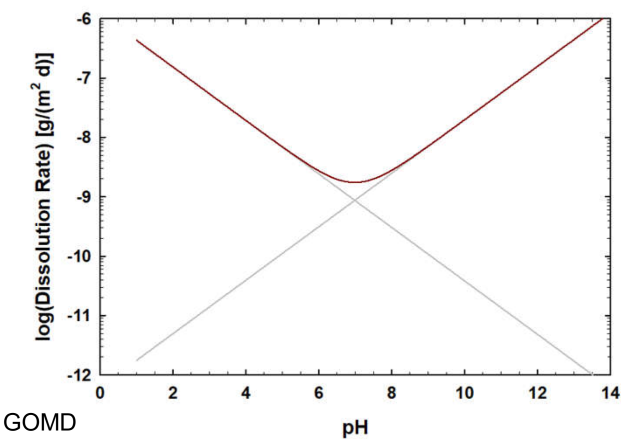
$$\equiv Si \quad O \quad Si \equiv + OH^- \leftrightarrow \equiv Si \quad OH + \equiv Si \quad O^-$$

$$\equiv Si \quad O \quad Si \equiv + H_2O \leftrightarrow \equiv Si \quad OH + \equiv Si \quad OH$$



Faster corrosion rates, higher extract concentrations, extract ratios similar to bulk glass

- Corrosion rates increase with increasing reactant concentrations (OH^-; increasing pH)

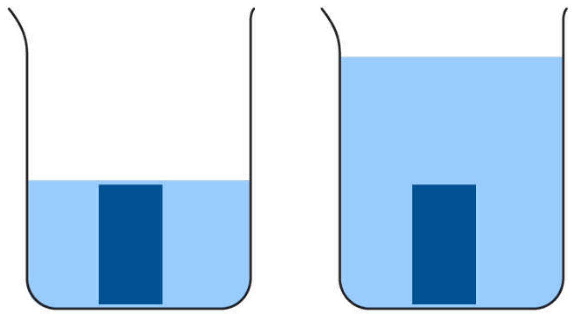


D. Strachan, '*Glass Dissolution as a function of pH: Mechanisms and Future Experiments*' 2018, ACerS GOMD

Normalization of corrosion data greatly aids in understanding

Surface area:

- Solution concentration
  vs. Glass mass dissolved
  vs. Altered thickness



Concentration of element (i)	>
Mass of dissolved glass	=
Thickness of corrosion layer	=

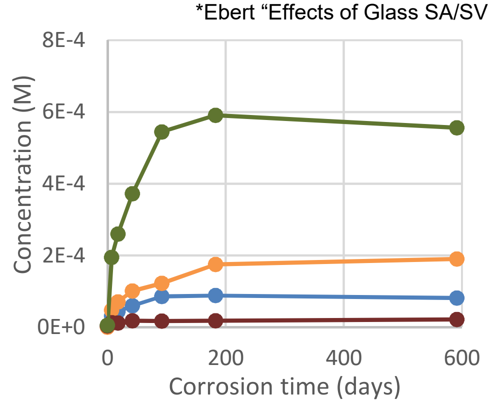
SA/V allows for scaling of 'material response' across fill volumes and container size

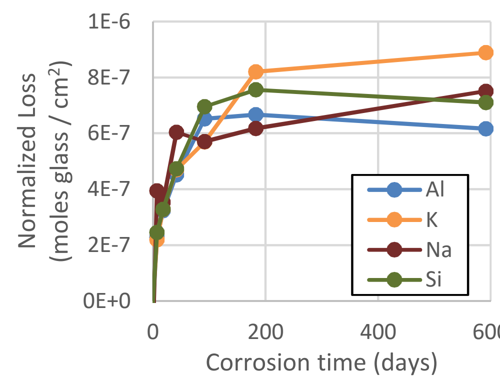
Glass Chemistry / Normalized Loss:

- Normalized loss is helpful… requires uniform surface chemistry

$$NL(i) = \frac{m_i \quad m_{i,t_0}}{SA \cdot f_i} = \frac{c_i \quad c_{i,t_0}}{SA/V \cdot f_i}$$

*Ebert "Effects of Glass SA/SV ratio on Glass corrosion" 1994.

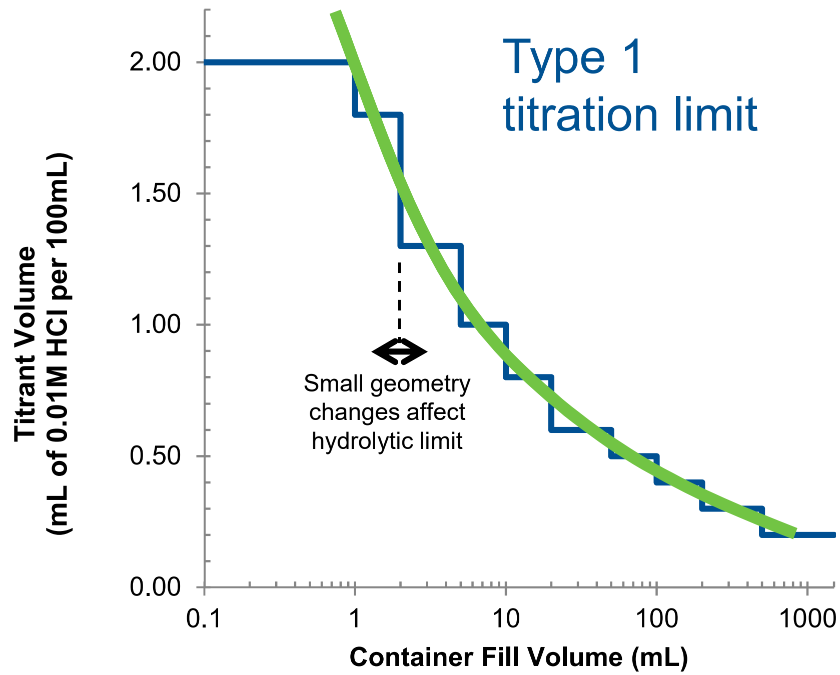




Normalized loss can indicate congruency and solution saturation information

Example of SA/V normalization for surface hydrolytic limits

- Pharmacopeial hydrolytic tests are currently bracketed by fill volume, which causes discrete ‘jumps’ in the limit for small changes in geometry
  - USP<660>, Ph.Eur. 3.2.1, ISO4802
- The overall trend in limit versus container size reflects a constant material response with variable dilution
- Normalizing titration volume response to SA/V would allow all containers to be compared to a single accept/reject limit and reduce confusion

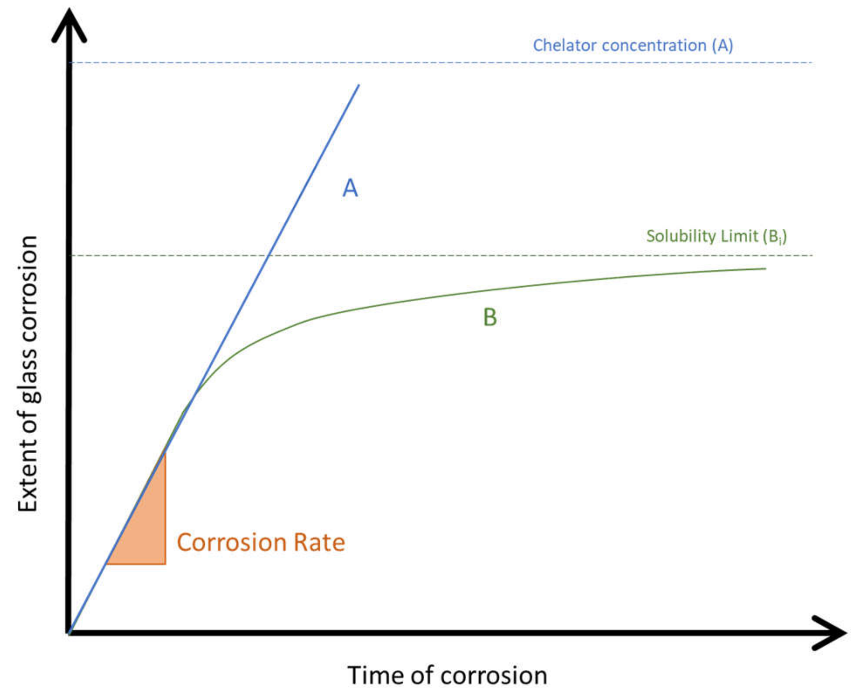


Corrosion process described by 'rate' and 'extent'

Transition State Theory mathematically describes changes in corrosion rate over t, T, pH, SA/V and solution chemistry

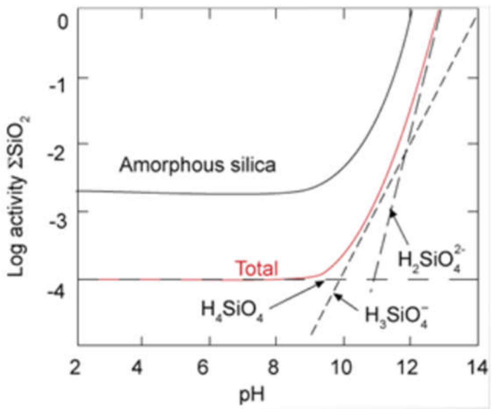
$$R = k_i a_{H^+}^{\pm\eta}\left[exp\left(\frac{E_a}{RT}\right)\right]\left[1 \quad \frac{Q}{K}\right]$$

- Corrosion <u>rates</u> follow Arrhenius relationships
- The <u>extent</u> is influenced by solution chemistry (corrosion product solubility, presence of chelators, etc.)
- The initial rate (aka forward rate) can be difficult to observe at room temperature



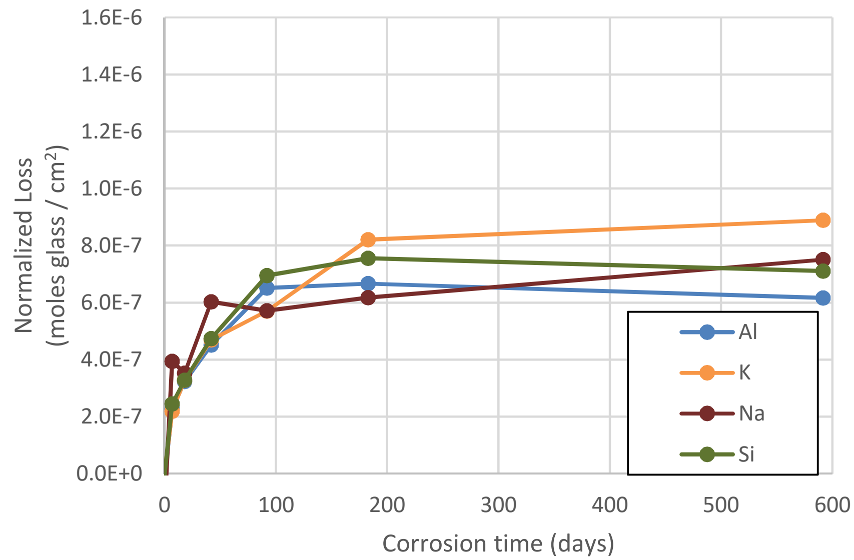
Non-linear kinetic trends

- The solubility of silicic acid is low for most neutral and acidic conditions



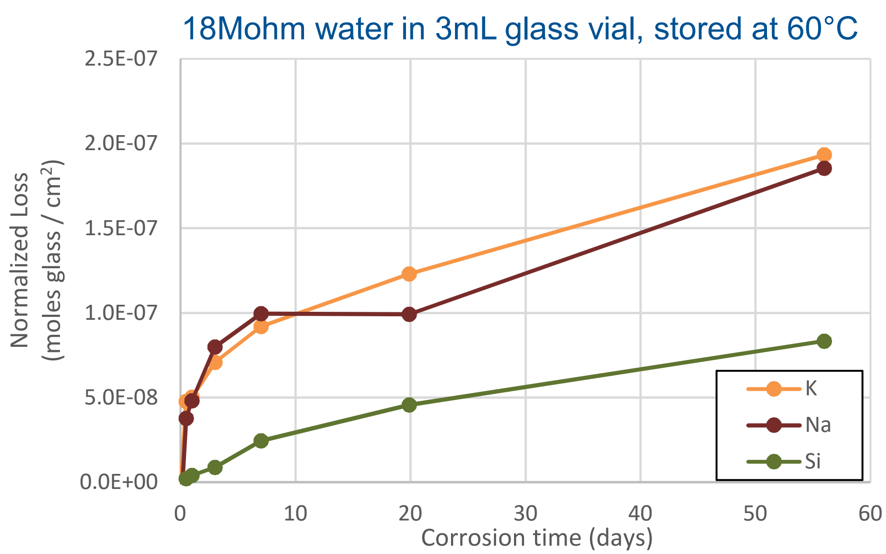
- Corrosion slows as concentrations increase (Q) relative to solubility (K), following TST
- Chelators complex with glass extracts, changing their activity

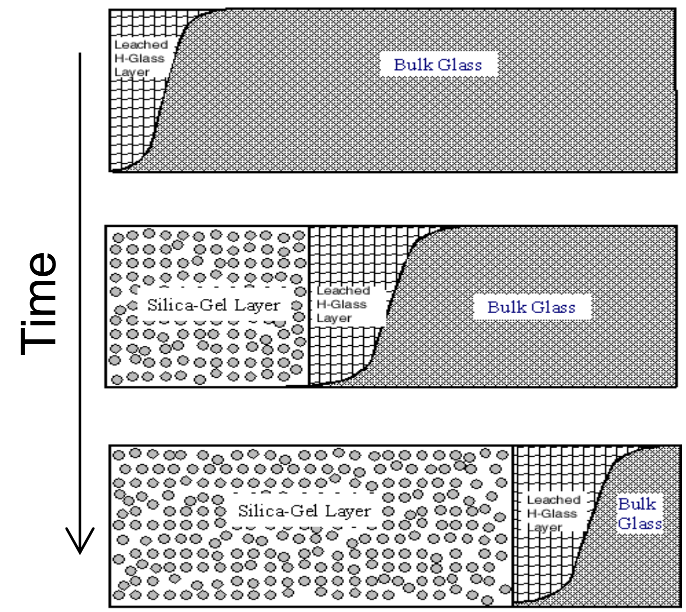
0.1M NH_4OH in 3mL glass vial, stored at 37°C



Non-linear kinetic trends

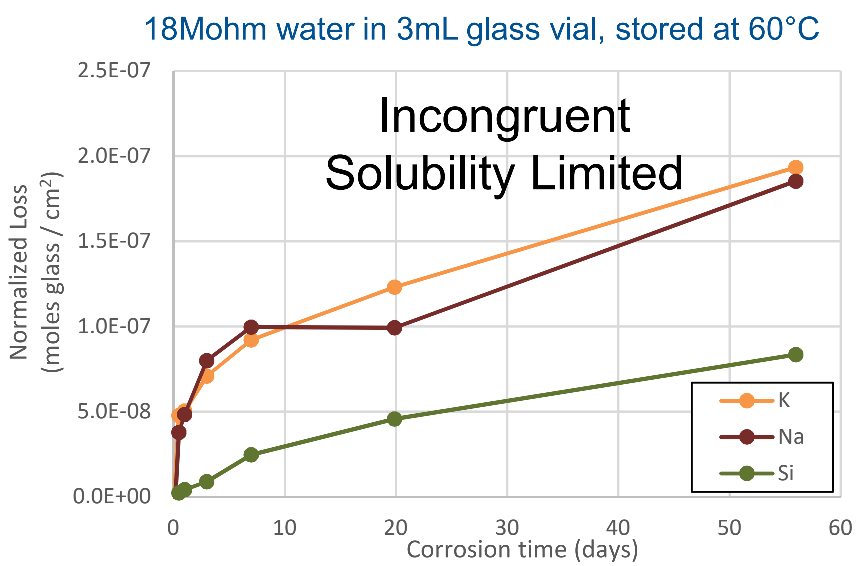
- Incongruent leaching leads to increasingly-thick leach layer
- Time required for diffusion of reactants and products increases following root-time kinetics

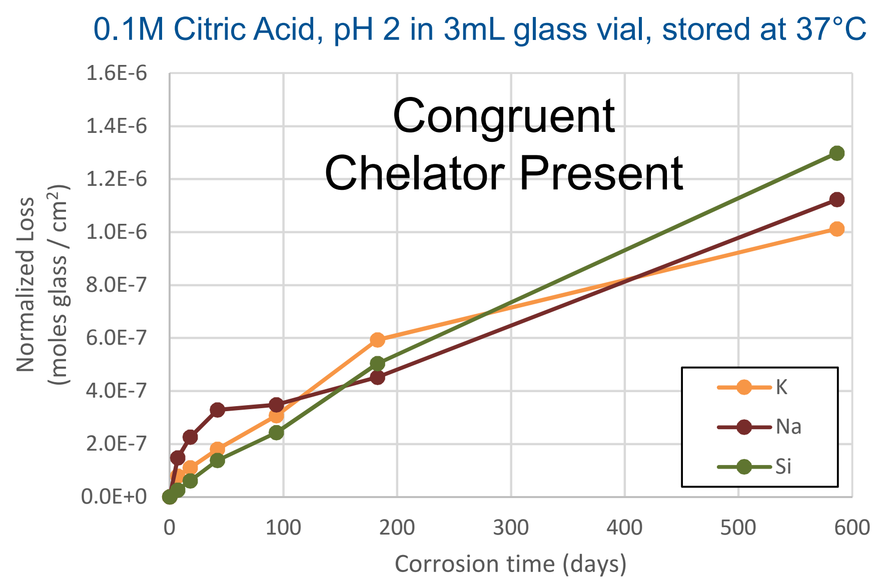




* Pantano

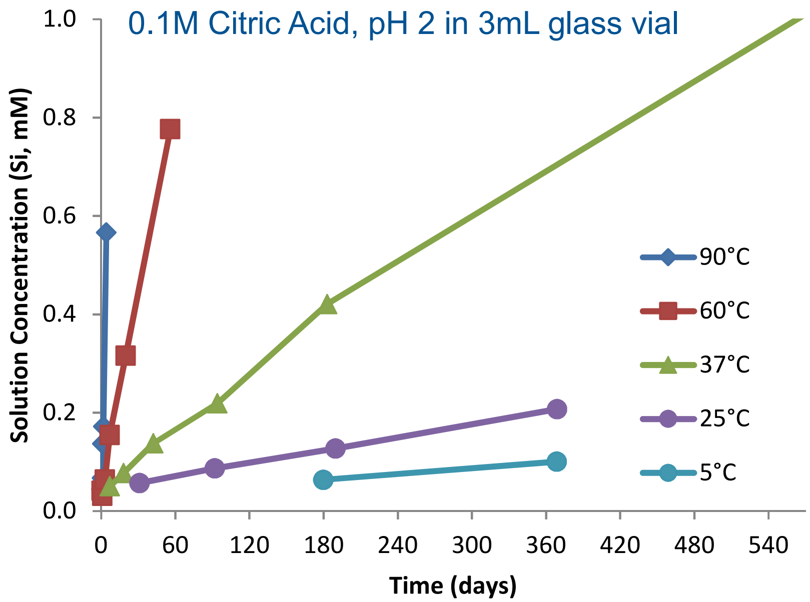
Chelators change E&L trends by reducing activity of products

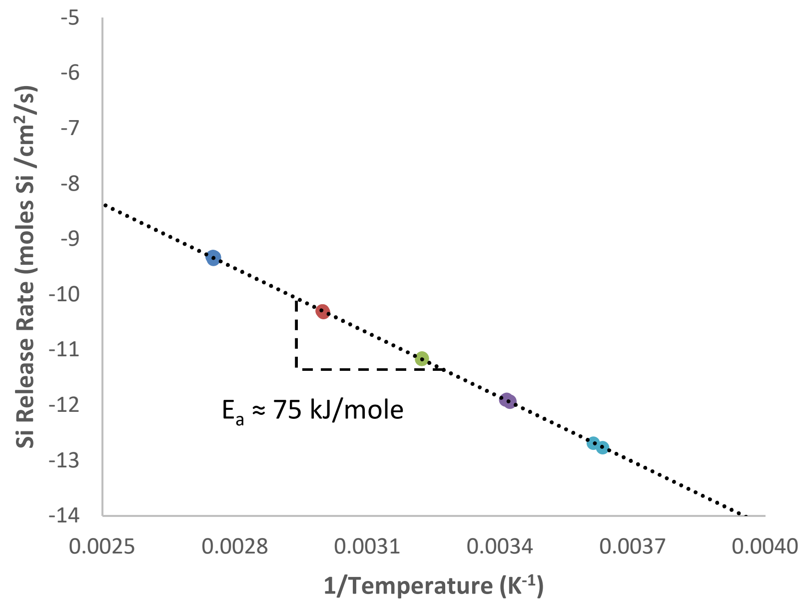




- Citrate, Acetate, and EDTA are common chelators in pharmaceutical solutions
- Chelators can influence congruency and increase extent of corrosion

T-dependence of rate (separate from solubility) follows Arrhenius function





$$R = k_i a_{H^+}^{\pm\eta}\left[exp\left(\frac{E_a}{RT}\right)\right]\left[1 \quad \frac{Q}{K}\right]$$

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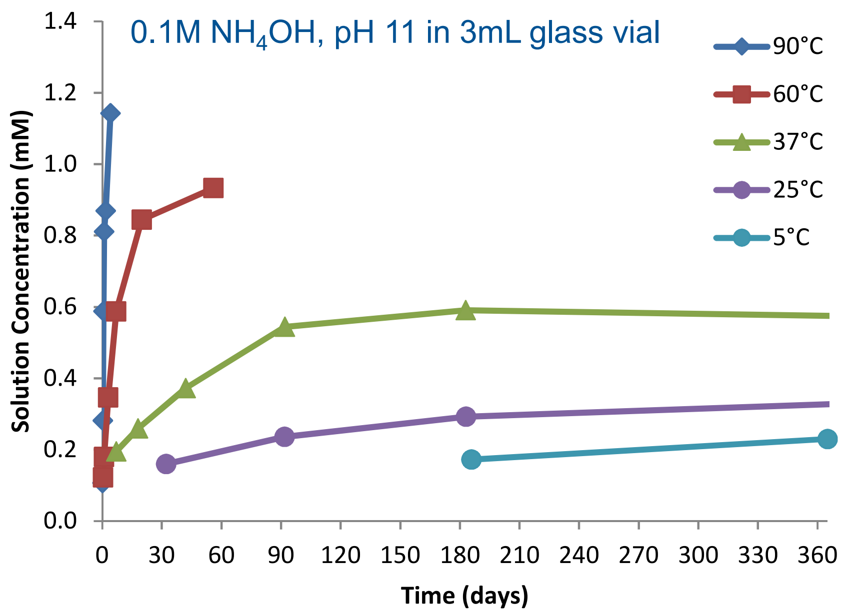
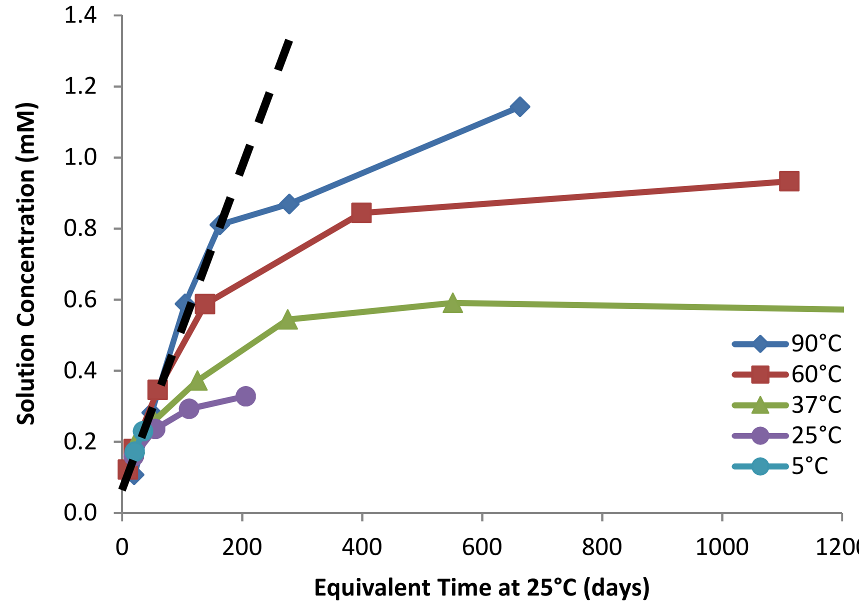
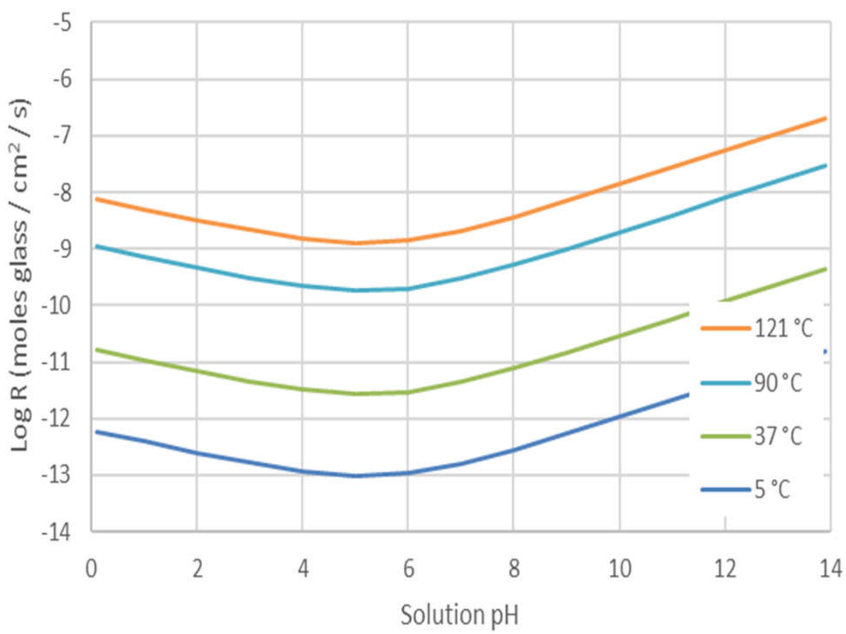




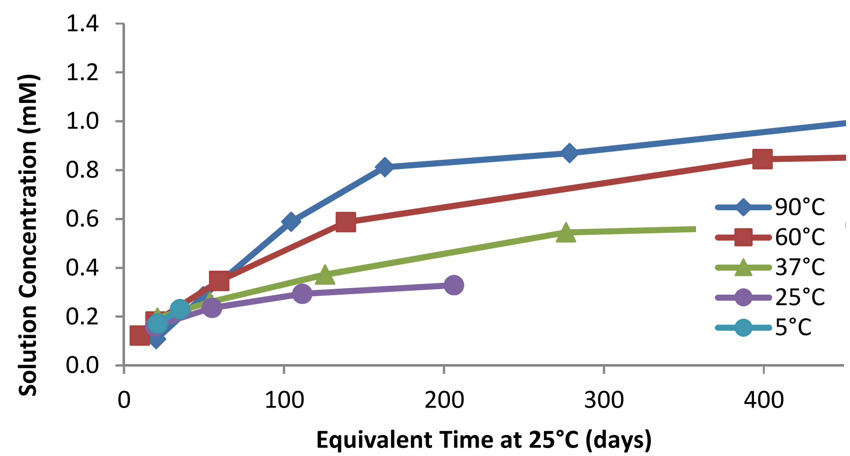
$$R = k_i a_{H^+}^{\pm\eta} \left[exp\left(\frac{E_a}{RT}\right) \right] \left[1 \quad \frac{Q}{K} \right]$$

- Initial rate is captured by Arrhenius function
- Solubility limits are also temperature-dependent

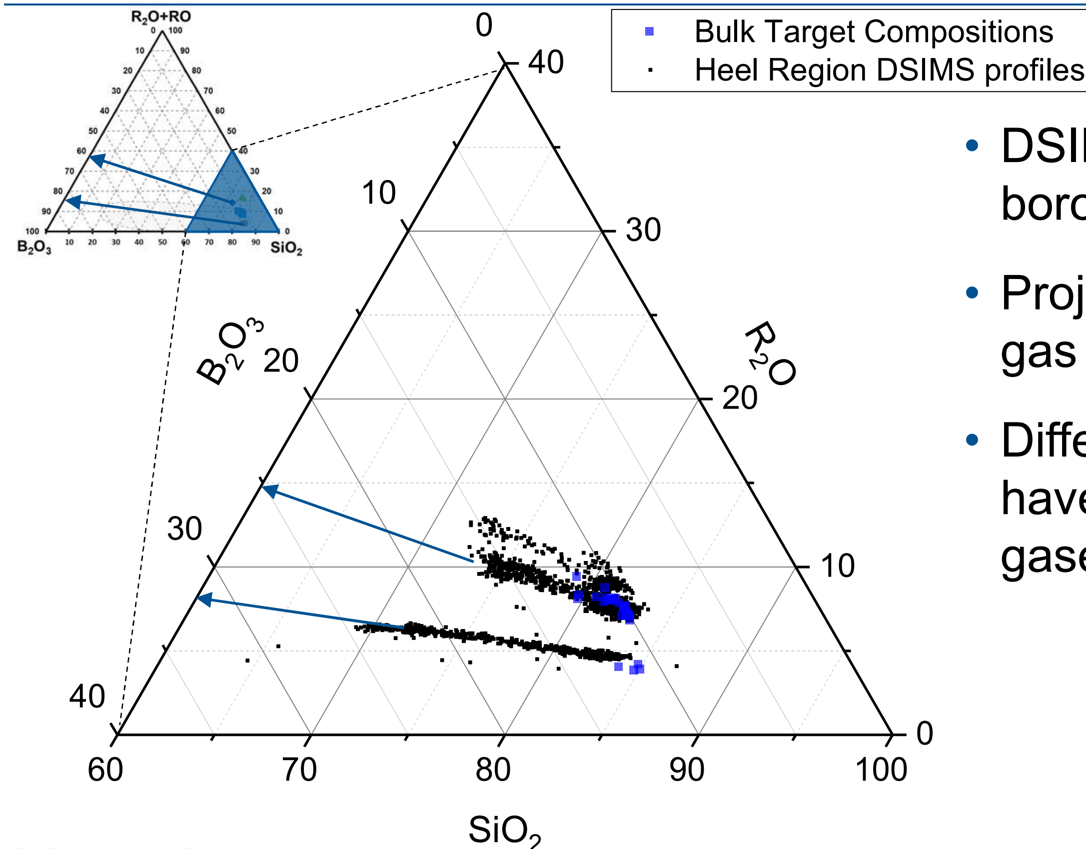
Initial rate (separated from solubility) varies smoothly with pH and T



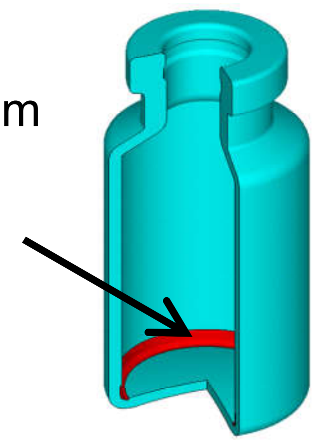
- This fundamental behavior is consistent with any high silica content glass
- The forward rate is difficult to distinguish in pharma examples because solubility limits are so low. But, this is overcome by merging data from several times and temperatures



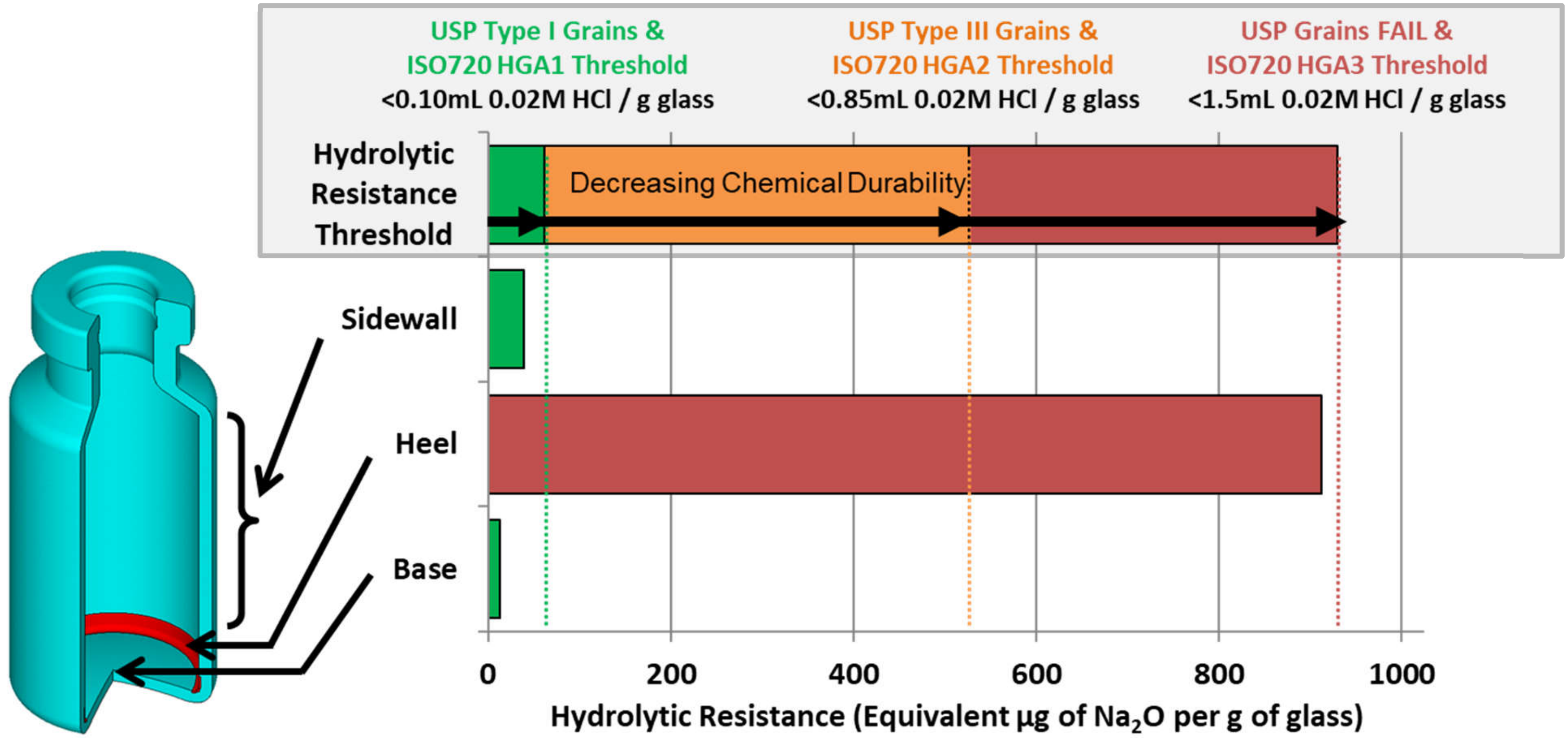
Inner surface contains a wide range of glass compositions in drug contact



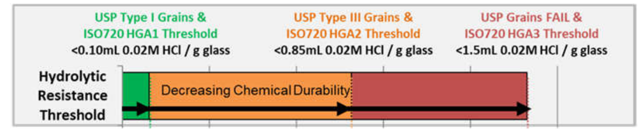
- DSIMS profiles of commercial borosilicate container heels
- Projections illustrate the equilibrium gas phase Na/B ratio
- Different bulk glasses have different equilibrium gases



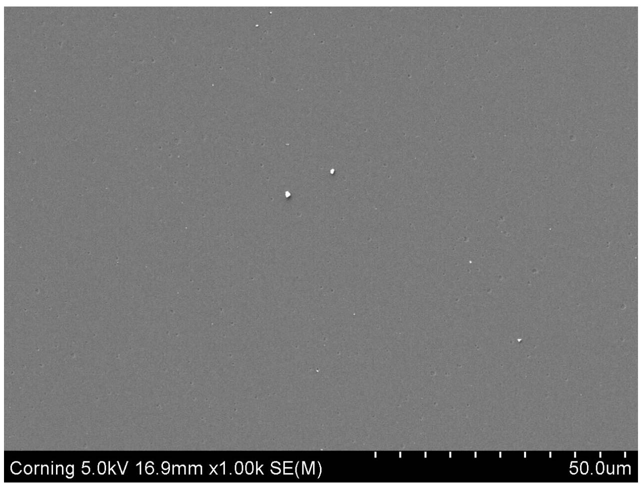
These chemistry changes greatly degrade chemical durability



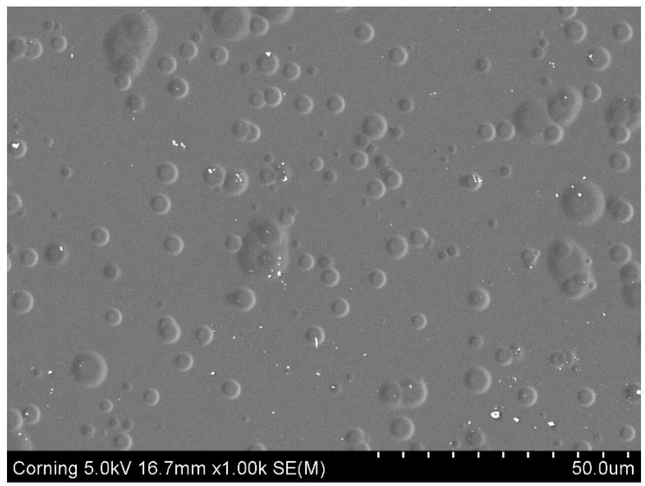
Examples of surface features from regions of different surface chemistry



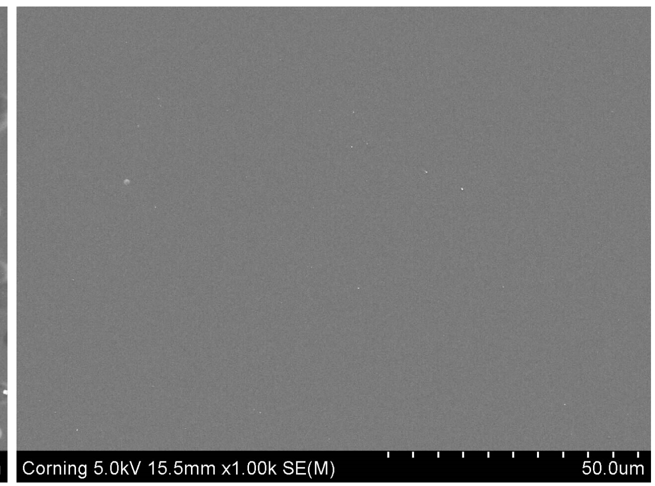
Borosilicate vial, filled with pH 8.2 Glutaric Acid solution, 60 days at 60°C



Sidewall



Heel / Lower Sidewall



Center of Base

- After exposure to liquid, the heel shows surface texturing from dissolution of some modified areas of the surface

A 21st Century Pharmaceutical Glass

CORNING Valor™ Glass

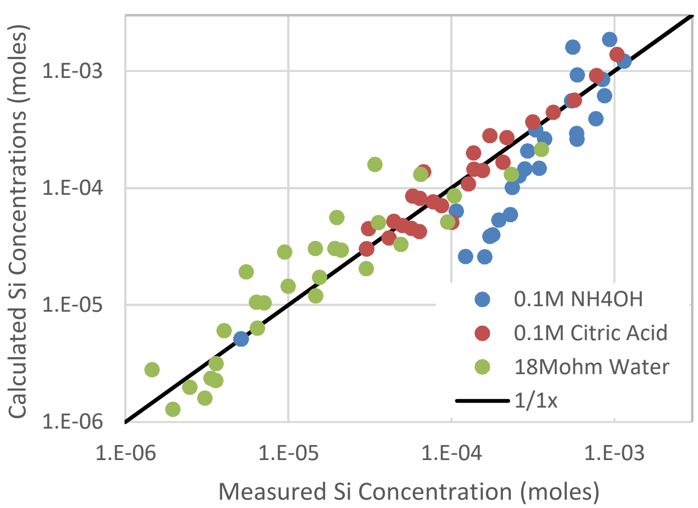
Aluminosilicate vials meet USP <660> Type I hydrolytic criteria and:

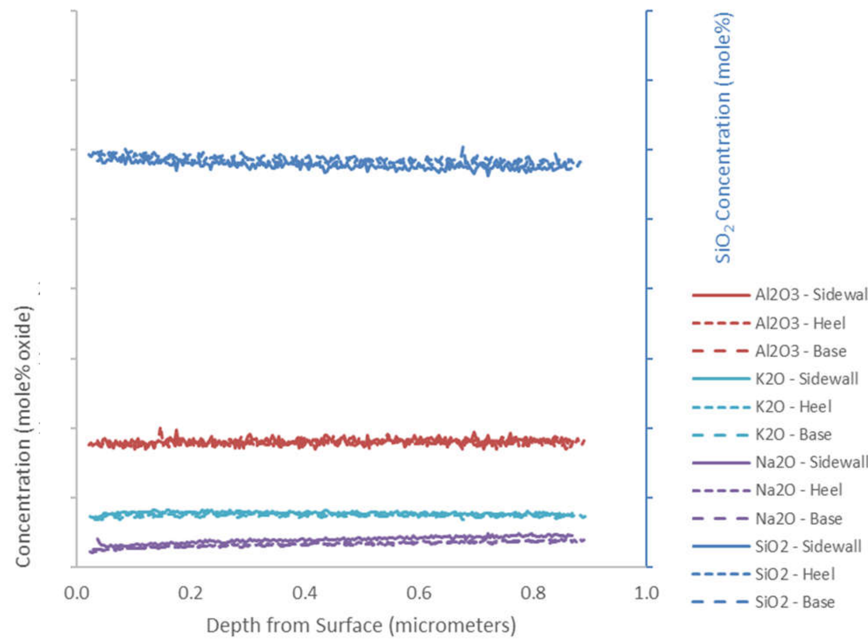
- Eliminates glass lamellae
- Substantially reduces particulates
- Resists damage and breakage
- Prevents* cracks

* In laboratory testing, Valor Glass vials provided at least 30x protection against cracks than conventional borosilicate glass vials.

Uniform surface chemistry of aluminosilicate vials yields predictive E&L

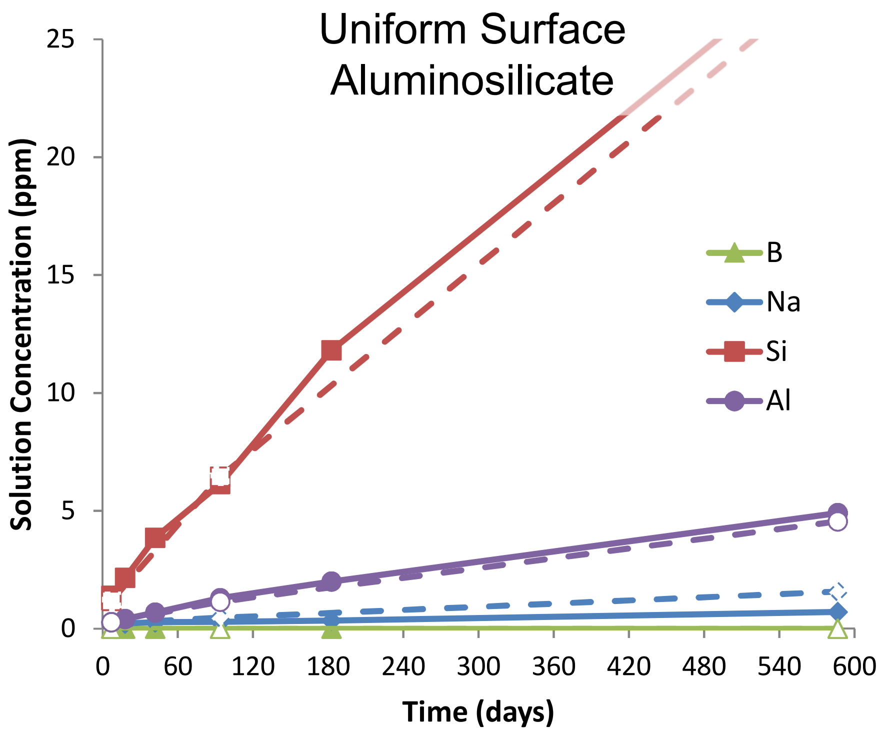
- A simple TST expression enables prediction of E&L trends over a wide range of conditions:
  - pH 2 thru 11
  - 5 thru 121°C
  - Range of SA/V
  - Storage through 3 years

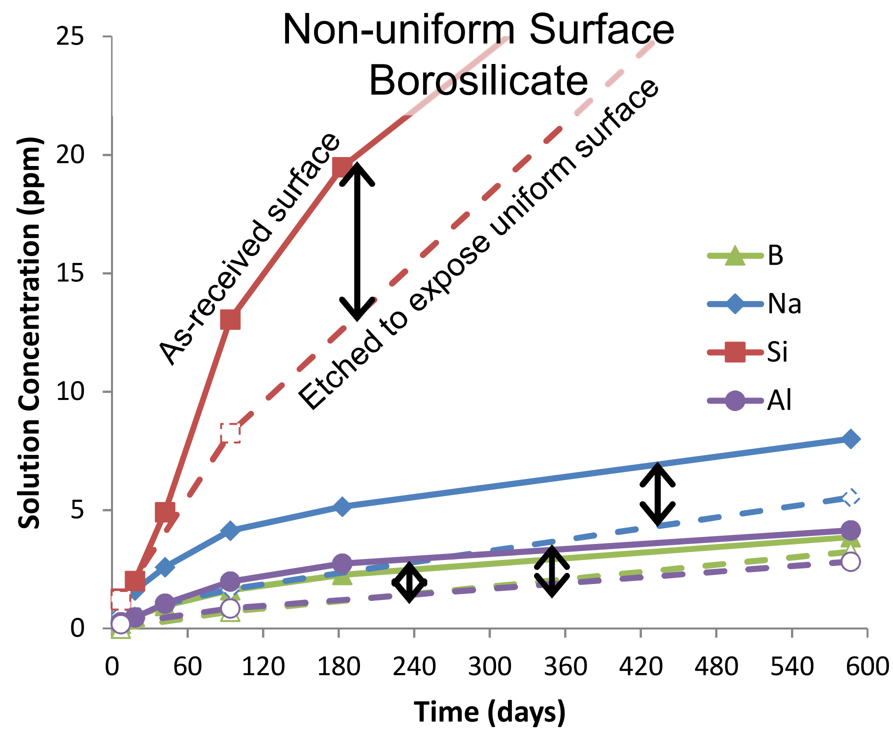




Non-uniform borosilicate surfaces produce non-smooth E&L trends

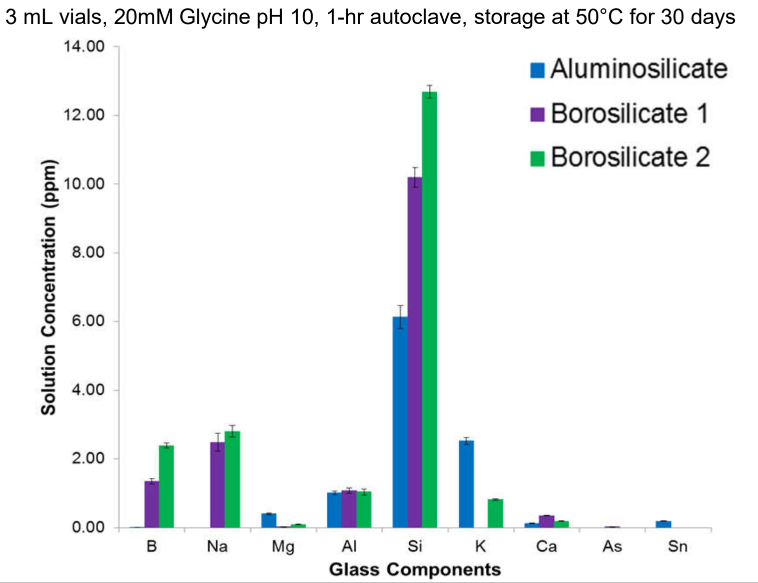
0.1M Citric Acid, pH 2, stored at 37°C in size-matched 3mL vials, SA/V ~3.2cm^{-1}





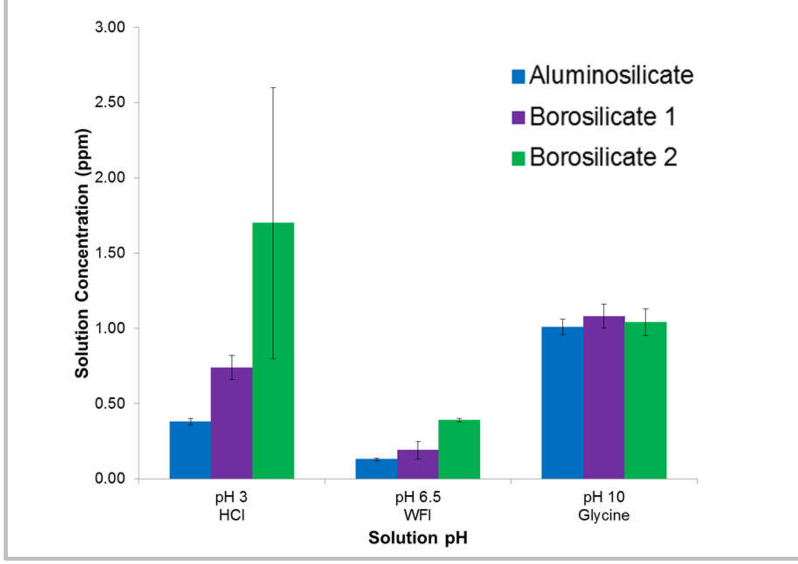
The extractable profile of this aluminosilicate container indicates it is well-suited for pharmaceutical storage

Extractable Performance



Even under extreme conditions, extractables remain comparable for aluminosilicate and borosilicate

Al Extractions Under Various pH Conditions



Despite higher Al concentration in bulk glass, Al extractables are comparable to borosilicate glasses

Summary

- Both borosilicate and aluminosilicate glasses corrode by the same mechanisms, that are highly pH dependent.
- Glass corrosion rates are thermally accelerated according to Arrhenius relationships. Solubility limits also increase with temperature, although with different activation energies.
- The extent of corrosion depends heavily upon solution chemistry and its influence on the solubility of corrosion products.
- E&L can be modeled varying time, temperature, pH and solution chemistry, however these models require uniform surface composition.
- Valor® Glass containers are boron-free and maintain uniform surface composition, enabling predictable trends in E&L.

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