# Decreasing the rate of delamination of pharmaceutical glass containers.

**Shireesh Prakash Apte***

Harmony Science Academy, Euless, TX 76040, USA

Editorial

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Conventional wisdom for deterring or decreasing the rate of glass delamination includes adjusting the pH and the ionic strength of the formulation solution, and sourcing glass that is relatively more resistant to delamination as determined from the DoE. The literature is replete with methods to detect delamination and to decrease its rate. It does not yet appear to be recognized, however, that the rate of delamination may be influenced by making and treating the glass vial as a Galvanic (Voltaic) cell, wherein the glass would be made conductive, the metal (usually aluminum) seal would act as the anode and the glass in contact with the formulation would act as the cathode.

The mechanism of delamination is generally thought to be due to the outright surface dissolution of silica in contact with an alkaline solution or by mechanical 'separation' of glass lamella that are formed due to dissolution of the alkaline components of glass ($Na_2O$) in contact with an acidic solution. In either case, silicon is transformed from lower to higher oxidation states, covalent bond cleavage between the atoms constituting the polymer may occur at exposed sites and a 'gel layer' forms at the boundary between the intact silica and the solution. This gel layer may increase in thickness or may break off lamellae from the intact glass due to uneven tension.

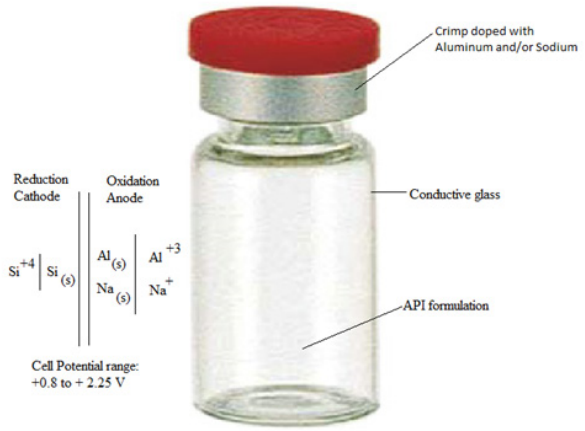
A component of glass, the basic oxide, $Na_2O$, is added (in the form of 'soda', sodium carbonate) as a flux to decrease the melting temperature of the glass during the manufacturing and molding process. It has a propensity to react with water, acid or $SiO_2$ to form silicates. These silicates, in turn, hydrate and cause 'stress fractures', causing the outermost layer of glass to 'peel away' from the underlying substrate glass layers, the classic delamination condition.

As an, as yet, unreported method of minimizing glass delamination, silicon in its +4 oxidation state and either aluminum or sodium could be used to set up an oxidation-reduction Galvanic (Voltaic) cell wherein the Silicon is reduced and the aluminum or sodium is oxidized. The glass could act as the 'salt bridge' by making it conductive (perhaps by doping it with transparent indium-tin-oxide or with conductive polymers). In this way, the silicates that are formed by aqueous/acidic or basic attack by the Active Pharmaceutical Ingredient (API) formulation solution could be reduced to silicon. This reaction could be anticipated to mitigate further erosion and/or delamination

* Corresponding author: Shireesh Prakash Apte, Harmony Science Academy, Euless, Texas, 76040, USA, Tel: 8175012984, E-mail: shireeshpapte@msn.com

by two mechanisms. First, the hydration via the Donnan membrane equilibrium would be significantly reduced, thereby reducing the propensity of tensile stress fracture delamination. Second, the formed silicon would reduce further permeation of the API solution into the glass structure.

The figure below provides an illustration of the idea. The Cell potential is positive thereby making the reaction spontaneous.




$SiO_{2(s)} + 4H^+ + 4e^- \rightarrow Si_{(s)} + 2H_2O$ -0.86 V

$SiO_3^{-2} + 6H^+ + 4e^- \rightarrow Si_{(s)} + 3H_2O$ -0.46 V

$HSiO_3^- + 5H^+ + 4e^- \rightarrow Si_{(s)} + 3H_2O$ -0.63 V

$H_2SiO_3 + 4H^+ + 4e^- \rightarrow Si_{(s)} + 3H_2O$ -0.38 V

The standard reduction potentials for Aluminum and Sodium are -1.66 and -2.71 V respectively according to the equations below:

$Al^{+3} + 3e^- \rightarrow Al_{(s)}$ -1.66 V

$Na^+ + e^- \rightarrow Na_{(s)}$ -2.71 V

The problem is for the Silicate molecule to 'find' the reduced forms of aluminum or sodium. These could be 'found' if the glass were to be made conducting; either by using transparent indium-tin-oxide or by using conductive polymers. The conducting glass salt bridge would serve as a source of electron transfer from the metals doped into the crimp to the silicate molecule in the glass. Reduction of silicates to silicon would achieve the necessary effect of slowing down the rate of delamination. This solution is very much akin to using a 'sacrificial' anode in a hot water heater.

What place does an editorial, that is at first glance, unrelated to pharmaceutical excipients or food chemicals, have in this Journal? While primary packaging is not an 'excipient' as such, its impact on pharmaceutical API stability parallels that of pharmaceutical excipients. The idea itself could stimulate a search for conductive transparent materials for use in pharmaceutical glass containers. It is a new way of looking at an old problem for which the empirical, DoE road seems to be at an end and the only 'solution', if it can be called that, is to pick and choose vendors and/or lots based on relative ratios of oxides of aluminum, boron and sodium, and empirical in-house DoE results.

As with any new idea there may be additional potential hurdles to overcome, some which may not be trivial. For example, could not the depletion of metal from the rim of the crimp compromise product sterility by loosening the seal? Will depletion of metal from the crimp render it ungainly in appearance and unsuitable for pharmaceutical use? Can this electro-chemical reaction take place under the conditions described? Will the dopants that make the glass more conductive themselves not leach out into the API formulation or change the properties of the glass to make it unsuitable for pharmaceutical use? Could excess electrons not leach out of the glass into the API formulation and reduce labile components (API or excipients) in the formulation? Most of these are (largely) engineering problems and may be overcome by design changes. It is hoped that the method described here will be included and/or may prove useful toward ongoing research efforts in trying to find a solution to this well described but not well understood problem.