Method for Measuring the Chemical Heterogeneity of Glass Containers

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Introduction

The importance of the glass surface has received increased scrutiny in the last several years including the publication of the FDA advisory on delamination in 2011 and the introduction of the Glass Surface Test to USP <660> in 2012. In the production of glass containers, the forming process (converting) is the primary mechanism that alters the surface chemistry. Changes in the surface chemistry have important implications. For example, the generation of delamination flakes has been linked to the heterogeneous surface chemistry produced when glass components volatilize and deposit due to exposure to a flame.[1-4] Current methods for evaluating pharmaceutical containers such as USP <660> and <1660> do not sufficiently define the variable quality that can be observed in containers that meet Type I requirements. Some shortcomings of current testing include:

- Lack of positive controls- This prevents test method validation.
- Forming variability- Absence of delaminated flakes from testing one lot or characterization of leachable profile does not ensure similar performance in future lots.
- Monitors an indirect response- Sodium concentration in solution is not a direct cause or indicator of delamination propensity and is not the only potential source of chemical heterogeneity (e.g., boron and silicon).
- Response dilution- 90 % fill volumes do not represent drug contacting surface and can dilute response from low durability regions

Spectroscopic techniques such as X-ray Photoelectron Spectroscopy (XPS) or Dynamic Secondary Ion Mass Spectrometry (DSIMS) can provide a more detailed evaluation of changes in surface chemistry. These techniques also have limitations including high cost, significant analysis time/technical training (not friendly for production setting), influence of sample preparation, and small area investigated (less than 1 mm^2 on one part).

In this paper, a new approach for investigating surface chemical heterogeneities is presented that can be implemented in a production setting. The method compares the USP <660> Surface Glass Test responses in "as received" (molded or tubular) and "after etching" forms using a reduced fill volume. The low filling volume more accurately measures the response from the glass surface that would be in contact with a pharmaceutical. Moreover, the combination of a low fill volume and etch response investigates the level of surface chemical heterogeneity in the heel region, the area most commonly associated with surface chemistry changes and delamination.

Methods

"As received" containers are processed according to the USP <660> Surface Glass Test with the following notable deviation: the filling volume is 12.5 % of the brimful capacity. The titration volume is recorded as the "as received" response. The filling volume was selected to maximize sampling of the base and heel region and minimize sampling of the sidewall.

A second USP <660> Surface Glass Test is conducted "after etched" to measure the bulk glass response. The etching process removes the material deposited during the converting or molding process. Containers used for the "etched" response can either be a completely new set or the retained (already tested) containers from the "as received" test. At least one micron of the surface is removed using a

mixture of HCl/HF acids, with target concentrations of 2.3 M HF/4.6 M HCl. The containers are exposed to the acid for a period of 3-5 minutes. These conditions are sufficient for most Type I glass compositions, but the weight loss should be measured to ensure sufficient surface removal. After exposure to the etchant solution, acidic residue in the containers is removed through soaking in two room temperature water baths for 5 minutes each. Subsequently, the containers are rinsed with USP Purified Water six times. The containers are processed according to the USP <660> Surface Glass Test using the same fill volume (12.5 % of the brimful capacity). The titrant volume is recorded as the "etched" titrant response.

A ratio of the recorded titrant volumes, called the chemical durability ratio (CDR), is calculated. The ratio provides an estimate of the level of surface heterogeneity.

$$Chemical\ Durability\ Ratio\ (CDR) = \frac{"As\ received"\ titrant\ response}{Etched\ titrant\ response}$$

Results and Discussion

Equivalent titrant responses for "as received" and "etched" vials produce a CDR value of unity, which indicates that the surface of the "as received" vials is equivalent to the bulk glass and therefore minimal differences exist. Ratios that exceed unity have an elevated titrant volume for the "as received" relative to the "etched" containers. In this case, material has been deposited on the surface from volatilization during the converting/molding process. Higher ratios correspond to greater levels of volatilization and deposition. As the ratio increases, there is an elevation in leachable concentrations that will be observed in the pharmaceutical and increased risk of delamination. As demonstrated in Figure 1, the ratios for many Type I commercially-available borosilicate containers are significantly higher than unity. Significant variability in the CDR performance between lots could highlight the risk of leachable-pharmaceutical interactions.

These observations agree with trends reported in the literature and the FDA advisory. Namely, molded containers exhibit a lower CDR value (Figure 1) and therefore have a lower delamination risk than tubular containers. Large containers (thicker walls) exhibit higher CDR values because the forming process require more heat and pose a higher risk for delamination than smaller containers (3 mL vs. 50 mL in Figure 1).

Of all commercially-available borosilicate pedigrees tested to date, a ratio of 9 was the highest value observed. It should be noted that specially-produced containers from 13 populations with observed delamination (positive controls) produced ratios from 6-12. These positive controls do not represent all possible surface chemistries that can lead to delamination; therefore, additional work is being conducted to identify the lowest ratio for containers with observed delamination. From this work, a threshold will be identified for containers that warrant additional investigation with the pharmaceutical. To date, the lowest ratio observed is ~6 and therefore containers with CDR values that exceed this value would be suspect for delamination.

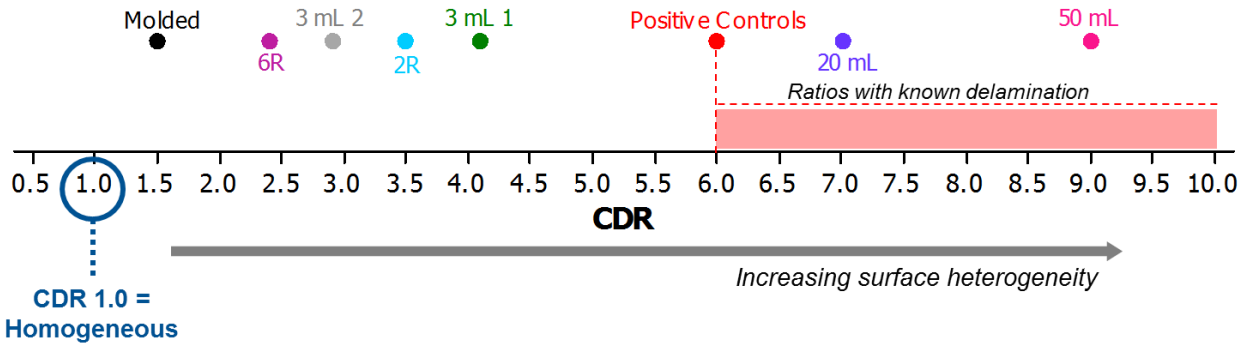

Figure 1. CDR values for a variety of containers represented as nominal fill volumes. Containers from 5 manufacturers have been tested with 2-3 replicates per numerator and denominator per pedigree.

Conclusions

The CDR method offers significant advantages to some of the current test methodology, including:

- Interrogates the glass surface that will contact the pharmaceutical (instead of fracture surfaces as with the USP <660> Glass Grains Test)
- Avoids dilution effects and represents pharmaceutical fill volumes (90% fill volume for Surface Glass Test masks high risk regions of vial surface)
- Samples a larger container population (i.e., not single container and location)
- Decreases testing timing relative to other delamination tests (hours as opposed to months)
- Can be implemented in a production setting familiar with USP <660> testing

Preliminary data suggests the CDR values of vials deemed 'Type I' by USP <660> can span a relatively large range. This indicates that considerable performance variation exists within the current definition of Type I containers. More work is needed to resolve the CDR threshold for increased delamination risk (current data shows ratio will be 6 or less). It is clear that values closer to unity represent more consistent surface chemistry (relative to the bulk) and therefore have lower delamination risk and more predictable leachable profile.

Given these advantages for distinguishing performance relative to existing test methods, the CDR method is likely best implemented as a complement to the existing USP<660> Surface Glass and Etched Surface Tests with the ability to distinguish delamination propensity and more representative leachable profile.

References

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