Best Practices for Glass Delamination Testing Studies

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SCHOTT pharma services provides compatibility testing for drug products in glass vials[1] including a delamination screening package aligned with USP <790>[2], USP <1660>[3], and EP 3.2.1.[4] recommendations. Over the last decade, the design of such studies was progressively improved to provide reliable data for risk assessment for drug container compatibility. The essential factor for the suitability of such investigations is the categorization of different observations with respect to their criticality and that features need to be found which are early indicators for the later occurrence of delamination (i.e. applied predictive screening test methods "should look for precursors that lead to delamination"[3]).

The containers to be tested and filled with drug product or placebo solution, can be drawn from real-time stability studies or stored under accelerated ageing conditions. The extent of glass corrosion and chemical attack is assessed by analyses of the inner glass surface morphology, the concentrations of extracted elements in solution, and by identification of particles and flakes. Some typical results derived with such studies have been previously published[5,6] with additional information concerning glass leaching recently discussed[7].

SCHOTT pharma services uses a combination of the recommended analytical techniques. Illustrative results are summarized in the following section.

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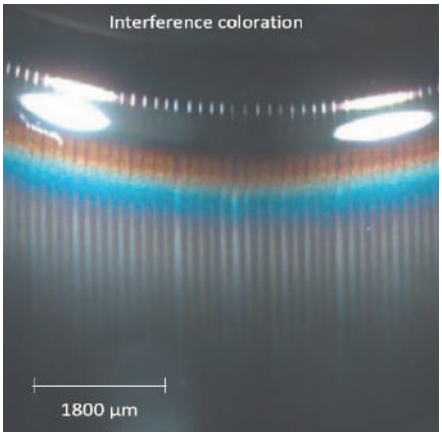
Visual and Optical Inspection

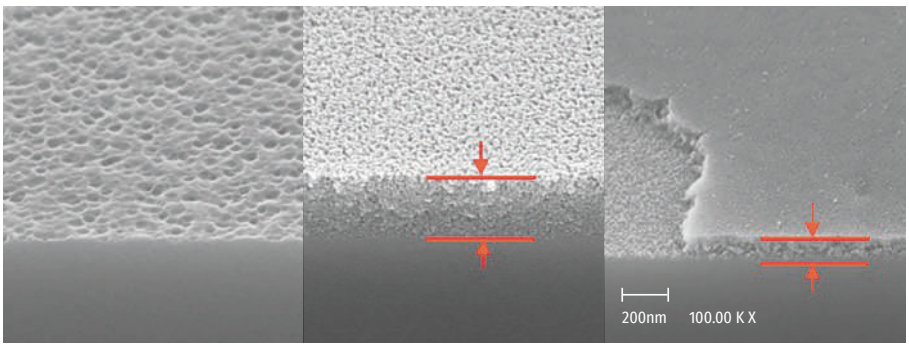
Flake-like particles by visual inspection



Coloration ring by stereo-microscopy

- Used to detect particles via visual inspection by eye and camera (filled vials) and to visualize coloration and scattering (for empty and for emptied vials)
- Allows for the identification of containers with high particle load and with changed surface and surface near regions to determine the worst samples of a set by stereo-microscopy

SEM Cross-section Analysis



Roughening *Reaction zone* *Delaminated area (left) and reaction zone (right) (Note: scale bar valid for all three micrographs)*

- Used to determine the extent of chemical attack of inner glass surface and of surface near regions
- Allows for classification between different levels of glass corrosion.

Typical features are roughening, formation of reaction zones and/or delaminated areas at the interior surface in contact with the drug product

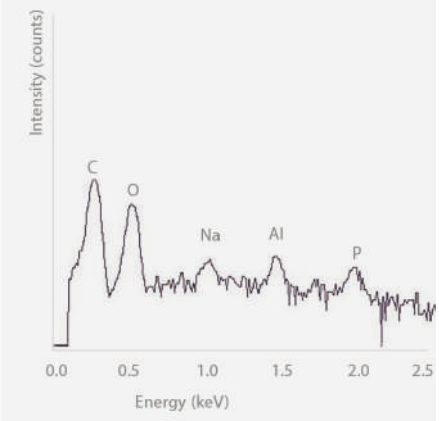
ICP Analysis

Element (mg/L)	Citrate buffer (pH 6.0)	Sodium bicarbonate (about pH 8.0)	Phosphate buffer (pH 7.0)
B	2.1	2.0	1.1
Al	3.0	0.05	0.06
Si	20.1	8.2	9.2

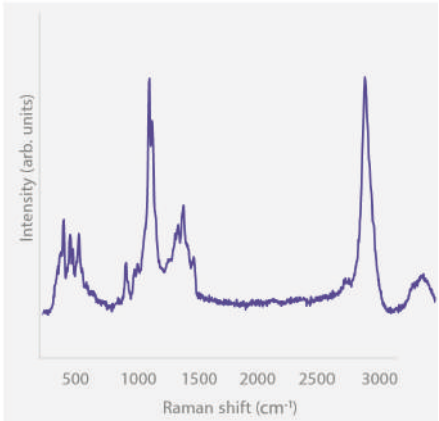
Concentration of selected leachables found after storage for 24 weeks at 40°C with different filling solutions

- Used to quantify the amounts of leached glass elements
- Allows for the confirmation of the chemical mechanism of drug container interaction

SEM/EDS and Raman Microscopy



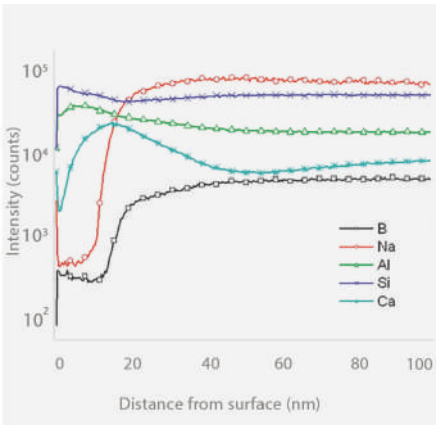
Exemplary EDS spectrum of an inorganic flake-like particle

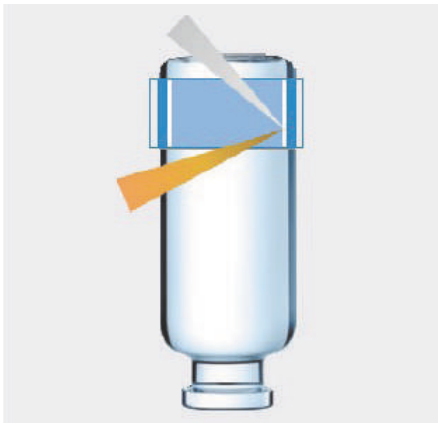


Exemplary Raman spectrum of an organic flake-like particle

- Used to analyse the composition of particles after filtration
- Allows identification of morphology (SEM), elemental components (SEM/EDS), and molecular structure (Raman) of isolated particles to distinguish between glass flakes and other particles

TOF-SIMS





Altered elemental composition of surface near layer with B and Na depletion

- Used to characterize the elemental composition of the near surface region of container interior
- Allows a better understanding of the mechanism of drug container interaction and induced glass corrosion

Exemplary Study Protocol

1. Visual inspection by eye and magnifying video camera with respect to the presence of particles or flakes (10 filled vials per time point according to Tables 1 + 2).

2. Optical inspection of emptied containers per time point: Stereo-microscopy with extended depth of focus to qualitatively determine if there are any indications for reaction zones or scattering present on the interior surface (10 vials per time point according to Tables 1 + 2). Selection of two "worst" samples on the basis of stereo-microscopic inspection for subsequent SEM cross-section analyses.

3. SEM (scanning electron microscopy) cross-section analyses on the interior surface of two "worst" vials for selected test conditions and selected time points as described in Tables 1 + 2; analyses of three areas: wall near bottom, middle of the vial body, and wall near shoulder. These investigations reveal the presence of a potential reaction zone.

4. ICP (inductively coupled plasma) analyses of 10 mL drug solution pooled from the vials for selected test conditions and selected time points according to Tables 1 + 2 to quantitatively determine the amount of "glass" elements leached into solution for selected "glass" elements (e.g. Si, B, Ca, Al) to ascertain if the amounts and ratios found are normal or if there is a pronounced chemical attack.

5. Filtration of the solution of one selected vial according to Tables 1+2 through a silver membrane (pore size approx. 0.2 µm) using a vacuum filtration unit. Subsequent SEM/EDS and Raman analyses of found particulate matter to determine the elemental composition and morphology of the particles by SEM/EDS and the molecular structure by match of Raman signals to library. Optional: (If the mechanism of glass corrosion is unclear or reaction zones are observed.)

6. SIMS (secondary ion mass spectrometry) depth profiling of the interior surface to get information about the composition of the surface near region.

The techniques described above are applied at different time points under accelerated storage conditions. These conditions are defined on the basis of the drug product application and customer requirements. Exemplary study designs for predictive delamination screenings for drug products with a shelf-life of three years at 5°C (Table 1) and 25°C (Table 2) are shown on the following page.

The tables illustrate the test methods applied for one set of vials filled with drug product and stored for different time points and include the number of characterized samples.

Rationale behind the Study Protocol

Storage Conditions:

The definition of the accelerated storage conditions requires an estimation of an acceleration factor. In the case of a delamination or a glass leachable study, the kinetics of solid-state reactions should be considered. In such cases the impact of increasing the temperature can be described by an Arrhenius equation $k = A \exp(-Ea/RT)$ (k: rate constant, R: universal gas constant, Ea: activation energy, T: temperature, A: frequency factor).

The calculation of the acceleration factor which is the ratio k(T2)/k(T1) requires an

Method	Empty vial	Storage conditions/time points			
		After filling	Storage at 40°C		
	Control	0 weeks	4 weeks	8 weeks	12 weeks
Visual Inspection	–	10	10	10	10
Optical Inspection	5	10	10	10	10
SEM cross-section	2	2	2	2	2
ICP analyses*	–	Yes	Yes	Yes	Yes
Particle analyses by SEM/EDS and Raman if flake-like particles are found	–	–	1	1	1
SIMS (optional)	–	1	–	–	1

*: Drug solution pooled from multiple vials

Table 1: Exemplary study design for a drug product with a shelf-life of three years at 5°C tested by using accelerated storage at 40°C

Method	Empty vial	Storage conditions/time points			
		After filling	Storage at 60°C		
	Control	0 weeks	6 weeks	11 weeks	16 weeks
Visual Inspection	–	10	10	10	10
Optical Inspection	5	10	10	10	10
SEM cross-section	2	2	2	2	2
ICP analyses*	–	Yes	Yes	Yes	Yes
Particle analyses by SEM/EDS and Raman if flake-like particles are found	–	–	1	1	1
SIMS (optional)	–	1	–	–	1

*: Drug solution pooled from multiple vials

Table 2: Exemplary study design for a drug product with a shelf-life of three years at 25°C tested by using accelerated storage at 60°C

estimation of the unknown activation energy Ea. The lower the Ea-value the smaller the acceleration. For the dissolution of a borosilicate glass (Pyrex, buffered at pH 7) an Ea-value of 54 kJ/mol[8] was published and we use this value to calculate the storage period at different temperatures. Using this approach, we obtain an acceleration factor of about 13.5 when storing a drug product at 40°C instead of 5°C For a drug product with a shelf-life of three years at 5°C the storage period at 40°C shortens to 12 weeks.

Please note that reactions with activation energies lower than 54 kJ/mol will have lower acceleration factors, while the acceleration will be higher for reactions with higher activation energy.

Probability Y to find a feature for one sample	Probability P to find a feature within 10 samples (N=10)	Probability P to find a feature within 5 samples (N=5)	Probability P to find a feature within 3 samples (N=3)
50%	99.9%	96.9%	87.5%
33%	98.3%	86.8%	70.3%
10%	65.1%	41.0%	27.1%

Table 3: Probability to find glass delamination and/or early indicators for number of samples investigated per time point

Number of Samples:
We recommend at least 10 vials per time point and per sample set and five additional empty vials per vial container type as reference samples.

It is quite unlikely to observe a delamination effect by only applying a standard USP <790> / EP 2.9.20.[2,9] test method, because of the low frequency of randomly drawn vial samples showing visible flakes and because of the low sensitivity of the method. Therefore, we are using in-house inspection methods in addition that allow the identification of containers with small flakes load and/or changed regions to determine the worst samples of a set by stereo-microscopy.

Early indicators for delamination like "reaction zones" will be found with a much higher probability for a population of vials (compared to the probability to find the final stage of delamination). Therefore, we adjusted the number of vials to find early indicators with a high probability. If the probability to find a feature (e.g. reaction zone) for a single vial out of one time point is Y, we can calculate the probability P to find this feature at least once in a group of N vials with the equation $P = 1-(1-Y)^N$, as shown in Table 3 below. It becomes clear that the reduction of the number of vials is significantly increasing the chance to miss a feature, which is why the aforementioned study design is recommended.

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Laboratories of SCHOTT pharma services are DIN EN ISO/IEC 17025 accredited (DAkkS) and FDA registered.

SCHOTT pharma services can access more than 40 years experience in analytical testing of pharmaceutical packaging containers. All quality relevant documents are electronically available, ensuring a hassle-free audit process.

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