

STEVANATO GROUP MARKET UPDATE

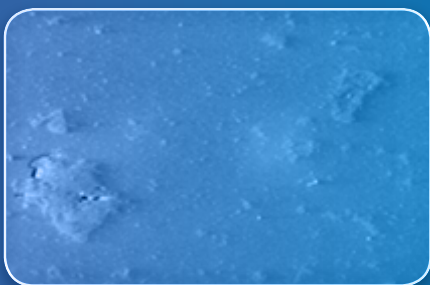
GLASS DELAMINATION | FACTS - PREVENTION - RECOMMENDATIONS



Pic 1. Shiny glass lamellae in liquid



Pic 2. Analysis and Classification



Pic 3. Altered glass surface, SEM-pic

Dear Reader,

As the intravenous administration of solid glass particles could seriously affect patient health⁽⁰⁾, Stevanato Group is treating glass delamination with high priority, even if up to now we did not receive any complaint related to our Pharmaceutical Tubular Containers. We also want caution against overreaction and generalized statements based on specific recent events on the market. It is important to carefully analyze information as not all products are exposed to the same level of delamination risk.

Nevertheless, Stevanato Group is committed to support our customers in order to clarify the situation and to respond to requirements in order to mitigate delamination risk or even to control this phenomenon.

Half a year ago, we already started a study in order to predict delamination and to finalize a correlation with the major parameters, which are not only related to the glass converting process, but also include glass raw material, buffer conditions and post treatment of the container. We assigned significant resources in order to analyze the influence of the key parameters as much as possible and to come up with recommendations and a tailor made solution for new drugs or already known cases on the market.

Boris Schmid
Corporate QA Director
Stevanato Group

Prof. Emanuel Guadagnino
Scientific Advisor of
Stevanato Group

This is a first general market update about our delamination investigation:

Summary of Glass Delamination

Glass delamination is generally described^(1,2,3) as the detachment of thin layers from the inner surface of glass containers, causing the formation of brilliant, shiny lamellae with an approximate size from 20 to 150 μm .

This phenomenon may occur when an altered surface layer is formed over the original surface with significantly different physical parameters from the bulk glass underneath. Because of the different expansion coefficients, any thermal or mechanical shock can favor the detachment of flakes⁽⁴⁾.

Normally this phenomenon is not immediately visible, unless the containers are filled with a solution and possibly shaken. In pharmaceutical glass packaging it is mainly observed in vials (with liquid), because lamellae are generated from the bottom (where enriched silica layers are produced during the forming process) or from the lower body part (where stresses are present before annealing).

There are different parameters which can accelerate or slow down the glass corrosion and the delamination process. In any case, the glass raw material, forming process, alkalinity of the filling solution and the storage time seem to play a major role⁽⁵⁾.

Key parameters

Several significant parameters were found to cause a strong influence on glass delamination (order by process flow) like:

- raw glass material
- forming process
- surface treatment
- annealing
- nature of the filling liquid
- pH
- sterilization
- shelf life

We proved, that the combinations of the different parameters are potentially resulting in different delamination characteristics which means, there is no general rule for glass delamination prevention.

Support for analysis, classification and solution

As delamination (or any particles) might be critical for patient safety, each case must be analyzed, if the flakes were originated by delamination or if they were caused by contamination or a complex building process within the filled liquid. This determination can be done by isolating the flakes and by an evaluation with a microscope or SEM analysis.

Our market screening showed us, that not all cases were clearly identified as glass delamination. So it is essential to analyze carefully together with the customer each appearance of flakes/particles in order to identify the situation and then to address the root cause.

We are linked with several experts and laboratories in order to analyze the phenomenon and to recommend the most probable solution or to start a customized design of experiment.

Controlled Thermal Forming process

It is recognized, that forming the container with a tightly controlled process has generally a positive impact on the delamination characteristic as it creates less thermal stress and less enriched silica layers.

Stevanato Group has a long tradition and large experience in producing glass on vertical indexed machines using appropriate burner- and forming technology. Each product has clearly defined speed and flame positions which are kept constant during production. This controlled forming process is also reflected by the fact, that OMPI glass containers meet EP specification without any sulfur treatment.

Delamination prevention

A thermally controlled forming process in combination with properly selected raw material and exhaustive information about the intended use of the container, allows OMPI to recommend the best possible solution for a "low delamination container".

The surface alkalinity of the finished article, e.g. based on ISO or EP testing, is used to characterize such a thermally controlled forming process. This parameter, if it is evaluated by its own without considering the influence of other key factors, may sometimes be misleading. It is well known that high borosilicate glass (expansion 33) or sulfur treatments will lead to low surface alkalinity^(6,7)

but nevertheless low ISO and EP values are not always a guarantee against the risk of delamination, for instance when the filling liquid is an alkaline solution ⁽⁸⁾ and/or a corrosive organic acid like citric acid ⁽⁹⁾. To better estimate the “delamination risk” we have developed a series of combined tests including accelerated ageing tests with measurement of the dissolved silica, evaluation of surface morphology by SEM analysis and a colorimetric method to monitor the integrity of the inner glass surface immediately after forming.

Once having characterized the key parameters in close collaboration with the customer, OMPI is able to provide customized low delamination containers to specific pharmaceutical products.

Outlook - future improvements

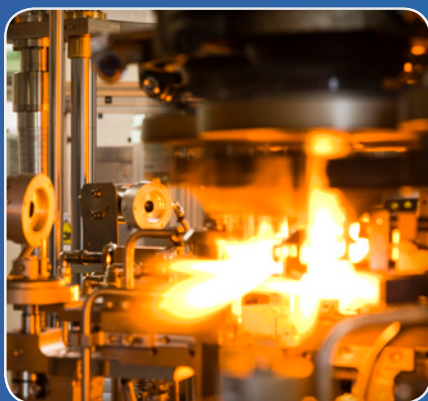
As we form part of an international network and committees, we are committed to carry out our investigations in close cooperation with the glass industry, important pharmaceutical customers and laboratories.

Our intention is to finalize a statistical in process test in order to monitor the delamination characteristics of any individual lot. Based on the preliminary results, a promising correlation was found between the occurrence of surface alterations and the formation of flakes after accelerated ageing tests.

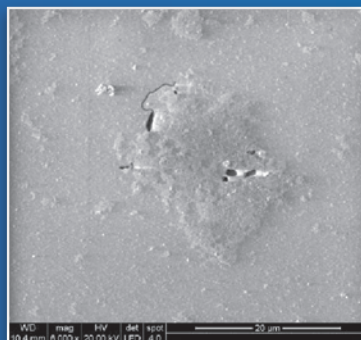
A colorimetric test is being developed to highlight inner surface areas which are recognized as possible sources of delamination. The selected adsorption of the indicator on critical areas of the vial as produced, can be considered as an index of the incipient delamination route, which may occur when the vials are subject to extraction under stressed conditions. We are collecting results to confirm whether this method can be used within an acceptable reliability as an index to predict on-line the delamination risk of a vial. An accelerated ageing test is generally run to confirm the findings.

In a second phase, we intend to quantify the impact of the different process steps on the delamination characteristic of low delaminating containers in order to understand and even control better the delamination characteristic.

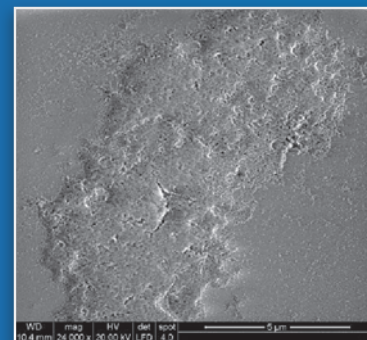
BENEFIT FROM OMPI PROCESS



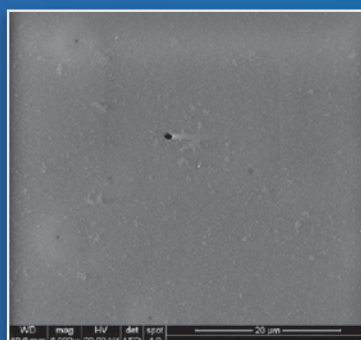
Pic 4. OMPI controlled thermal forming process



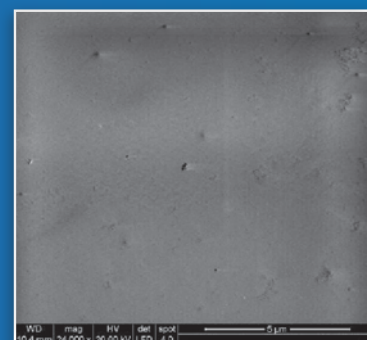
Pic 5. Surface alteration after ageing test of a not controlled thermal forming process



Other supplier



Pic 6. Resistant surface after ageing test with OMPI controlled thermal forming process



Stevanato Group

Recommendations

Based on our more recent studies, including an extensive design of experiments and accelerated aging tests, we identified the following recommendations ^{Note 1)} to mitigate the risk for glass delamination:

For low pH formulated drugs (pH <7.0), aqueous neutral solutions

Any kind of Type I glass containers can be used. We would just recommend that the glass containers shall meet Pharmacopoeia specifications before any specified sulfur treatment is applied. Furthermore the sulfur treatment, if required by the client, should be designed in a way to guarantee that the modified surface layer is reduced to the minimum necessary thickness.

For high pH formulated drugs (pH >8.0)

In-house testing of high silica borosilicate (expansion 33) and sulfur treated vials in contact with alkaline extraction solutions, showed a steep increase of undissolved silica particles ⁽¹⁰⁾. We recommend to use untreated normal borosilicate glass ^{Note 2)} (expansion 51) and to possibly reduce the exposure time.

For drug buffered with silica complexing agents (e.g. organic acids like citrate, tartrate, glutarate, EDTA etc) ^(9,11)

As these acids are known to behave as strongly alkaline solutions, we recommend to use untreated normal borosilicate glass ^{Note 2)} (expansion 51) and to possibly reduce the exposure time. Heat treatments and final sterilization are additional risk factors.

For drug buffers with a high ionic strength (high NaCl or KCl content) ^(12,13)

We recommend to use untreated normal borosilicate glass ^{Note 2)} (expansion 51). The use of sulfur treated vials is to be restricted to preparations with pH around 7 or lower.

Notes:

Note 1) As the recommendations are based on a specific testing design by Stevanato Group in collaboration with an external laboratory, they are not covering all possible parameters and shelf life conditions which can be met by any filled product. Therefore it is necessary to evaluate and to approve each application based on real ageing and stability tests established by the customer.

Note 2) Glass containers from a controlled thermal forming process, e.g. from OMPI process.

References:

- 0) "Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs", FDA Advisory 110325, 25.03.2011
- 1) P.Bremond, "Contribution a l'étude de la dissolution et de la disgregation superficielle sous form de paillettes des verres au contact de l'eau et des solutions aqueuses", Verres et Refractaires, No1, 1948, 15-25
- 2) F. Bacon & O.G. Burch, "Effect of time and temperature on accelerated chemical durability tests made on commercial glass bottles", Journal of Am. Ceram. Soc., Vol.23, No1, 1940, 1-9
- 3) K.J.Diebold, "Microscopical evaluation of glass delamination in pharmaceutical vials: a look at three different vial manufacturers", Modern Microscopical Journal, October 2003, 1-14
- 4) R.G.Iacocca & M.Allgeier, "Corrosive attack of glass by a pharmaceutical compound", Journal of Mat. Sci., 42, 2007, 801-811
- 5) R.G.Iacocca et al., "Factors affecting the chemical durability of glass used in the pharmaceutical industry", Pharm. Sci. Tech., August 2010, on-line publication
- 6) F.Geotti-Bianchini, E. Guadagnino, M. Verità, C.G. Pantano, T. Paulson, J.Hamilton "Surface reactions of Type II sulfur treated glass containers during autoclave testing in water", Proceedings of the XVIII International Congress on Glass (ICG XVIII), San Francisco, CA, USA, 1998, July 5-10, pp6
- 7) N.M.Harris, "Effets de traitement de desalcalinisation on la reactivite hydrolytique d'un verre sodo-calcique", Riv. SSV, No 5, 1984, 91-97
- 8) D.E.Clark, C.G.Pantano & L.L.Hench "Corrosion of Glass", Books for industry, New York 1979
- 9) F.R.Bacon & F.C. Raggon, "Promotion of attack on glass and silica by citrate and other anions in neutral solutions", Journal of Am. Ceram. Soc., 92 (4), 1959, 199-205
- 10) S.J.Borchert et al., "Accelerated extractable studies of borosilicate glass containers", Journal of Parenteral Science and Technology, Vol.43, No2, 1989, 67-79
- 11) A.Paul, "Influence of complexing agents and nature of buffer solutions on the chemical durability of glass. Part I, Glass Technol., Vol.19, Dic. 1978, 162-165
- 12) H.Scholze, "Bedeutung ausgelaugten Schicht fuer die chemische Bestaendigkeit: Untersuchung an einer Kalk-Natronglass", Glastech. Ber., 58, No5, 1985, 116-124
- 13) A.Biavati, "Correlation between hydrolytic ion release and pH changes in Type II glass containers", Pharm. Ind. 59, 2, 1997, 175-178



NEXT EVENT RELATED TO THIS TOPIC:
PDA/FDA Glass Quality conference.
23-24 May Arlington, USA



Technical report available after:
Rx-360 Symposium on Glass
Delamination.
25 May Arlington, USA



Please contact our Area Sales Manager
or contact sales@stevanatogroup.com
to coordinate any request or to get
further information on this topic.