Scanning electron microscopic study of glass container degradation in infusion solution

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Abstract. Solid particles found in an infusion solution under development were examined by scanning electron microscopy combined with X-ray fluorescent elemental analysis. The main fraction of the particles was found to be flakes of corroded glass. The elemental composition of the glass shred surface has proved that the particles originate from the glass matrix, despite the slightly acidic pH of the solution contained. Based on the results, the use of this glass-type as container for this infusion has been rejected.

1. Introduction
The use of infusions in medical therapy is growing annually. The devices available for home use have opened a new segment in sales and widen the demand each year. The global market for infusion devices is expected to be valued nearly $9.7 billion by 2014.[1] However the solutions used are produced under very strict conditions regulated and controlled by authorities such as FDA or other national and international organizations, the containers used are recently more and more under focus due to newly observed physical and chemical transformations.

Some of the numerous requirements these containers need to meet are: mechanical strength to resist the impacts during production, sterilisation storage and use, chemical inertness against the contained fluids, oxygen and vapour impenetrability, stability (no dissolution of the components and no material degradation shall occur).

The two main types of the containers are plastic bags and glass bottles. Their properties regarding the above mentioned criteria are summarised in table 1.

Table 1. Properties of infusion container materials

| Property               | Plastic infusion bag | Glass bottle  |
|------------------------|----------------------|---------------|
| easy to handle         | yes                  | no            |
| resist to sterilisation| difficult            | yes           |
| oxygen permeability    | difficult            | excellent     |
| vapour permeability    | difficult            | excellent     |
| Chemical inertness     |                      |               |
| no dissolution         | difficult            | ?             |
| no degradation         | difficult            | ?             |
The unarguable advantage of the plastic bags over glass bottles is their easy handling. While glass containers break easily, no one has to take special care for the plastic bags during packaging, transportation and use.

The resistance to sterilisation is opposite. The most widely used method is the use of autoclaves, where high temperature vapour is applied under elevated pressures. While glass resists to this process it is demanding to find the appropriate plastics. The same applies to the permeability both vapour and oxygen. The plastic films applied as infusion containers are coextruded or laminated because it needs more than one material to fulfil all these expectations. Though the questions around mechanical properties of the plastic bags can be solved by the use of multilayer films, the introduction of new materials might result in unwanted dissolution of the components [2, 3].

The reaction of various glasses with basic media is well known [4]. Some glass applications – like artificial bones, biomaterials – need the development of special glasses and thorough study of their in vitro and in vivo degradation [5]. The appearance of fine glass flakes as degradation product in alkaline media is reported [6]. The American [7] and European regulations [8] provide guidelines for the glass material allowed to use in pharmaceutical industry. The most widely used type of glasses are silicate glasses due to their chemical resistance, but even this type of glassware is unsuitable for storage of alkaline solutions.

To enhance chemical resistance various processes are developed. The use of sulphur containing surface treatments, have a long history in glass industry [9,10]. During the process called de-alkalisation, a thin surface layer is created, in which the alkali-ion concentration is lower than in the underlying matrix. This decreases the number of chemically active points on the surface, and makes the glass more resistant to chemical attack.

An infusion product still in development phase has arrived to our test facility from a major pharmaceutical company for examination of solid particles in the liquid phase. The presence of the contamination was observed during a light scattering study which has drawn the attention to their presence, but provided no information about the chemical nature of the particles. The compositional data is essential in order to reveal the source of the unwanted floating contamination.

Since the infusion glass was filled up after sterile filtration of the slightly acidic infusion solution (pH: 6.8), the following sources of contamination were presumed:
- excipient precipitation
- precipitation of the active ingredient
- contamination from outer source
- ineffective filtration

2. Experimental
To investigate the origin of the particles a scanning electron microscopic study was performed by use of a Hitachi TM-1000 Tabletop Scanning Electron Microscope equipped with energy dispersive X-ray fluorescent elemental analyser.

The sample was homogenised by vigorous shaking, and then filtered three times through the same 0.45 µm PTFE membrane (Phenex™, Part. No.: AF0-0510). The membrane was dried at 50°C during 24 hours. After drying and 2 hours of cooling, the particles were transferred to a black tape for better visualisation.

3. Discussion
After SEM analysis and XRF spectrum recording 5 main types of the particles could be separated:
- Fe-Al sedimentation
- Al-fibres
- amorphous alkaline type glass particles with high Cl content on the surface
- CaO₄(OH)₃ particles with K-Si-Al or K-Al-SI-Na compound-crystals
- amorphous alkaline type glass particle with high Cl and S contents on the surface.
The elemental composition of the particles found is summarised in Table 2.

| Element | Fe-Al particle | Al-fiber | glass particle high Cl content | CaO particle | glass particle high Cl ans S content |
|---------|---------------|----------|-------------------------------|--------------|-------------------------------------|
| Al %    | 14.2          | 100.0    | 5.3                           | 1.2          | 3.3                                 |
| Si %    | 0.3           | nd       | 7.4                           | 0.7          | 4.0                                 |
| Fe %    | nd            | nd       | nd                            | nd           | nd                                  |
| Na %    | nd            | nd       | 6.3                           | nd           | 10.8                                |
| Cl %    | nd            | nd       | 18.8                          | nd           | 26.5                                |
| K %     | nd            | nd       | 13.3                          | 2.9          | 13.6                                |
| Ca %    | nd            | nd       | 48.9                          | 95.1*        | 32.0                                |
| Si %    | nd            | nd       | nd                            | nd           | 9.9                                 |

* in form of CaOx(OH)y undefined stoichiometry composite

The group of glass particles with high Cl and S content on the surface was found to be the main component - approximately 90% - of the glass shred. SEM sample pictures are shown in figure 1, while a sample XRF spectrum is shown in figure 2.

Figure 1. SEM sample pictures of the solid particles (Fe-Al sedimentation, Al-fibres, amorphous alkaline type glass particles with high Cl content on the surface, amorphous alkaline type glass particle with high Cl and S content respectively).
The chemical composition of the particles does not support those preliminary assumptions that deal with excipient or active ingredient precipitation. The record of the sample has revealed that the bottle prior to the arrival to our site was opened and then recapped with aluminium flip-off cap. This is the origin of the - very rare - Al and Fe particles.

The main fraction - approximately 90% of the whole mass - consists of amorphous alkaline glass shred. The appearance of S on the particles is explained by the surface treatment of the glass, prior to filling with the infusion solution. The high Cl content on the particle surface is originated from the infusion. The Ca-containing particles show the decomposition of the glass as well. They are solid bubbles, leftover particles in the glass matrix, remained undissolved during the glass manufacturing process.

4. Conclusion
In contrast to the expectations degradation of glass containers can take place in neutral and slightly acidic solutions. This study has shown, if active sites remain – as in case due to production faults – aqueous solutions attack the material. The resulting glass shred and flakes make the product unsuitable for intravenous and other medical applications.

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