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Short communication

Stereomicroscopy as a potent analytical method for detection of glass micro-particles generated during snap-opening of ampoules

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Introduction

A large number of pharmaceutical formulations have been packaged using glass containers and ampoules, mainly due to its important characteristics that allow sterile production of recipients for drugs and other sterile substances (Schaut and Weeks, 2017). Ph.Eur. defines that for medicines intended for parenteral administration, only type I glass containers are suitable, i.e neutral glass, with a high hydrolytic resistance due to the chemical composition of the glass itself (Ph. Eur. 01/2019:30201). To meet the needs of different pharmaceutical applications, production of a variety of ampoules should be compliant with ISO 9187; quality control for ampoules should cover every phase of production.

The Ph. Eur. provides that the container chosen for a given preparation shall be such that the glass material does not release substances in quantities sufficient to affect the stability of the preparation or to present a risk of toxicity. However, there are reports on formation of glass micro particles during opening the ampoules and contamination of the medicine within (Carraretto et al., 2011; Hafez et al., 2012; Ghorpade and Shinde, 2022). These glass particles usually cannot be detected by naked eye, so more advanced technology is needed such as stereomicroscopy. It is clear that the presence of extrinsic particles in parenteral preparations can be a sign of a systematic issue and is unwanted.

The aim of this research was to determine the detectability of possible formation of glass micro-particles generated during the snap-opening of ampoules. Stereomicroscope was used for evaluation of size and form of the generated particles, in order to enable more meaningful insight for this critical phenomena pointing toward serious medical issue.

Materials and methods

Materials

Stemi 508 Carl Zeiss Microscopy GmbH microscope with *Axiocam ERc 5s* camera and built-in *Zeiss ZEN 2.6 (Blue edition)* software was used.

Five types of glass ampoules with different injectable fluids, from different manufacturers, were studied. A total of 30 ampoules were used, of various size and volume (1, 3, 4, 5 and 25 mL). A plastic ampoule opener was used during the snap-opening of the ampoules in order to reduce the risk of percutaneous injuries of the researchers.

Methods

The glass ampoules were wiped with alcohol. After a randomized selection, the ampoules were snap-opened manually and the sample was aspirated directly from the ampoules using 20 mL sterile syringes with 20G and 23G needles in order to avoid additional contamination from the ampoule neck. Each of the content was transferred to a sterile cell culture plate and was examined microscopically against a dark background. The diameter of the particles was determined using the built-in software, then they were photographed and the data was saved.

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Results and discussion

Due to the mandatory parameter in specification of parenteral preparations that the content of the ampoules is free from visible and sub-visible particles, these products might possess hidden health risk if during the opening of the glass ampoules by breaking it, secondary particulate contamination is introduced.

The final control check of the solution is performed by the medical professional who opened the vial before the parenteral application. Still, some of the reports (Joo et al., 2016) on aspirated then injected contaminants, indicated a need for more profound and systematic surveillance study on different batches / products / manufacturers.

Out of total 30 ampoules (5 ampoules per batch from 6 different products and different manufacturers) that were snap-opened, glass particulates were detected in all of the examined samples. The particulates were identified by their luminescence under the microscope's lighting, and their size ranged from 82 μm to 2.5 mm. The particles were of different shapes: round, flake-like, oblong and some with very sharp irregular shapes. Sharp-edged particles were more commonly detected in the ampoules with smaller volumes, in comparison to the ampoules with bigger volumes. This may be due to lack of suitable length proportion between the head of the ampoule (i.e. the part above the neck) and the total length of the ampoules.

The size range of the glass particles brings the severity of the potential and possible underestimated risks for patient health and safety. According to scientific reports (Perez et al., 2016), injected particles with diameter less than 0.5 mm may have negative effects (like: embolic, thrombotic and other vascular events, foreign body granuloma, etc.), and in case of larger fragmentation (above 0.5 mm), there can be immediate harmful mechanical effects to the human body.

In general, despite the carefulness during the opening, each sample was contaminated with glass particles, which were able to be aspirated through the syringe needle. This leads us to take in consideration the possible problems that impact on quality of the glass container. The problem with the quality may be due to different chemical composition of the glass, the width of the glass, the dimension ratio and position of the ampule neck related to the dimension of the whole ampoule, the critical parameters that impact the closing process of the ampoules, as well the thoroughness of validation of the whole manufacturing process.

Conclusion

Glass contamination of ampoules for parenteral use is an important and serious medical issue. This study confirmed that manual snap-opening of the ampoules is associated with high contamination with glass particulates. The issue seems not related to the batch, product, nor manufacturer. Possible cause might be linked to the manufacturing process, which means that stricter validation methods need to be implemented when it comes to primary glass packaging.

No matter the root-cause of the possible secondary particulate contamination of solution in glass ampoules, additional quality control parameter should be introduced for each parenteral preparation with such contact packaging. Considering the dimension range of the detected particulates, a stereomicroscope is not only a useful tool, but also necessary method for detecting contaminants that would obviously remained undiscovered by naked eye. The fact that this technique is underused is surprising, since nowadays there are many instruments available for lab use as well as for fieldwork, and the results can be combined with other methods for detection of many contaminants.

Having in mind that there are many safer packaging materials than breaking ampoules (plastic and glass pre-filled syringes, containers, vials, pens, bags… with plastic/rubber/silicon sealing), can it be that the use of glass braking ampoules is coming to an end?

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