J. Pharm. Pharmacol. 1997, 49: 1165–1166
Received July 15, 1997
Accepted July 21, 1997

Letter to the Editor

Detection of a Black Deposit in Intravenous Fat Emulsions

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The European Pharmacopoeia 1997 gives a short description of particulate contamination in injectable products: "Particulate contamination of injections and intravenous infusions consists of extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in solutions." The US Pharmacopeia 1995 and more recently the European Pharmacopoeia 1997 have described physical tests for the purpose of enumerating sub-visible extraneous particles within specific size-ranges. The US Pharmacopeia has defined maximum limits of particulate contamination. In the European Pharmacopoeia, however, specific limits of the maximum particle content will be stipulated in the relevant monograph. This work is not yet complete for the European Pharmacopoeia.

The test for visible particles is based on visible inspection in a defined viewing station; in the sub-visible range the particle counters used are based on the light-blockage principle (US Pharmacopeia & European Pharmacopoeia). Finally, filtering and particle counting by microscopy can also be used. Clear solutions with a viscosity similar to that of water can be analysed by particle-counting instruments. For other large-volume parenterals, for example fat emulsions, particulate contamination must be analysed by filtering and particle counting by microscopy.

The British Pharmacopoeia 1993 previously used particle counters based on the electrical zone-sensing principle, and maximum limits of particulate contamination were also defined. The British Pharmacopoeia has now adopted the methods of the European Pharmacopoeia (See the addendum to the British Pharmacopoeia).

When following the European Pharmacopoeia procedure for investigation of extraneous visible particles in fat emulsions, no particulate matter was visible with the naked eye when inspected in the viewing station. To investigate particles in the sub-visible range, the fat emulsion was filtered in a laminar-flow cabinet through a gridded membrane filter (0·45 μm) before counting of the particles by microscopy. Only 0·6 particles mL^{-1} larger than 10 μm and 0·1 particles mL^{-1} larger than 25 μm were detected. Without reservation the sample passed the US Pharmacopeia criteria (12 particles mL^{-1} larger than 10 μm and 2 particles mL^{-1} larger than 25 μm) for particulate contamination. Using a test for particles (described below) different from those published in the pharmacopoeia, we have previously identified a black sediment in intravenous fat emulsions from one manufacturer. The particles were metallic because they could be moved by a magnet placed outside the glass bottle. After discussion with the manufacturer, the production process was improved and subsequently we were unable to identify even traces of such contaminants in these products. Fat-emulsion products from two other manufacturers are also marketed in this country. Although we have not found particles in products from one, particles were detected in fat-emulsion products from the other. Six bottles from one batch containing 200 mg mL^{-1} fat emulsion and 6 bottles from 2 batches containing 100 mg mL^{-1} were investigated. Black deposit was found in all the bottles investigated.

The technique used for detection of black, heavy particles in fat emulsions is trivial, but reliable. Contamination of the sample by the investigator is not possible because the bottle seal is not broken during the experiment. The bottles are locked in a position at an angle of approximately 30° from the vertical. After a month or more in this position gravity has moved the heavy particles to the junction between the sloping bottom and the wall of the glass-bottle, forming a grey-black deposit (Fig. 1). To exclude the possibility of optical phenomena in the glass, the position of the black deposit is marked outside the glass and then the bottles are rotated carefully through 90° about the axis of the bottle, while at the same time keeping the slope of approximately 30°. The deposit starts moving downwards, and after approximately 2 h a black streak can be seen along the bottom. After 3 days the black deposit has more or less collected at the bottom of the junction. If the bottle is treated incautiously, the deposit disappears, but it can be detected again by use of the same technique. Fig. 1 shows two groups of contaminants, a cloud of black dust in which individual particles cannot be seen, and many clearly defined larger particles.

Some of the sediment is affected by a magnet. The bottle with the sediment is first rotated through 90° about the axis. A bar magnet is placed against the glass bottle at a point past which the sediment must move on its way to the bottom. Approximately 5–10% of the black material is retained by the magnet. It is conceivable, however, that some of the black material occasionally sticks to the wall of the bottle near the magnet. When the magnet is removed, the material moves downwards ruling out all doubt about the magnetic properties of the retained material.

The evident observation of the particles in the bottle and the results from particle counting on the filter, seem contradictory.

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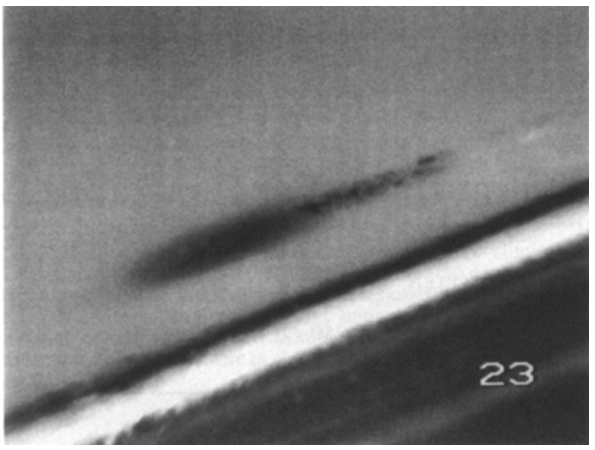

FIG. 1. Black deposit in intravenous fat emulsion; the photograph was taken through the wall of the original glass bottle. A colour video camera with macro lens and a colour video printer were used to produce the picture without further magnification. Bar = 3 mm.

A possible explanation is that many of the very small particles pass through the perforations in the filter. The long time taken for the particles to settle is another indication of the small size of the particles. This hypothesis can be tested. After careful shaking of the bottle and assuming that the particles are distributed evenly throughout its volume, 50 mL of the emulsion was filtered. The particles on the filter were counted, giving results similar to those described above. The unfiltered solution (450 mL) was again fixed in the position described and after approximately one month, a black deposit was again found in the bottle. The large particles apparent in the photograph can be explained by the formation of aggregates from small particles.

Infusion of the sediment into the patient is by introduction of 'contaminants from within', which must be avoided. Identifying products from one more manufacturer with sediment in their fat emulsions, indicates problems with the production machinery not previously envisaged. A search on Medline did not reveal articles about similar problems.

As a postscript it should be remarked that the products investigated passed the US Pharmacopeia test for particulate matter by a wide margin. The question must be raised whether the US Pharmacopeia test and even the new European Pharmacopoeia test for particulate matter are sufficient because the use of these products cannot be excluded by following the criteria in the Pharmacopoeia.

Acknowledgement

We wish to thank Dr Laszlo Borka for photography and help with the microscope.

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