Particulate Contamination

Definition
Particulate contamination describes the unintended presence of extraneous, mobile and undissolved particles in a parenteral solution. These particles can be of various size, defining them as detectable by visual inspection (in general ≥ 50 µm) or as sub-visible with a range of 2–50 µm in size in general. Especially the sub-visible sized particles demand specific analytical tests for their detection (BSP 2009; USP 2009).

Causes
Several causes of particulate contaminations of IV fluids are known. This is because drugs are available in various containers (for example vials, ampoules, pre-filled containers and premixed solutions) and their usage and manipulations are highly diversified. Consequently, many types of particle contamination can occur (Fig. 2):
- Glass
- Plastic
- Rubber
- Undissolved particles/drugs

Glass ampoules especially pose a high risk of particulate contamination, as glass fragments may enter the ampoule when it is opened (Fig. 1) [Douglas et al. 2001]. If a needle (for example 18G) is used for removing a glass ampoule’s content, small glass particles can pass through the needle into the syringe and easily be injected into patients. This risk remains if drugs are routinely administered via the injection port of the intravenous cannula, which is a safety measure designed to decrease sharps injuries to the medical staff [Lye 2003].

Plastic contamination occurs frequently due to particles from the infusion container’s raw material itself and from the injection port due to its usage with sharp items [Walpot et al. 1989]. The insertion of a needle through the stopper of a medication vial or infusion container can shear off a small piece of the stopper. This particle may float in the medication or IV solution. If the particle is small or masked (e.g. by the label, a matching background or a colored vial), the contamination may be unnoticed. The particle may then be aspirated into a syringe and injected into a patient [Roth 2007].

Undissolved solids in drugs or parenteral solutions can also be an origin of particulate contamination [Durgan et al. 2004].

A further frequent cause of particles occurs as a consequence of incompatibilities. This is an undesirable reaction between an admixed drug and the carrier solution, the container or further drugs added to the IV solution itself. Incompatibilities can also be present when various solutions are mixed in infusion lines and catheters for parenteral administration. As one consequence of an incompatibility, precipitations can occur leading to the particulate contamination [Josephson 2006, RCN 2005, Douglas et al. 2001].

The occurrence of contamination was shown by Preston et al. [2004], who identified glass particles bigger than 130 µm in 57 % of the controlled injectable solutions. Additionally, Lye [2003] found in a number of more than 500 glass ampoules an average of 0.22 glass particles per unit. The injection of such particles into the body of the patient is therefore a prominent risk.
Fig. 1: Glass fragments may enter the ampoule when it is opened.

Fig. 2: Electronmicroscopy of various particles found in samples of IV preparations prior to use.
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Consequences

Fig. 3: Overview of parts and organs of the human body mainly affected by particulate contamination of IV fluids.
Symptoms and clinical signs
All types of particles present in the intraluminal compartment which are not eliminated by a filter are directly entering the human body (Fig. 3). These particles from plastic, glass or rubber can have unfavorable effects, especially in patients who are already ill. Particles as small as 1.5 µm can cause blockages in patients, whereas particles of 6 µm can cause blockages in healthy subjects [Lehr et al. 2002; Anonymous 2004]. Damage to various organs, such as the lungs, kidneys, liver and spleen are described in general [Yorioka et al. 2006, Lye 2003, Puntis et al. 1992, Walpot et al. 1989, Turco et al. 1971], but particularly affected are severely ill patients [Jack et al. 2009, Oie et al. 2005, DeLuca et al. 1975, Schroeder et al. 1976, Turco et al. 1971]. Patients with prior organ damage are especially sensitive, as particles can exacerbate their impaired blood micro-circulation [Anonymous 2004, Lehr et al. 2002]. A further clinical sign that can be caused by glass particles from glass ampoules is phlebitis [Yorioka et al. 2006, DeLuca et al. 1975, Schroeder et al. 1976]. Phlebitis is evident as local warmth, with pain, swelling and reddening at the affected site of parenteral administration [Grünewald et al. 2004].

The infusion of glass particles can lead to pulmonary silicotic changes and nodular fibrosis of the liver, spleen and small intestines as a result of foreign body reaction [Lye 2003, Sabon et al. 1989]. Also, glass fragments in drugs have been shown to induce an adult respiratory distress syndrome and pulmonary artery granuloma in immature infants [Yorioka et al. 2006, Puntis et al. 1992, Walpot et al. 1989]. Contamination with silicone particles can lead to granulomatous lung disease [Bowen et al. 1981]. Other complications recorded in association with plastic migration include lung disease [Rodriguez et al. 1989], myocarditis [Kossovsky et al. 1990], and skin rash [Ellenbogen et al. 1975]. These contaminations have been reported after migration of large volumes of plastic. Little is known about the effect of silicone in humans over a long period. Animal studies demonstrated minimal reactions in the brain [Dewan et al. 1995a] and lungs [Dewan et al. 1995b; publications ex Dewan et al. 2002]. Rubber complications range from clinically occult pulmonary granulomas to local tissue infarction and pulmonary infarction. [Roth 2007, Lehr et al. 2002].

Particles from plastic, glass or rubber can cause phlebitis and also damage the lungs, kidneys, liver and spleen. Apart from harming patients, this may lead to additional treatment costs as well as extended duration of hospital stays.

Prominent risks
- impairment of microcirculation
- blockages of blood vessels
- damage to various organs
- phlebitis
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Consequences

Risk related costs for the healthcare institution
Given the wide spectrum of patient complications caused by the various particles from plastic, glass and rubber found as contamination, it has to be assumed that particulate contamination can lead or contribute to extended duration of hospital stay as well as additional treatment costs.

A cost evaluation of the risk can be done by assigning costs to their related clinical treatment and resulting extended length of stay. The cost can be calculated using the average daily cost [Gianino 2007, Bertolini 2005] of the expected clinical treatment. Fig. 4 shows the results of such a calculation for selected examples of complications.
According to the severity of its direct and indirect complications, preventing the entrance of foreign particles into the patient's circulatory system can result in significant budget savings for the healthcare provider. In the case of health complications such as severe organ dysfunctions requiring full ICU treatment, a hospital may save up to 56,670 € per single case.

**Conclusion**

According to the severity of its direct and indirect complications, preventing the entrance of foreign particles into the patients circulatory system can result in significant budget savings for the healthcare provider. In the case of health complications such as severe organ dysfunctions requiring full ICU treatment, a hospital may save up to 56,670 € per single case.

**References**


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Fig. 4: Estimation of possible additional costs as a consequence of complications caused by particulate contamination. In order to facilitate the attribution of each complication to the cost calculation, severity levels were introduced.

ARDS: Acute Respiratory Distress Syndrome. RICU: Respiratory Intermediate Care Unit
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Preventive strategies

Fig. 5: Open ampoule or vial according to standards of care. Use filter straw for withdrawal of the infusion.

Fig. 6: In-line filter and infusion set filter prevent the infusion of particles into the patient.
Preventive strategies

The strategy to prevent particle contamination at the point of origin is based on many aspects, such as using quality products to avoid the generation of particles (e.g., stopper of vials) or using products with a low intrinsic particle load (e.g., plastic containers instead of glass ampoules). Another important factor is the avoidance of drug incompatibilities.

If a particulate contamination has occurred, the usage of in-line filters provides an important safety benefit. In addition, filters function as an early warning system, providing optical control of the infusate and stopping the infusion when the filter becomes obstructed [Kuramoto et al. 2006, Anonymous 2004].

Particle contamination may be reduced by using an in-line filter and filter needle to withdraw drugs from glass ampoules prior to administration [Panknin 2007, Heiss-Harris et al. 2004, Preston 2004, Lye 2003]. The in-line filter devices can remove particulate contamination, micro-biological contamination and air from infusion solutions (not all devices used can remove all three types of contamination).

It is, however, not standard practice to perform filtration [Jack et al. 2009, Ball 2003]. Filters in the intravenous line may be positioned close to the patient access. Dispensing pins (spikes) also provide protection against particles in solution [Ohgke et al. 1997].

In-line filters are recommended for:

- Non lipid-containing solutions (0.2 μm filter) [Ball 2003, Lehr et al. 2002, Bethune et al. 2001]
- Lipid infusions or total nutrient preparations (1.2 μm filter) [Ball 2003, Bethune et al. 2001]

The ISO 8536-4 norm (for infusion sets) recommends filtration for patient protection. Generally, the fluid filter used has a nominal pore size of 15 μm [ISO 8536-4].

Preventive strategies

- **avoid glass ampoules**
- **use filter straws or filter needles**
- **incorporate appropriate filters into IV administrations**

The British Pharmaceutical Nutrition Group (BPNG) has issued a guideline about how to avoid contaminating the body with insoluble particles [Ball 2003, Bethune et al. 2001]:

- Solutions being added to parenteral nutrition taken from glass ampoules or vials should be added to the final parenteral nutrition admixture through a filter with a maximum pore size of 5 μm. Filter needles and dispensing pins (spikes) with particle filter minimize the risk of injecting glass particles into patients (Fig. 5).
- Appropriate filters should be used during the administration of parenteral nutrition to patients who require intensive or prolonged parenteral therapy, namely immunocompromised patients, neonates and children, and patients receiving home parenteral nutrition.
- When used, in-line filters should be placed as close to the patient as possible (Fig. 6).
- The 1.2 μm filters should be used for the administration of solutions containing lipids, including all-in-one admixtures, and changed every 24 hours.

Several associations and official bodies recommend the incorporation of a filter in the intravenous line:

- British Pharmaceutical Nutrition Group (BPNG)
- Royal College of Nursing (RCN 2005)
- National Coordinating Committee on Large Volume Parenterals (NCCLVP)
- Intravenous Nurses Society (INS)
- Food and Drug Administration (FDA)
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**Ecoflac® plus**
The state of the art IV solution container that offers safe and convenient application of all IV procedures from drug admixture to drug delivery.
- The superior properties of the resealable port membrane prevent coring of elastomeric particles when punctured with a needle or an infusion set.

**Intrafix® SafeSet**
IV set for safe and convenient infusions.
- A 15 μm particle filter prevents the infusion of particles.
- Using 15 μm particle filter in IV sets is recommended in the international standards for infusion sets for single use in ISO 8536-4 (gravity) and in ISO 8536-8 (infusion equipment for use with pressure infusion apparatus).

**Safeflow / Ultrasite®**
Capless valves for safe and convenient access to the infusion line.
- B. Braun’s needle-free infusion systems reduce the risk of particulate contamination by preventing coring of membranes.

**Intrapur® and Sterifix® Infusion Filters**
A whole range of filters for safe infusion therapy.
- Membranes of 0.2 μm and 1.2 μm separate particles and lipid macro micelles larger than the pore size of the filter.
Mini-Spike®
Vented dispensing pins for safe and convenient fluid transfer with syringes.
- Particles such as undissolved lyophilisates in the fluid are retained due to the inbuilt 5 µm filter.

Sterifix® filter straws
Filter straws for particle free withdrawal and filtration of fluids from ampoules.
- A 5 µm filter prevents the administration of glass particles, which can occur when ampoules are opened. The filter is already integrated in the hub of the straw.

Mini-Plasco® connect / Mini-Plasco®
The plastic ampoule offers small volumes of IV solution for drug preparations.
- Low intrinsic particle load as Mini-Plasco® plastic material does not produce such particles.
- Can easily be opened without particle creation.
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Literature


BSP: British Pharmacopoeia, 2009


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The summarized scientific information in this document has been prepared for healthcare professionals. It is based on an analysis of public literature and guidelines. The intention is to give an introduction to the risks commonly associated with infusion therapy and to increase the awareness of healthcare workers to these kinds of problems. Due to its summary nature, this text is limited to an overview and does not take into account all types of local conditions. B. Braun does not assume responsibility for any consequences that may result from therapeutical interventions based on this overview.