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Particle size in parenteral fat emulsions, what are the true limitations?

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Abstract

Intravenously administered fat droplets exceeding 5 μm in diameter are believed to cause adverse reactions, in particular emboli in the lungs. We investigated the fat particle size and particle size distribution of commercially available parenteral fat emulsions. Both laser diffraction and light obscuration were used as a detection technique. With the light obscuration technique a significant number of particles > 5 μm in diameter was detected in all investigated emulsions. The investigated emulsions have been in use for several years, without reports of important adverse reactions in this respect. Therefore, it is concluded that the requirements concerning the particle size limitations in fat emulsions should be reconsidered.

Keywords: Particle size; Parenteral fat emulsions; Adverse reactions

Intravenous fat emulsions have been on the market for more than 40 years. They are used in large volumes in parenteral nutrition as well as in smaller quantities as drug carrier systems for lipophilic drugs (Li and Caldwell, 1994).

It has been clearly demonstrated that appropriately prepared fat emulsions (with a mean fat particle size comparable to that of chylomicrons) can be given safely in large quantities to humans (Geyer et al., 1951). In animal studies, Fujita et al. (1971) found a relationship between particle size and toxicity. They showed that the toxicity increases with higher average particle size and broader particle size distribution. They concluded that the amount of fat emulsion administered and the number of large particles is a major determinant of the incidence of adverse reactions.

Large particles are believed to be responsable for adverse effects. However, the upper size limit is still disputed. Many authors take 5 μm as the upper limit, since larger particles pose a risk of lung embolism (Singh and Ravin, 1986; Driscoll et al., 1995). The section on intravenous infusions

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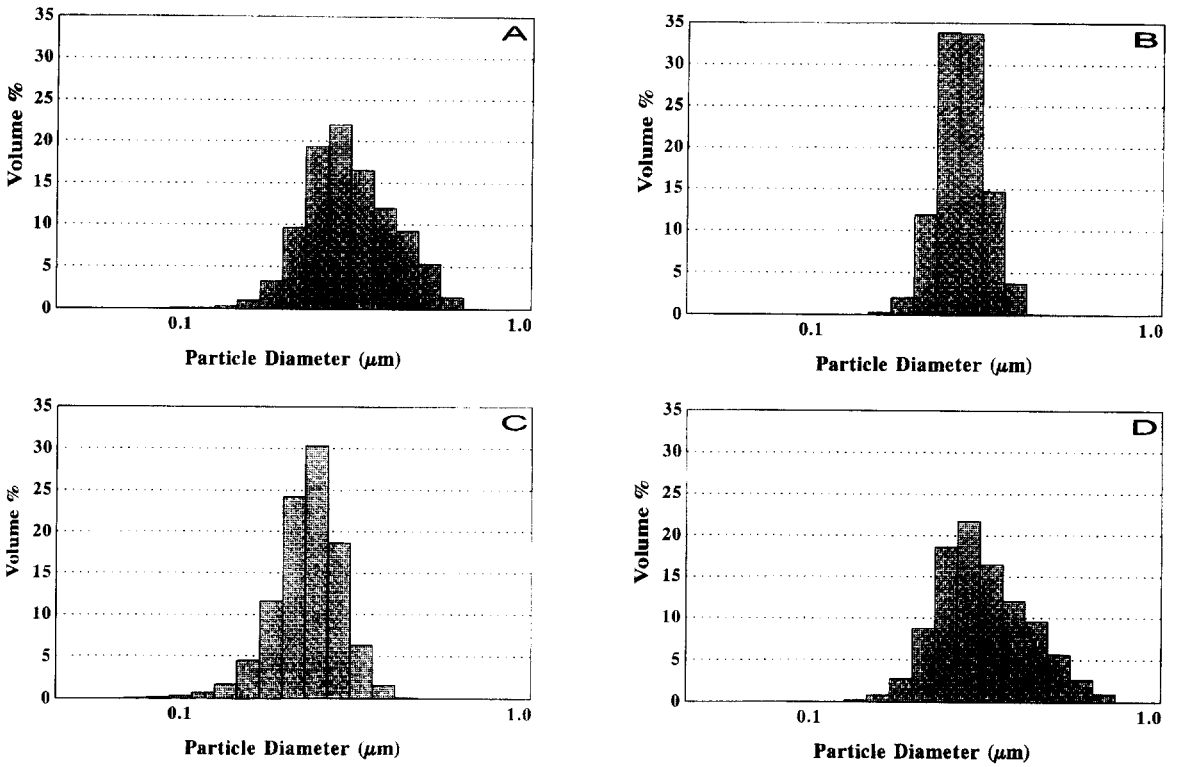

Fig. 1. Bar graphs of particle-size volume distribution in Intralipid 10% (A), Lipofundin MCT/LCT 10% (B), Diprivan-10 (C) and Kabimix (D), determined by laser diffraction (Mastersizer®).

in the British Pharmacopoeia (1980) states that the diameter of globules of the dispersed phase of emulsions may not exceed 5 μm. However, this is the only official particle size limit for injectable emulsions ever mentioned. In later editions of the BP this requirement has been removed. A requirement for particles in intravenous infusions in general is mentioned in for example the section particulate matter of the United States Pharmacopeia 23 (US Pharmacopeia, 1995). However, it is questionable whether this limit is applicable to the globule size of parenteral fat emulsions.

New perceptions on the in vivo behaviour of fat emulsions have diminished the emphasis previously laid on the 5 μm upper limit. It has been demonstrated that any possible blockade of blood capillaries in the lung may be reversible due to the biodegradation of fat droplets (Müller and Heinemann, 1992; Schwarz et al., 1994). Moreover, it has been reported that lipid particles with diameters even greater than 7.5 μm can deform and pass through the pulmonary vasculature without difficulty (Burnham et al., 1983).

Many stability studies demonstrate the presence in TPN admixtures of particles much larger than 5 μm. For example, Metha et al. (1992) found particles up to 40 μm in their all-in-one admixtures.

Since emulsions are intrinsically unstable, rapid changes in particle size and particle size distribution are considered to reflect poor physical stability. Therefore, a great deal of attention has been paid to the analysis of these two characteristics. A number of techniques have been used, including microscopy, electrical zone sensing and light scattering (laser diffraction and photon correlation spectroscopy). Recently, a technique using light obscuration has become available. This method, using a single-particle optical sensing technique, allows counting of large numbers of particles. Therefore a small number of large particles in the emulsions can be detected (Washington, 1992).

We used both laser diffraction (Mastersizer S®, Malvern, UK) and light obscuration (Accusizer®, Particle Sizing Systems Inc, Santa Barbara, CA) as a detection technique. The Mastersizer® measures particles in the range of 0.05–3500 μm. Laser diffraction provides scattering patterns containing information regarding the particle size. From these patterns the particle size can be calculated. Since the light beam illuminates many particles simultaneously, the instrument provides a distribution of particle sizes, but does not accurately count the number of particles (Washington, 1992). The samples were injected undiluted and automatically diluted by the system.

The Accusizer® measures particles in the diameter range of 1–150 μm. To avoid coincidence error, which is primarily caused by a high sample concentration, the samples have to be prediluted. In our experiment each sample was diluted 1:5000 with nearly particle-free reversed osmosis-water. This dilution yielded consistent and reproducible results and caused no significant modification of size distribution. The threshold for counting was set at 1.05 μm.

We have investigated the particle size and particle size distribution of some commercially available parenteral fat emulsions: two plain fat emulsions (Intralipid 10%®, Lipofundin MCT/LCT 10%®), one all-in-one TPN admixture (Kabimix®), and one fat emulsion used as a drug carrier (Diprivan-10®, a parenteral fat emulsion containing 1% of the anaesthetic propofol).

With the Mastersizer® none of the emulsions tested showed particles with a diameter > 1 μm (Fig. 1). In Lipofundin MCT/LCT as well as in Diprivan-10 no particles with a diameter larger than 0.58 μm were detected. For Intralipid and Kabimix we found upper size limits of 0.78 μm

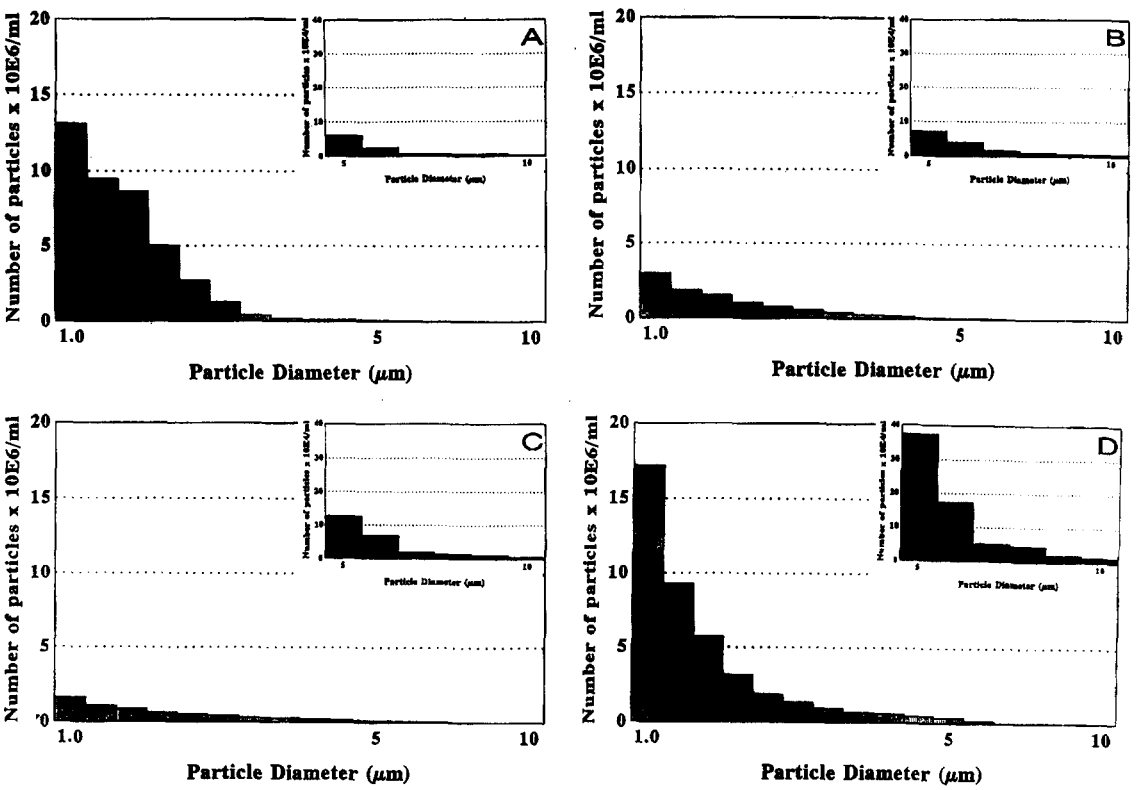

Fig. 2. Bar graphs of particle-size number distribution above 1.05 μm in Intralipid 10% (A), Lipofundin MCT/LCT 10% (B), Diprivan-10 (C) and Kabimix (D), determined by light obscuration (Accusizer®).

and 0.91 μm, respectively. Contrary to the results obtained with the Mastersizer®, the Accusizer® detected particles larger than 5 μm in all samples (Fig. 2).

The difference in results from both techniques can be explained by the lack of sensitivity of the Mastersizer® in determining small numbers of larger particles in a bulk of smaller particles. Even if 99.99% of all particles have a diameter smaller than 1 μm, there might still be many particles with a diameter larger than 1 μm, which remain undetected by the Mastersizer® since it is not a single particle counter.

Light obscuration has recently been used in studies on TPN emulsion stability. Driscoll et al. (1995) used this technique to study the effect of six independent factors on the stability of i.v. nutritional emulsions. They showed that emulsions in which $>0.4\%$ of the fat particles are above 5 μm, are likely to become unstable.

From the single fact that infusion of significant quantities of large fat particles does seldomly lead to adverse reactions, it appears that the requirement in BP 1980, concerning particles exceeding 5 μm, is obsolete. Now that new particle detection techniques have emerged, new requirements for the limitation of particle sizes in intravenous fat emulsions have to be established. It would seem logical that next to the mean particle size requirement, also limitations be specified for the particle size distribution. Special attention should be paid to the number of large particles and the upper size limit. Each requirement should include the techniques and methods to be used.

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