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The production of parenteral feeding emulsions by Microfluidizer

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Summary

A novel homogenizing device, the Microfluidizer, has been used for the preparation of soya oil/water emulsions using egg lecithin as emulsifier. The resultant emulsions have been compared with those produced on a small scale by ultrasonication, and 'Intralipid' 10% and 20% as examples of commercially available products. The Microfluidizer produced emulsions with droplet size and polydispersity similar to those of the commercial product 'Intralipid' , and with lower polydispersity and droplet size than those produced by ultrasonication. Emulsion droplet sizes were smaller and distributions narrower when the apparatus was operated at a higher temperature. The Microfluidizer also had several practical advantages over ultrasonication for the preparation of small quantities of emulsions for experimental purposes, and would appear to be a useful technique for the preparation of intravenous fat emulsions.

Introduction

Patients receiving i.v. nutrition have a need for essential fatty acids, which is usually provided by i.v. infusion of an emulsion of triglycerides in water, emulsified by lecithin. The behaviour of these preparations in vivo, and their preparation and stability, has been the object of much study, and is well understood (see e.g. Allen and Lee, 1969; Davis, 1974; Davis et al., 1985; Washington and Davis, 1987). Commercial products, typified by 'Intralipid 10%', are made using a valve homogenizer, which is available for batch volumes of 0.5 litre and larger. Smaller quantities for development and experimental purposes are often prepared by ultrasonic probe. Although inexpensive and convenient, the probe method has a number of disadvantages, including excessive sample heating, contamination of the product with titanium from the probe, broad droplet size distributions and poor droplet size reproducibility.

The Microfluidizer (Fig. 1) is a relatively new homogenizing device which is based on the submerged jet principle. A practical review has appeared elsewhere (Washington, 1987a and b). The premix flow is forced by a high pressure pump through an 'interaction chamber'; this consists of a system of channels in a ceramic block, which split the premix into two streams. These are recombined at high velocity to produce droplet shear; the product can be recycled for optimum results. Batch sizes are conveniently 20–200 ml for the M110 Microfluidizer studied here, but versions

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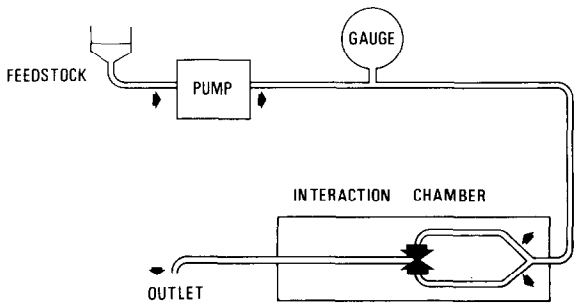

Fig. 1. Microfluidizer: schematic diagram.

for both smaller and production-scale operation are available. The apparatus has been studied as a possible method for preparing liposomes in bulk (Mayhew et al., 1984).

The primary requirements for intravenous emulsions are a lack of large (diameter > 1 μm) emulsion droplets, and the absence of contamination from the homogenizer itself. Emulsion droplet diameter can be evaluated using laser diffraction particle sizing, which is sensitive to particles in the size range 1–100 μm. Additionally, the emulsion should have a mean droplet diameter below 0.5 μm, that of most commercial products being in the range 0.25–0.4 μm.

We have already demonstrated that the Microfluidizer can be used for the production of fluorocarbon blood substitute emulsions (Sharma et al., 1986) and poly-(hydroxybutyrate) particles (Koosha et al., 1987) via emulsion processes. We have extended these studies to produce soya oil/water emulsions stabilized by egg lecithin, using a laboratory M110 Microfluidizer and an ultrasonic probe, and have compared the results with those of commercial emulsions made using a valve homogenizer (Intralipid 10%).

Materials and Methods

Soya oil was obtained locally from J. Sainsbury PLC. The egg lecithin emulsifier used was i.v. grade Lipoid E80 kindly donated by Lipoid KG. 'Intralipid 10%' (batch no. 61166) and 20% (batch no. 62833) were obtained from the Hospital Pharmacy, Queens' Medical Centre, Nottingham.

Emulsions (50 ml) were prepared by dispersing the lecithin (0.6 g) in water (45 ml) using a small laboratory blender (Silverson Machines Ltd.), followed by addition of the oil (10% or 20% as required). The whole was then homogenized for 10 min at 10000 rpm (Silverson blender) and poured directly into an M110 Microfluidizer for processing. The process variables available were operating pressure, temperature, and number of cycles through the Microfluidizer. For experiments at 10 °C and 70 °C, the Microfluidizer was immersed to a depth of 10 cm in ice slurry or hot water, respectively. Premix samples (50 ml) were prepared identically for ultrasonic emulsification, and ultrasonicated for 30 min while immersed in an ice bath, using an ultrasonic probe (Dawe 7532B Soniprobe).

All droplet sizes are z-average mean diameters measured as described by Douglas et al. (1984) using photon correlation spectroscopy (Malvern Instruments 7025 correlator, Siemens 40 mW He-Ne laser). Data were transferred directly to a Commodore 3032 computer and analysed by the method of cumulants using application software supplied by Malvern Instruments.

The relative proportions of droplets of diameter greater than 1.2 μm were measured using laser diffraction (Malvern 2600 particle sizer). The accuracy of both sizing techniques was checked using standard polystyrene microspheres (Polysciences). It should be noted that the figures quoted for the proportion of droplets larger than 1.2 μm are only relative measures, since the laser diffraction sizer is not able to make an accurate assessment of the number of droplets smaller than this diameter. The actual number of droplets of diameter greater than 1.2 μm is a very small proportion of the total number of droplets.

Results

Commercial emulsions

The droplet diameters and polydispersity of the preparations Intralipid 10% and 20% are shown in Table 1. The droplet diameters were 267 and 334 nm respectively, which is typical of many commercial i.v. feeding emulsions.

TABLE 1

Droplet diameters of 'Intralipid 10% & 20%'

System	Mean droplet diameter ± S.E.M.	Polydispersity ± S.E.M.
Intralipid 10%	267 ± 2 nm	0.11 ± 0.02
Intralipid 20%	334 ± 2 nm	0.12 ± 0.02

Emulsions produced by ultrasonic probe

These were prepared using 5%, 10%, and 20% soya oil, with 1.2% egg lecithin in each case. The droplet diameters and polydispersity of the preparations are given in Table 2. The 10% soya oil emulsion had a similar mean droplet diameter to the corresponding commercial emulsion, but a higher polydispersity (0.18 vs 0.11). The 20% emulsion had a much larger droplet diameter (518 nm vs 334 nm for Intralipid 10%) and a larger polydispersity (0.35 vs 0.12).

TABLE 2

Droplet diameters of emulsions produced by ultrasonic probe

System	Mean droplet Diameter ± S.E.M.	Polydispersity ± S.E.M.
5% Soya oil	230 ± 5 nm	0.18 ± 0.02
10% Soya oil	271 ± 3 nm	0.17 ± 0.02
20% Soya oil	518 ± 20 nm	0.35 ± 0.02

Microfluidized products

It was first necessary to find the optimum number of cycles for the emulsion through the Microfluidizer. The droplet diameter and polydispersity of a 10% emulsion as a function of number of cycles through the Microfluidizer are shown in Figs. 2 and 3, respectively, at the maximum operating pressure of 10000 psi. The droplet diameter decreased from 380 nm for a single cycle, to a plateau of 250 nm after 4 cycles, further processing having a negligible effect. A similar effect on the polydispersity was observed, from a value of 0.2 for one cycle to 0.12 for 4 cycles. Consequently all subsequent samples were processed for 6 cycles to

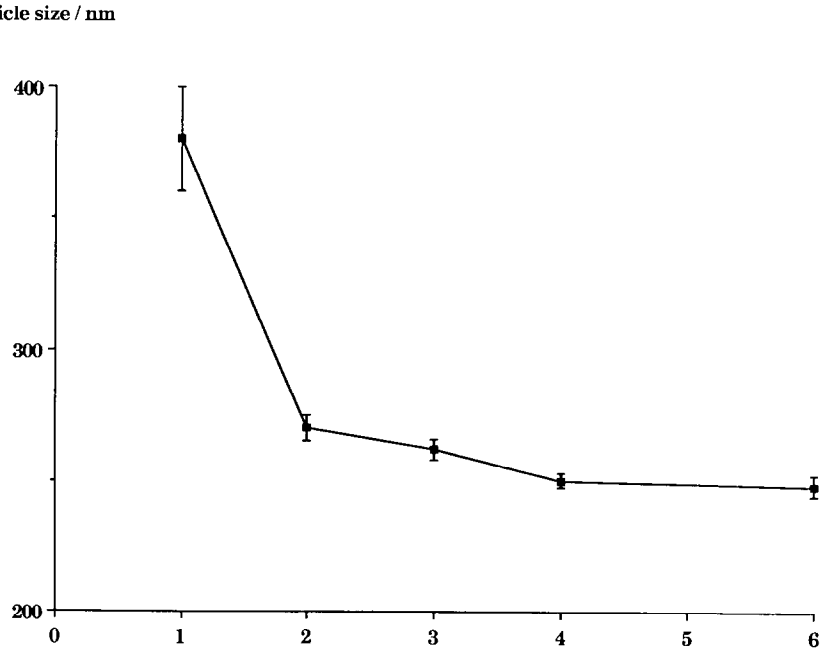

Fig. 2. Emulsion droplet diameter vs number of passes through the Microfluidizer (10% oil phase, processed at 10000 psi.; mean ± S.E.M.).

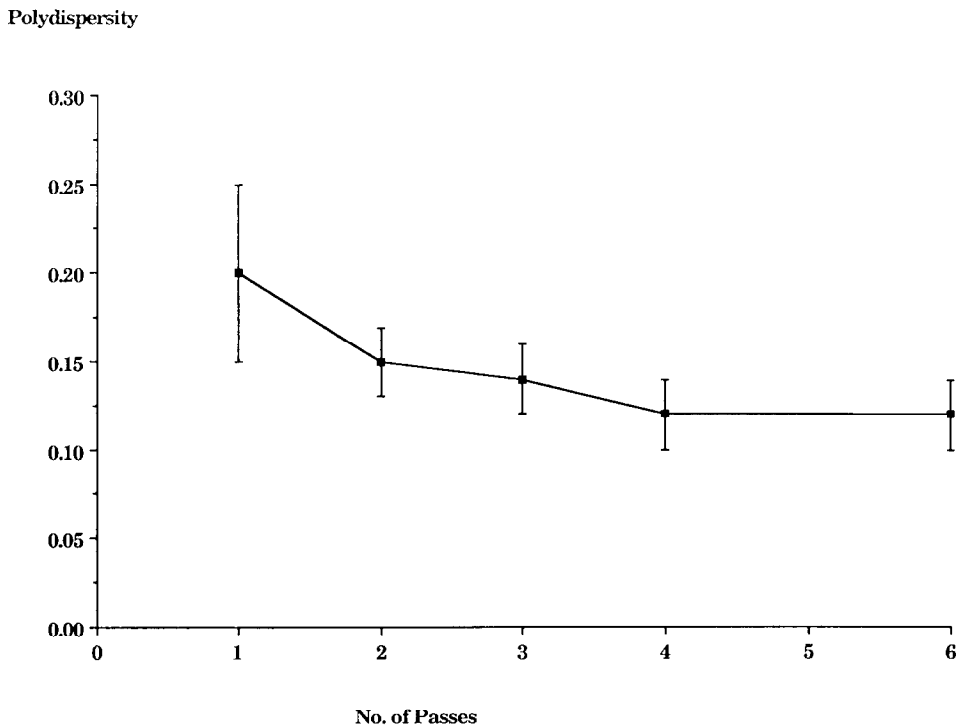

Fig. 3. Emulsion polydispersity vs number of passes through the Microfluidizer (10% oil phase, processed at 10000 psi.; mean ± S.E.M.).

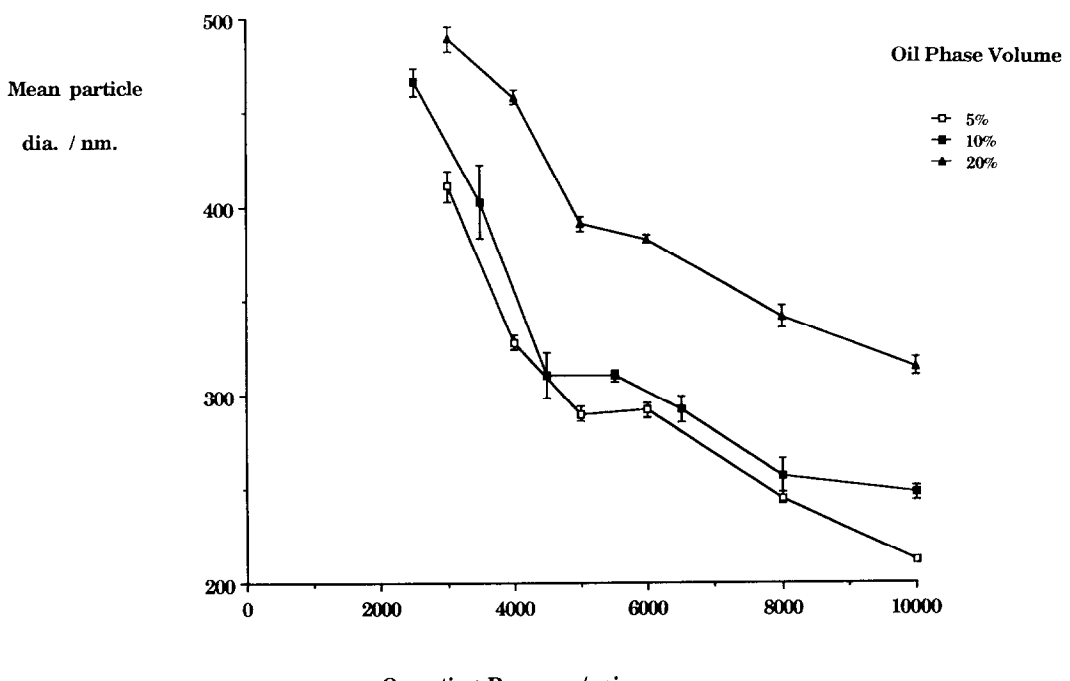

Fig. 4. Emulsion droplet diameter vs Microfluidizer operating pressure (6 cycles, mean ± S.E.M.).

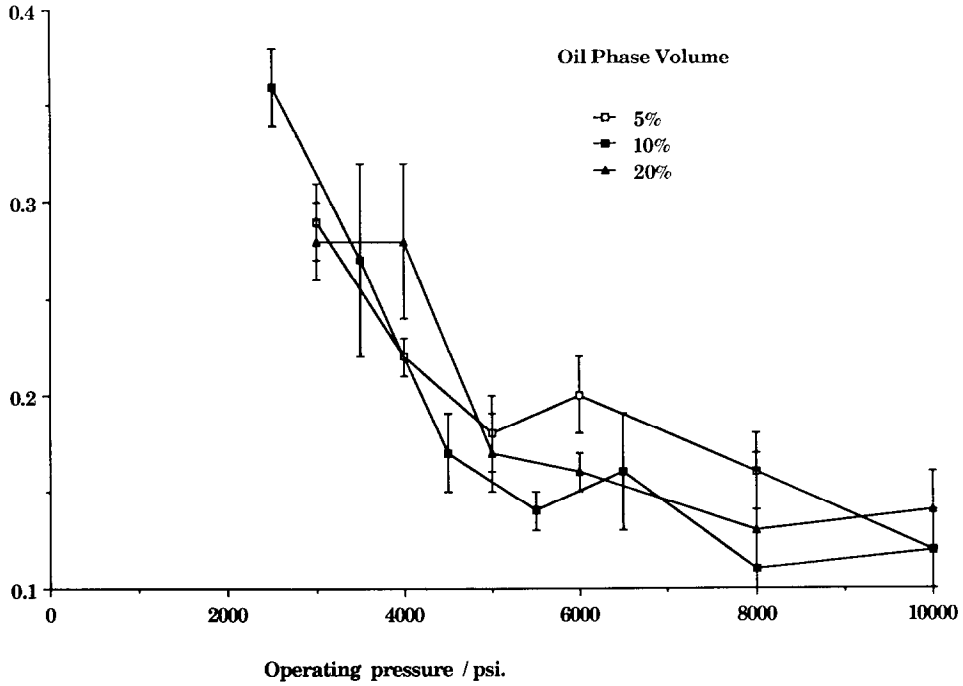

Fig. 5. Emulsion polydispersity (vertical axis) vs. Microfluidizer operating pressure (6 cycles, mean ± S.E.M.).

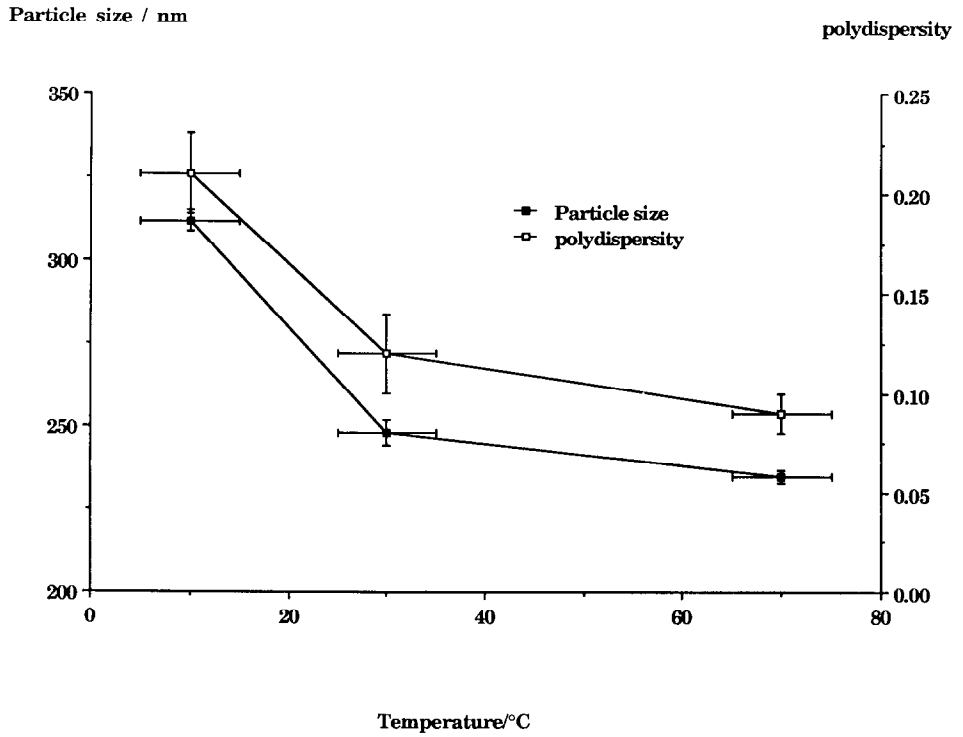

Fig 6. Effect of processing temperature on mean droplet diameter and polydispersity of emulsions prepared by Microfluidizer (10% oil, 10 000 psi, 6 cycles, mean ± S.E.M.).

ensure minimum droplet diameter without excessive processing.

Emulsions were prepared using 5%, 10%, and 20% soya oil, with 1.2% egg lecithin. The premixed feedstocks used had mean droplet diameters of 8 μm (5% oil), 13 μm (10% oil) and 16 μm (20% oil). The influence of the homogenizing pressure on droplet diameter and polydispersity for the three formulations is shown in Figs. 4 and 5, respectively. In all cases the droplet diameter and polydispersity decreased with increasing pressure. The emulsions containing the highest proportion of oil produced the largest droplets and the highest polydispersity at a fixed homogenizing pressure. The droplets produced at the highest pressure (10 000 psi) were of a similar diameter and polydispersity to those of the corresponding commercial products.

The effect of temperature on the droplet diameter and polydispersity is shown in Fig. 6. The temperature of the product could be controlled to $\pm 5\,^{\circ}C$, the uncertainty being due to the fact that the emulsion temperature measured at the outlet may have been slightly different to that in the Microfluidizer interaction chamber. Increasing the process temperature caused a marked decrease in the droplet diameter and polydispersity of the product emulsion, the minimum diameter achieved for a 10% oil emulsion being 235 nm at a process temperature of $70\,^{\circ}C$, with a polydispersity of 0.09.

Fig. 7 is a histogram representing the relative proportions of droplets of diameter greater than 1.2 μm in (a) a 10% emulsion processed by Microfluidizer at different pressures, (b) the commercial systems Intralipid 10% and 20% and (c) a 10% emulsion produced by ultrasonication. It should be noted that these proportions are relative, and no attempt has been made to relate these measures to the number of droplets smaller than 1.2 μm. The proportion of large droplets decreases as the homogenization pressure increases, the emulsions

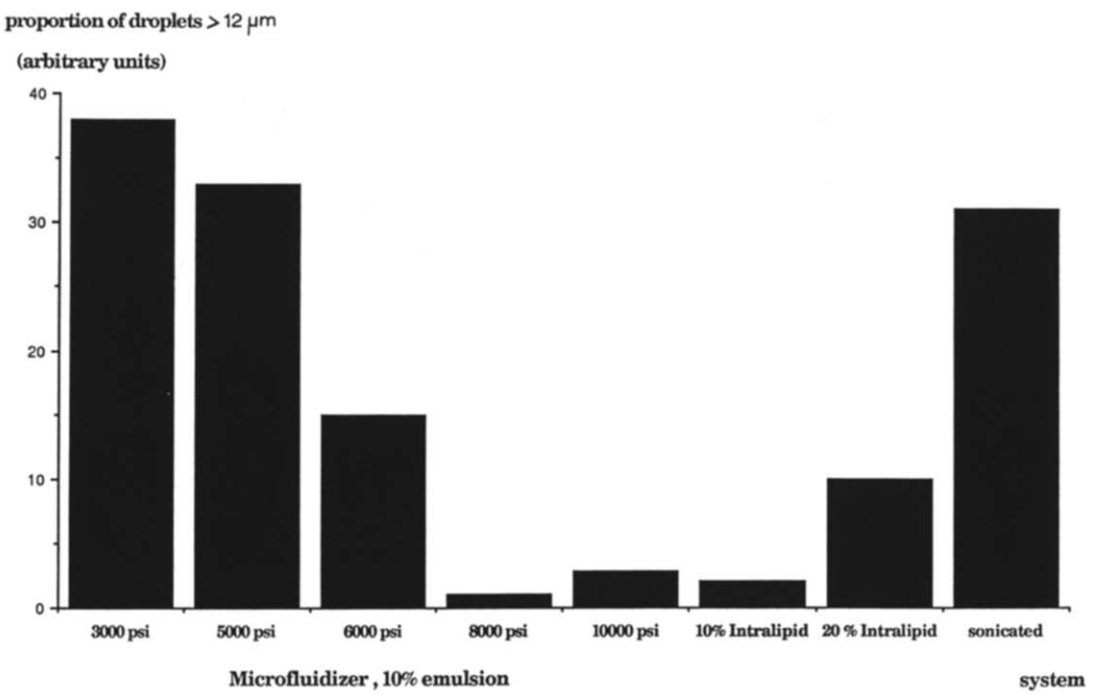

Fig. 7. Relative proportions of droplets of diameter > 1.2 μm for different methods of manufacture (all Microfluidized samples were 10% oil processed for 6 cycles).

prepared at pressures above 8000 psi having similar concentrations of large droplets to the commercial system Intralipid 10%. The emulsion produced by sonication had a significantly larger proportion of large droplets. The proportion of droplets of diameter greater than 5 μm was too low in all of the emulsions to be detected by the Malvern 2600 particle sizer.

Discussion

The droplet diameter of emulsions prepared with the Microfluidizer reached a minimum after 4 cycles through the machine, after which no significant reduction in droplet diameter was observed. Similarly, the polydispersity of the emulsion fell to a plateau after 4 cycles, and was unchanged by further processing. This led to short process times of the order of 3–5 s per ml of sample.

The emulsions prepared using the Microfluidizer at pressures greater than 8000 psi had a droplet diameter equal to or less than that of the corresponding commercial product. Under no conditions could droplet diameter be reduced significantly below 230 nm, and it would appear that this ultimate droplet diameter is a function of the physical and interfacial properties of the oil and emulsifier. The polydispersity similarly reached a plateau of 0.12 at high pressures. Both of these parameters can be reduced slightly by processing at higher temperatures. No droplets of diameter greater than 5 μm were observed in any of the samples, even at the lowest processing pressure of 2500 psi.

Increasing the proportion of oil led to larger droplet diameters both for the ultrasonic probe and the Microfluidizer. This was to be expected, since to maintain the same droplet diameter at a higher oil phase volume requires more emulsifier to coat the additional surface area. This was not available to the system, so larger droplets with lower individual surface area resulted. The polydispersity similarly was higher at higher oil phase volumes for both emulsification techniques, although the diameter distributions produced by the Microfluidizer were considerably narrower than those produced by the ultrasonic probe, and were comparable with those of the corresponding commercial product.

In use the Microfluidizer displayed a number of significant advantages over an ultrasonic probe for the production of small quantities of emulsion:

(a) The temperature rise was much lower; approximately 5 °C per cycle when no cooling was used. By comparison, ultrasonicated samples must be immersed in an ice bath during emulsification to remove large amounts of excess heat which can even boil the sample and destroy the emulsion.

(b) Ultrasonic probes release significant amounts of finely divided titanium into the sample. This manifests itself as a black layer on the base of the container after several days settling. No such material was observable at 10 × magnification in the microfluidized samples.

(c) No unemulsified oil droplets could be observed on the surface of the sample, a common occurrence with sonicated emulsions, due to the shearing process not being evenly distributed through the emulsion.

(d) Sample processing was rapid (2–3 min for a 50-ml sample in contrast to 30 min by sonication.)

Consequently it would seem that the Microfluidizer is ideally suited to the production of small quantities of soya oil emulsions for experimental purposes, being both rapid and providing a high-quality product similar to commercial materials, which is free from large oil droplets and particulate contamination.

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