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Partition of antimicrobial additives in an intravenous emulsion and their effect on emulsion physical stability

J. Han[a], C. Washington[b,*]

[a] *Institute of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, UK*
[b] *Pharmaceutical and Analytical Research and Development, AstraZeneca, Silk Rd. Business Estate, Macclesfield, Cheshire SK10 2NA, UK*

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Abstract

A number of antimicrobial agents are potentially applicable to the preservation of small-volume parenteral emulsions. However, the physical stability of these emulsions is of paramount importance in ensuring their safety, and it is possible that antimicrobial additives could reduce the emulsion stability by a number of mechanisms. We have studied the effects of several antimicrobial agents on the physical stability of Diprivan®, an intravenous anaesthetic emulsion. A particular problem is that many antimicrobial additives require an acidic pH in order to be effective (e.g. sodium benzoate, sodium metabisulphite) and the emulsion surface potential is insufficient to stabilize the emulsion to coalescence under these conditions. In addition several antimicrobial agents (e.g. methyl paraben and benzoic acid) partition into the oil phase of the emulsion, requiring the use of increased concentrations to remain effective. We describe an assay technique to quantify the oil partition, liposomal partition, and droplet surface adsorption of the additives. This illustrates that significantly more additive is partitioned out of the water phase than might be predicted from simple oil/water partition experiments.

Keywords: Emulsion; Triglycerides; Diprivan®; Antimicrobial; Preservatives; Colloid stability; Partition

1. Introduction

The assurance of antimicrobial quality in parenteral emulsions is a difficult problem that is normally approached by terminal autoclave sterilization. Although this results in a sterile product before opening, extrinsic contamination during use can lead to rapid subsequent microbial growth. A notable example of this difficulty was encountered when a number of infection clusters were temporally associated with the use of the intravenous anaesthetic emulsion Diprivan® (AstraZeneca). This product has a high degree of sterility, and contamination has been attributed to careless aseptic technique by the end-user, for example repeat syringe fillings or

* Corresponding author. Tel.: +44 1625 518256; fax: +44 1625 501794.
E-mail address: Clive.Washington@astrazeneca.com (C. Washington).

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set-aside open vials. Such misuse cannot be prevented by the manufacturer, so it is desirable to add an antimicrobial agent to the emulsion to slow or prevent microbial growth. However, the majority of antimicrobial agents approved for use in injectable liquids interact with the emulsion and may reduce its droplet stability.

One of the first propofol emulsions containing an antimicrobial agent was Propofol Intravenous Emulsion (Gensia-Sicor), which used sodium bisulphite and an acidic formulation pH. We have previously demonstrated that the combination of these two factors destabilizes the emulsion to shaking and freeze-thaw cycling to a major degree (Han et al., 2001). More recently formulations containing benzyl alcohol or tris buffer have been developed. In this paper we examine the effect of a number of commonly used antimicrobial agents on the stability of a typical intravenous emulsion (Diprivan®), and assess the likelihood that they could be used to provide an acceptable level of antimicrobial activity in an emulsion formulation without causing physical stability problems. The major restriction in the selection of the additives studied was that they must be soluble in water so that they could be added to the emulsion. It was thus not possible to test very hydrophobic additives, since the only feasible way to add these to the emulsion would be to dissolve them in the oil prior to homogenization. This was not considered a severe limitation, as hydrophobic additives would not partition significantly into the aqueous phase of the emulsion, so would not display a useful level of antimicrobial activity in the aqueous phase of the final product.

In addition to studying the effect of the additives on emulsion stability, we have also measured the partition of several antimicrobial additives between soya oil and water and between different phases in the emulsions. Despite the importance of the partition data to formulation research, little data in intravenous emulsion systems are available in the literature. It is well known that this partition reduces the amount of antimicrobial agent in the aqueous phase, in which bacterial action is likely to be most important. In emulsions with a very small droplet size such as Diprivan® or Intralipid® it is also possible for a significant fraction of an additive to be adsorbed at the droplet surface. Consequently the bulk oil/water partition coefficient, which does not allow for surface adsorption, may overestimate the amount of antimicrobial agent in the aqueous phase of the emulsion. The amount of adsorbed additive has been estimated by comparing the partition between oil and water in bulk, and between the oil droplets and water in the emulsion. This data then allows us to calculate the amount of additive that must be used in order to achieve specific antimicrobial levels in the aqueous phase of the emulsion.

Phospholipid-stabilized emulsions contain a surplus of phospholipids, which is present in the aqueous phase as liposomes (Westesen and Wehler, 1992; Ferezou et al., 2001). We have used ultracentrifugation to separate this surplus liposomal lecithin surfactant and measure the amount of antimicrobial additive which has been incorporated into the liposomes, thus quantifying the additives in the oil phase, the oil/water interface, the liposome and the aqueous phase.

2. Materials and methods

Diprivan® (1%, without EDTA, batch no. 15269-54) was supplied by AstraZeneca. The same batch was used throughout the experiments. All other reagents were from Sigma–Aldrich. Zeta potentials (in1 mM HEPES, pH 7.4) were measured using a Malvern Instruments Zetasizer 4 with a minimum of four consistent consecutive 30 s measurements. Emulsion pH was adjusted where appropriate using 0.1 M sodium hydroxide or hydrochloric acid to minimize electrolyte load. The additives used were benzalkonium chloride (0–1%), methyl paraben (0–0.25%), sodium benzoate (0–0.5%), benzyl alcohol (0–0.5%), phenol (0–1%) and EDTA (0–0.5%). The additive concentrations studied were appropriate to those found in a range of commercial products, although these are normally determined by microbiological optimization; there are rarely 'recommended' levels for antimicrobials. All additives were obtained from Sigma–Aldrich.

2.1. Stability testing

Emulsion stability was primarily measured using the accelerated shaking test described in our previous work (Han et al., 2001). Samples were shaken on a Burrell Model 75 wrist-action shaker (Burrell Scientific, Pittsburgh) operating at 300 strokes/min, full stroke amplitude (approximately 6 cm at the bottle) at room temperature ($23 \pm 1\,^{\circ}C$) for 16 h, unless otherwise indicated. We have previously used freeze-thaw

cycling (24 h at −20 °C) in addition to shaking as an accelerated stability protocol. However, freezing is generally avoided for intravenous emulsions and therefore is less relevant to the stability in real storage and transport conditions. In addition it poses interpretative difficulties when aqueous-phase additives are present, since the additive is concentrated as the water in the emulsion freezes; thus, tests do not take place at a well-defined additive concentration and the results can be misleading. Consequently we prefer the shaking test for these systems, although we also present some results from the freeze-thaw test to illustrate the differences that arise in the use of these tests.

Particle size distributions were measured using a Coulter LS230 particle sizer (Beckman Coulter, Luton, UK) with the 'PIDS' mode selected. For counting of larger (>1.5 μm) droplets, an optical particle counting PSS Nicomp AccuSizer 780 (Santa Barbara, CA, USA) was used in the extinction mode. Sample dilution protocols and calibration sequences were as described in our previous work (Han et al., 2001). Triplicate samples were measured for all particle size or count experiments. If samples showed visible free oil after shaking they were described as 'broken' and the droplet size distribution was not explicitly measured. When a sample contains free oil, this is not detected by the particle sizing instruments, so conclusions based solely on the distribution of the remaining micron-sized droplets can be highly misleading. The emulsions were also examined as required using an Olympus CHS light microscope (Olympus Optical Co. Ltd., Japan) with a CCD video camera connected to a computer image-acquisition system.

Unlike our previous studies, it was generally necessary to open the original sample containers to add antimicrobial agents, or to subdivide samples. All opened samples were refilled with N_2 before testing.

2.2. Partition studies

Preservative partition between soya oil and water (1:5 volume phase ratio as in Diprivan®) was measured by dissolving the additive in water, adding an equal volume of the oil phase, and rotating the samples in a sealed 20 mL bottle to bring the additive concentrations to equilibrium. Samples were withdrawn for intervals up to 24 h although equilibrium was normally established in 1–2 h (data not shown). In order to avoid inseparable droplet formation in the samples, it was necessary to rotate them at only 0.5 rpm in a specially constructed rotator. Only with this precaution was it possible to recover oil and water phase samples which were not turbid due to contamination with the opposite phase.

Partition in the emulsion was measured in two stages. The additive was dissolved in a minimum of water and added to the emulsion, and allowed to equilibrate for 24 h. The emulsion was then centrifuged using a Hetich centrifuge with a Hetich 1412 rotor at 17,000 × *g* for 25 min to cream the oil droplets without sedimenting the liposomal phase. The aqueous subnatant was then collected and the drug content was measured by HPLC. The oil droplets could not be recovered without some contamination by the continuous phase, so the concentration of the preservative in the oil phase was derived from the concentration in the aqueous phase and the total concentration of the preservative in the emulsion. Particle size measurements confirmed that there was no significant increase in droplet size during centrifugation (data not shown); thus, the emulsion surface area, and preservative distribution, was not influenced by the centrifugation.

The aqueous phase obtained by normal centrifugation was turbid due to the presence of the liposomal phase. To further clear the subnatant, it was necessary to use an ultracentrifuge (Beckman L8-M ultracentrifuge (Beckman Instruments Inc., USA) with a Type 50.3Ti rotor) at 179,000 × *g* (average) for 3 h. This sedimented the liposomes and allowed the recovery of a transparent sample of the aqueous phase of the emulsion uncontaminated by colloidal lipid or phospholipid structures.

2.3. Analytical methods for partition studies

The equipment used was a Beckman System Gold Programmable Solvent Module 126, coupled with an UV detector Module 166 and an Auto Sampler 507. A high purity Elite C18 (5 μ) 100 mm × 4.6 mm column was used. The mobile phase was acetonitrile:water 50:50 for benzyl alcohol and methyl paraben, and acetonitrile:0.01 M phosphate buffer (adjusted to pH 3.0) 50:50 for benzoic acid. Ethyl paraben was used as the internal standard for all additives studied. A calibration series was run with every set of samples, and the correlation coefficient (R^2) was always at least 0.998.

3. Results and discussion

In order to understand the influence of the additives, it was first necessary to study the effects of pH and ionic strength alone.

3.1. pH

Emulsions at pH 3, 4, 5, 6.5 and 8 were subjected to the 16-h shake test and it was found that emulsions at pH 3, 4 and 5 all developed free oil and therefore were not measured. Samples at pH 6.5 and 8 did not display appreciable changes in counts (data not shown). In order to elucidate the effect of pH in a more discriminating way a 3-h shaking test as a function of pH was performed on Diprivan®, and the results are shown in Fig. 1. The emulsion was stable in the pH range of 6.5–8, but reducing the pH below 5 led to progressively lower stability in both shaking and freeze-thaw tests. This is consistent with our previous study (Han et al., 2001), which showed that the zeta potential of Diprivan® was progressively reduced with decreasing pH, presumably due to variation in the ionization of the surface phospholipid, which has a surface pK_a of 3–4. This destabilizing effect of low pH on lecithin-stabilized emulsions is well known from studies of parenteral emulsion admixtures (Allwood and Kearney, 1998) and propofol lipid emulsions formulated at low pH (Han et al., 2001).

3.2. Ionic strength

Many of the additives studied contribute additional ionic strength to the aqueous phase of the emulsion in addition to any possible interfacial effect. Thus, we needed to measure the destabilization caused by a non-specific electrolyte such as sodium chloride in order to discriminate whether or not a specific additive caused an additional destabilizing effect.

The effect of adding sodium chloride to Diprivan® prior to shaking is shown in Fig. 2. Extensive coalescence prevented the measurement of accurate droplet counts, but the observed onset of coalescence at 25 mM is consistent with our earlier studies (Washington, 1990) which showed that the surface potential of a phospholipid-stabilized fat emulsion was progressively reduced without charge reversal by nonspecific electrolytes.

3.3. Benzalkonium chloride

Benzalkonium chloride is a cationic surface-active agent and germicide, so would be expected to strongly interact with negatively charged emulsion droplets. The effect of benzalkonium chloride on the zeta potential of Diprivan® is shown in Fig. 3. Increasing benzalkonium chloride concentrations cause charge neutralization followed by reversal, with a point of zero charge occurring at approximately 0.5%. This is typical behaviour for a specifically adsorbed species.

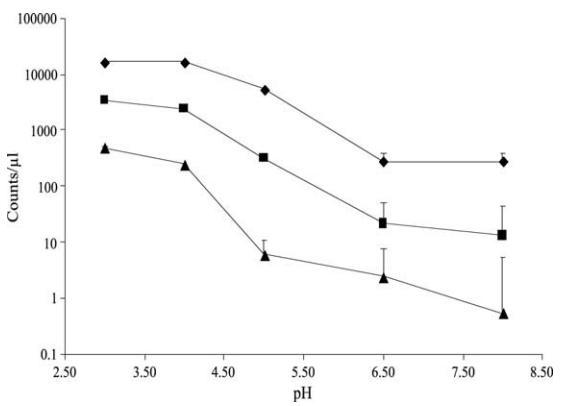

Fig. 1. Effect of pH on the stability of Diprivan® in the shaking test. Particle counts: (♦) >2 μm; (■) >5 μm; (▲) >10 μm.

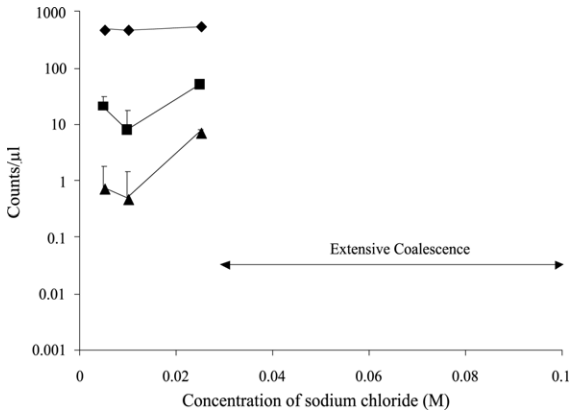

Fig. 2. Effect of ionic strength on the stability of Diprivan® in the shaking test. Particle counts: (♦) >2 μm; (■) >5 μm; (▲) >10 μm.

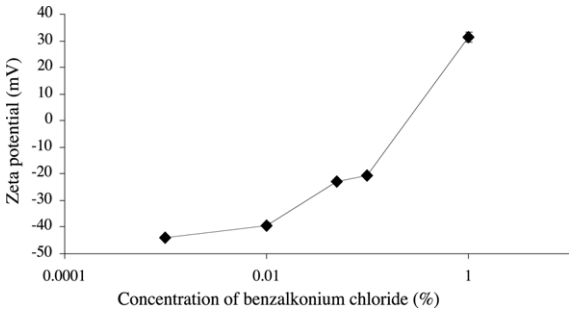

Fig. 3. Zeta potential of Diprivan® as a function of benzalkonium chloride concentration.

Benzalkonium chloride was found to destabilize the emulsion so strongly that it was not possible to complete the normal protocol for the shaking experiment. The particle size, 2 h after mixing at room temperature, of emulsions containing various concentrations of benzalkonium chloride, is shown in Fig. 4. As would be expected, the emulsion has the lowest stability near the point of zero charge (0.045%, g/mL), with a significant restabilization at higher concentrations due to the induced positive charge.

3.4. Methyl paraben

The particle sizes of emulsions containing various concentrations of methyl paraben after 16-h shaking are shown in Fig. 5. Methyl paraben did not produce any destabilization effect within the concentration range tested.

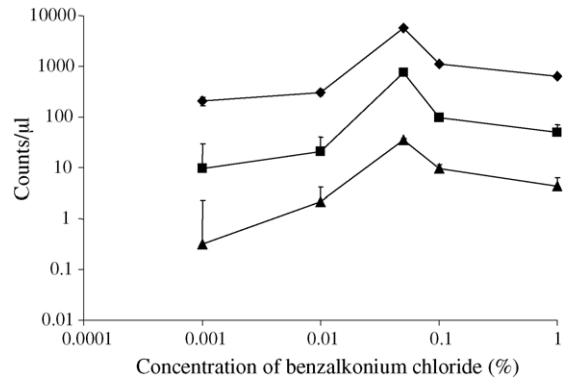

Fig. 4. Effect of benzalkonium chloride concentration on the stability of Diprivan®. Particle counts: (♦) >2 μm; (■) >5 μm; (▲) >10 μm.

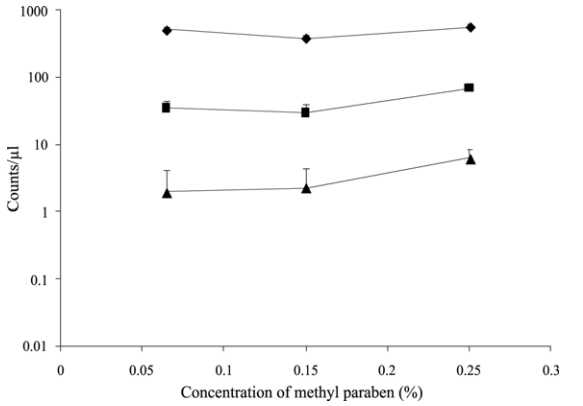

Fig. 5. Effect of methyl paraben concentration on the stability of Diprivan®. Particle counts: (♦) >2 μm; (■) >5 μm; (▲) >10 μm.

Partition data for methyl paraben at a concentration of 0.1% w/v is shown in Table 1.

Care must be taken in interpreting these results due to the complexity of the system. In the bulk oil and water system, the partition coefficient P is given by

$$P_a = \frac{C_{oil}}{C_w} \quad (1)$$

The soya oil/water partition coefficient indicates that, in simple oil/water mixtures, approximately 88% of the paraben is in the oil phase. The emulsion is much more complex, as it consists of four separate environments which can contain the additive. These are the external water phase, the oil droplets, the phospholipid-coated interfaces, and the surplus liposomal surfactant. We will denote the masses of additive in each phase as m_w, m_o, m_l and m_i, respectively, and the volumes of oil and water phase as V_o and V_w in unit volume of the emulsion. If the concentration in the aqueous phase after ultracentrifugation is C_w, then the fraction of additive in the aqueous phase is simply

$$F_w = \frac{C_w V_w}{m_{tot}} \quad (2)$$

Table 1
Apparent partition coefficient (P_a) of methyl paraben

Systems	P_a
Soya oil/water	7.26 ± 0.04
Diprivan®, normal centrifugation	7.79 ± 0.12
Diprivan®, ultracentrifugation	13.26 ± 0.46

Mean (n = 3) ± S.D.

where m_{tot} is the total mass of additive:

$$m_{tot} = m_w + m_o + m_l + m_i \quad (3)$$

If the concentration in the aqueous phase obtained by normal centrifugation is C_c, the fraction of additive in the liposomal phase F_l is given by:

$$F_l = \frac{(C_c - C_w)V_w}{m_{tot}} \quad (4)$$

The fraction of additive in the oil + interface compartment is obtained by difference:

$$F_{o+i} = 1 - (F_w + F_l) \quad (5)$$

To obtain the additive concentration in the oil phase of the emulsion droplets, we assume that the partition coefficient between bulk oil and water is the same as that between the emulsion aqueous phase separated by ultracentrifugation and the emulsion oil drop cores. The droplet curvatures are not sufficiently high to cause a major error in this regard. The additive fraction in the oil phase is then given by:

$$F_o = \frac{PC_w V_o}{m_{tot}} \quad (6)$$

Finally the fraction of additive in the oil droplet interfaces is given by:

$$F_i = F_{o+i} - F_o \quad (7)$$

After normal centrifugation approximately 89% of the paraben is in the droplet + interface phase. Ultracentrifugation of the subnatant removes a significant amount of paraben which must have been partitioned into the liposomal phase. Consequently a comparable amount of paraben must be present in the droplet interfacial phase, in order for the normally centrifuged emulsion to show a similar partition coefficient to that of the simple oil/water system. In fact it would be expected that the liposomal phase would contain a similar amount of paraben to the emulsion interfacial phase, since they both consist of phospholipid layers. Previous studies have indicated that, in the majority of triglyceride emulsions, approximately half of the phospholipid in the formulation is present as liposomes (Ferezou et al., 2001), the remaining part being adsorbed to the oil droplets. Consequently we would expect the capacity of these two phases for a third component to be similar, although these arguments would be modified by the size distributions and the accessibility of the internal layer of the liposomes. Further investigation is required to clarify these effects.

Table 2
Distribution of methyl paraben in Diprivan®

Compartment	Percent methyl paraben
Oil	42.0
Water	23.1
Liposome	10.7
Droplet interface	24.0

The fractions of paraben in each phase in the emulsion are given in Table 2.

Consequently the apparent concentration of methyl paraben needed to preserve an emulsion system is four to five times that which would normally be required, due to partition effects.

3.5. Ascorbic acid

The effect of ascorbic acid on Diprivan® stability was measured at two concentrations (0.01% and 0.1%) and at three pH (5, 6.5 and 8), since ascorbic acid requires an acidic pH to have antimicrobial action.

Fig. 6 shows the effect of ascorbic acid at different pH on the droplet count after the shaking test. Emulsions at pH 5 were not measured by AccuSizer because free oil could be seen as a result of strong destabiliza-

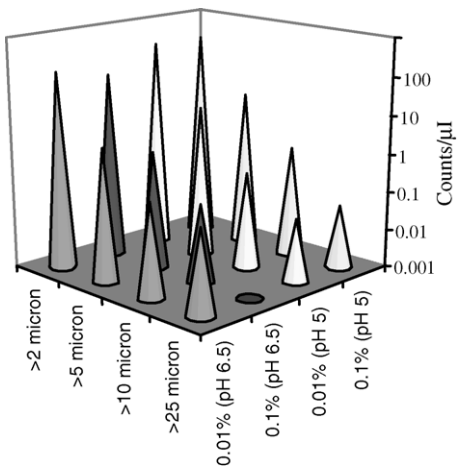

Fig. 6. Simultaneous effect of sodium ascorbate (0.01% and 0.1%) and pH (6.5 and 8) on the stability of Diprivan®. Columns represent particle count with size at the specific pH and additive concentration studied.

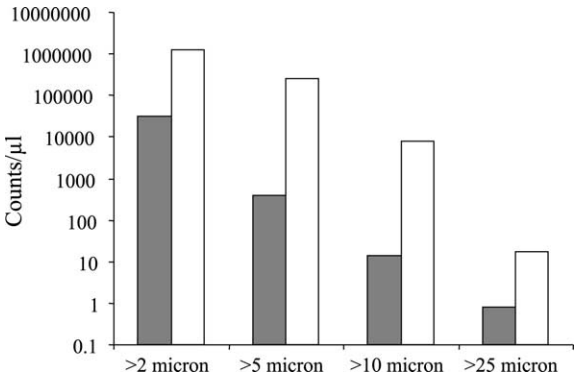

Fig. 7. Effect of sodium benzoate concentration on the stability of Diprivan®. Particle counts: (■) no sodium benzoate; (□) 0.5% sodium benzoate (38 mM).

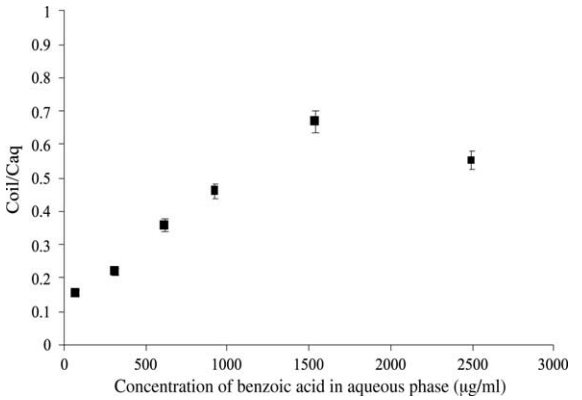

Fig. 8. Oil/water partition of benzoate as a function of benzoate concentration.

tion. At pH 6.5 and 8, the concentration of ascorbic acid did not have an appreciable effect. The destabilization was similar to that caused by pH alone (Fig. 1). The data suggest that ascorbic acid itself has no significant effect on the stability of the emulsion at either concentration tested. Although this suggests that ascorbic acid could be used to preserve Diprivan®, the low pH required to obtain antimicrobial activity would cause unacceptable destabilization.

Ascorbic acid is extremely hydrophilic and did not have a measurable solubility in soya oil; consequently its partitioning in soya oil or Diprivan® was not studied.

3.6. Sodium benzoate

Sodium benzoate is effective as an antimicrobial additive only below pH 5 (Reynolds, 1996). However, we now know that at pH below 5 all emulsions cracked (see Fig. 1) in the 16-h shake test, therefore the shake test was not performed. Freeze-thaw was used as a supplementary test in this case to study the effect of sodium benzoate on emulsion stability.

Emulsions containing sodium benzoate showed a major destabilization in the freeze-thaw test (Fig. 7). It is not possible to compute the total 'additive' destabilization due to pH plus ionic strength from these results. However, it is likely that the total destabilization would be greater than that caused by either pH or ionic strength alone. As a result it is likely that the destabilization caused by sodium benzoate is due to a combination of pH and ionic strength effects, and not due to any major specific interfacial interaction.

The partitioning of benzoic acid ($pK_a = 4.19$) is complex. Firstly the partition coefficient will vary strongly with pH since the benzoate anion will be more hydrophilic than the unionized acid, and the interfacial affinities of these species will also be different. Secondly benzoic acid is known to associate in low-dielectric solvents, so the partition coefficient will vary with concentration. Both these effects were confirmed in the studies. Fig. 8 shows the partition coefficient of benzoic acid at pH 4 between soya oil and water, in which the interfacial component is insignificant. As the concentration of benzoic acid was increased, the partition coefficient increased, presumably due to hydrogen bonding screening the charge interactions between individual benzoic acid molecules.

In emulsions a similar concentration effect is also evident although slightly less marked (Fig. 9). In this

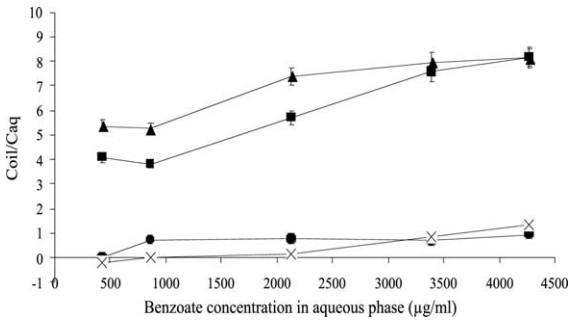

Fig. 9. Oil/water partition of benzoate as a function of pH. (■) pH 4, normal centrifugation; (●) pH 8, normal centrifugation; (▲) pH 4, ultracentrifugation; (×) pH 8, ultracentrifugation.

case the benzoic acid can also partition into the emulsion interfacial and liposomal phases, and for this reason the partition coefficients are higher than those measured in bulk oil and water. At pH 4 benzoic acid is strongly partitioned into the oil phase since it is only approximately 30% ionized at this pH. At pH 8 it is fully ionized and the majority is present in the aqueous phase.

3.7. Benzyl alcohol

The effect of benzyl alcohol on the stability of Diprivan® was measured over a concentration range of 0–0.5%, which is typical of its use as a preservative, and at pH 6.5 and 8. In the shaking test (Fig. 10) no significant increase in the large droplet count was seen, indicating that benzyl alcohol did not measurably destabilize Diprivan®. However, in the freeze-thaw test (data not shown for reasons of space) a significant increase in the large droplet count was observed, demonstrating some destabilization. This difference between the shaking and freeze-thaw tests is probably due to the increase in benzyl alcohol concentration that occurs in both the oil and water phases during the freezing process. At some point in the freezing cycle the benzyl alcohol concentration in the continuous phase will rise above the range studied in the shaking tests. It is also possible that the stability of the emulsion is influenced by the changing partition of the benzyl alcohol component as the emulsion is frozen. Finally we should note that benzyl alcohol itself freezes at −15 °C, whereas the emulsions were frozen to −20 °C, so it is possible that the benzyl alcohol inside the emulsion droplet crystallized, potentially disrupting the interfacial layer. These effects, although interesting, are not particularly relevant to the use of benzyl alcohol as an emulsion preservative, since emulsions would not normally be frozen.

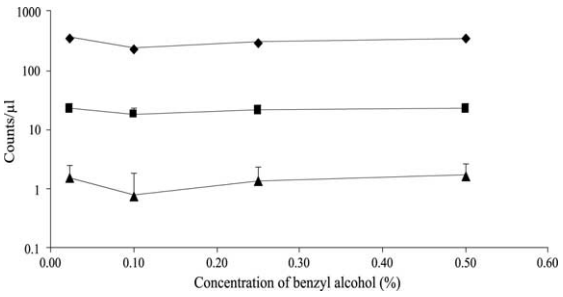

Fig. 10. Effect of benzyl alcohol on the stability of Diprivan® in the shaking test. Particle counts: (♦) >2 μm; (■) >5 μm; (▲) >10 μm.

Table 3
Distribution of benzyl alcohol in Diprivan®

Compartment	Percent benzyl alcohol
Oil	25.4
Water	52.3
Liposome	5.2
Droplet interface	17.1

The partition coefficient of benzyl alcohol between soya oil and water is 1.95, indicating that approximately 66% of the benzyl alcohol was present in the oil phase; this partition did not vary with concentration (data not shown). In Diprivan® the partition coefficient was 2.96 using conventional centrifugation and 3.65 using ultracentrifugation.

The computed fractions of benzyl alcohol in each compartment in the emulsion are given in Table 3.

Benzyl alcohol is much more hydrophilic than methyl paraben, and this is reflected not only in the higher aqueous concentration but also the relatively low affinities for the interface and liposomal phases. Consequently the level of benzyl alcohol that would be needed to achieve a specific antimicrobial effect in Diprivan® are approximately twice those that would be needed in a single-phase liquid formulation.

3.8. Phenol

Phenol was studied as an additive over the concentration range of 0–1%. Since phenol shows antimicrobial activity over a wide pH range, the samples were studied at the normal formulation pH of 8 for Diprivan®. In the shaking test a significant level of destabilization was observed (Fig. 11) which increased with increasing phenol concentration.

3.9. EDTA

EDTA (as sodium edetate) is used as an antimicrobial agent in Diprivan® at a concentration of 0.005%. In the present study the intention was to assess its influence on stability over a much higher concentration range, from 0 to 0.5%.

In the shaking test EDTA caused no measurable destabilization over the concentration range of 0–0.5%

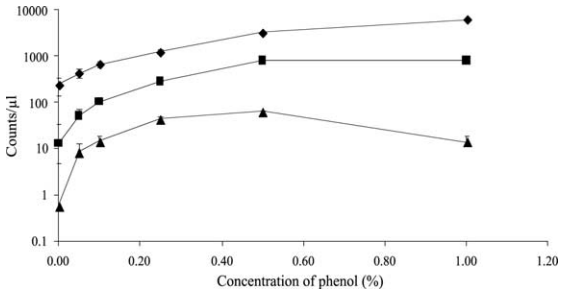

Fig. 11. Effect of phenol on the stability of Diprivan® in the shaking test. Particle counts: (♦) >2 μm; (■) >5 μm; (▲) >10 μm.

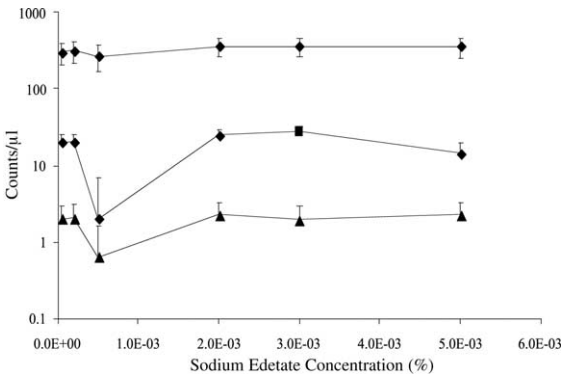

Fig. 12. Effect of sodium edetate on the stability of Diprivan® in the shaking test. Particle counts: (♦) >2 μm; (■) >5 μm; (▲) >10 μm.

(Fig. 12). EDTA is a strongly hydrophilic molecule and would not be expected to partition into the lipid or interfacial phases of the emulsion. Since it is an anion it would not interact with the negatively charged emulsion interface, and so no interfacially induced instability would be expected.

4. Conclusions

We have demonstrated that a range of interactions occur between emulsions and antimicrobial additives that can influence the stability of the emulsion. The partitioning of the more hydrophobic additives is well known, although to our knowledge this is the first reported analysis of the partitioning into liposomal and interfacial phases of the emulsion. The additives studied all caused some destabilization of the emulsion, particularly after their pH requirements were met. Sodium edetate was the least damaging, and its effects could only be detected at concentrations that were approximately 100 times greater than those used in Diprivan®. Neither benzoate and ascorbate could be used as preservatives since they require an acidic pH to achieve antimicrobial action, a limitation which we also previously demonstrated for sulphites (Han et al., 2001).

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