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Stability of a fat emulsion based intravenous feeding mixture

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Summary

(1) A stable fat emulsion (Intralipid) intravenous based feeding mixture has been developed in order to simplify nutritional support for patients with gastrointestinal disease. Mixing of Intralipid with other nutrients before administration has meant fewer bottle changes and allows a constant infusion through peripheral veins.

(2) The physical properties of the fat particles in Intralipid were studied before and after mixing with 3 different combinations of Vamin Glucose, dextrose and electrolyte. The effect of storage on lipid particle size was also examined. The mean particle size of the droplets increased slightly over a 48 h storage period at 4°C but no large droplets were observed.

(3) Measurement of the electrophoretic mobility of the droplets indicated that the mixture of a fat emulsion with amino acid, dextrose and electrolyte did not produce any permanent change in the stabilizing film of phospholipid.

(4) Total concentrations of divalent cations greater than 2.5 mmol $\cdot l^{-1}$, such as calcium and magnesium, lead to aggregation of fat droplets and the separation of the oil as a cream layer. These systems have poor short-term stability and consequently feeding mixtures containing Ca^{2+} and Mg^{2+} above should be used with care.

Introduction

Intravenous nutrition is regarded as a valuable adjunct to the treatment of gastrointestinal disease in cases where adequate nourishment cannot be taken by

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mouth or nasogastric tube. A soybean oil emulsion (Intralipid) may be used as a calorie source thus avoiding problems of hyperglycaemia and essential fatty acid deficiency which may occur when hypertonic dextrose is used for this purpose. Intralipid may also be given via peripheral veins, but until recently it has been assumed that it should be kept separate from other nutrients so as to avoid problems of instability. Sequential or simultaneous administration via a suitable administration set is then necessary. This is a more complicated procedure than the single 3 litre bag system commonly used when dextrose is employed as the calorie source. A stable feeding mixture comprising fat emulsion, amino acid, dextrose and electrolyte would greatly facilitate nutritional support since this would mean fewer bottle changes and allow constant infusion through peripheral veins for all or part of the period of intravenous feeding. Reports from France have indicated that such mixtures can be produced and that these are clinically acceptable (Solassol et al., 1976). However, no data on the physicochemical properties of these systems have been presented. The literature contains conflicting reports on the admixture of fat emulsions with other parenteral nutrients (Black and Popovich, 1981) although it is established that an unstable emulsion containing large oil droplets can be hazardous (Geyer et al., 1951; Atik et al., 1965; Le Veen et al., 1961).

Commercial fat emulsions of vegetable oils used in parenteral nutrition are stablized by lecithin (phospholipid mixtures) obtained from eggs or soybeans (Davis, 1974). The lecithin forms a thick interfacial film at the oil–water interface and this acts as a mechanical barrier to droplet coalescence. Coalescence is also prevented by mutual electrostatic repulsion due to a net negative charge that resides on the droplets. The negative charge can be reduced by the presence of electrolyte (Gray and Singleton, 1967; Dawes and Groves, 1978) and the droplets will then aggregate into larger entities. These aggregates then rise to the top of the emulsion to form a cream layer (Le Veen et al., 1965). Aggregation is reversed by agitation such as gentle shaking and thus does not represent permanent change in the average size of the emulsion droplets. On the other hand coalescence is an irreversible process that can eventually lead to a complete separation of the oil and aqueous phases (cracking of the emulsion). Emulsion droplets exceeding 6 μm in diameter are known to cause adverse reactions, particularly emboli in the lungs (Geyer et al., 1951; Fujita et al., 1971).

In this paper we describe our preliminary work on the stability of a fat emulsion based intravenous feeding mixture that has been used with success in patients with gastrointestinal disease.

Materials and methods

Materials

Intralipid (soybean oil in water emulsion (20%) stabilized by 1.2% egg lecithin) and Vamin Glucose—a balanced mixture of essential and non-essential amino acids in the physiological L-form together with glucose and added electrolytes were obtained from Kabi Vitrum.

The additive preparations

Addamel, Vitlipid and Solivito were obtained from Kabi Vitrum. Addamel contains electrolytes and trace elements and is intended for addition to Vamin amino acid solution in the parenteral nutrition of adults to cover uncompensated daily losses of electrolytes and trace elements. 10 ml contains 5 mmol of Ca^{2+} and 1.5 mmol of Mg^{2+} together with much smaller quantities of other metal ions (50 μmol and less). Vitlipid is an emulsion preparation used as a supplement to Intralipid in order to cover the daily requirements of the fat-soluble vitamins A, D_2 and K_1. The vehicle is similar to that of Intralipid. Solivito is a mixture of water-soluble vitamins intended as a supplement in parenteral nutrition. The electrolytes used in studies on emulsion aggregation (calcium and magnesium chloride) were of analytical grade.

Preparation of mixtures

The mixed systems described in Table 1 were prepared under aseptic conditions and stored in 3 litre Viaflex containers (Travenol, Thetford). These mixtures conform to possible clinical prescriptions. Simple mixtures containing diluted Intralipid with different concentrations of added magnesium and calcium chlorides were also prepared to follow the effects of divalent ions on the aggregation of fat particles. The effect of adding 2000 I.U. of heparin to a feeding mixture was also investigated. The dose was chosen on the basis that peripheral thrombosis can be reduced by the addition of small amounts of heparin to intravenous fluid (Stradling, 1978). It corresponded to the ultra-low dose heparin infusion reported to reduce deep vein thrombosis and pulmonary embolism (Negus et al., 1980), not infrequent complications in patients requiring intravenous feeding.

TABLE 1

THE EMULSION MIXTURES STUDIED

Mixture A	20% Intralipid 1 litre Vamin glucose 1.5 litre 10% dextrose 0.5 litre 51 mmol sodium chloride (as 30% solution) 54 mmol potassium chloride 30 mmol potassium dihydrogen phosphate
(Total monovalent electrolyte = 80 mmol·l^{-1})	
Mixture B	Mixture A + Addamel (10 ml)
(Total divalent electrolyte = 4.24 mmol·l^{-1})	
Mixture C	Mixture B + Solvito, 1 vial – Vitlipid, 1 vial
Mixture D	Mixture A + Addamel (5 ml)
Mixture E	Mixture D + heparin 2000 I.U.

Equipment and procedures

Particle size analysis

Particles in an intravenous fat emulsion can range in size from large droplets of 20 μm (or more in an unstable system) to small droplets of 100 nm or less. Consequently no one method of particle size analysis can cover the complete range. Three different methods have been employed in this work to sample the complete size distribution: (a) photon correlation spectroscopy (PCS) (laser light scattering method) (Berne and Pecora, 1977) (10 nm–2 μm); (b) Coulter counter (800 nm–20 μm); and (c) light microscopy (10 μm–100 μm). The emulsions were also examined visually.

Each instrument examined a different part of the size–frequency distribution curve and thus the derived size parameters (mean diameter, polydispersity (or standard deviation)) were method dependent.

PCS gave a true estimation of the mean number diameter (known to be about 250 nm for Intralipid 10%; Groves and Yalabik, 1975) but from sampling and statistical considerations was not appropriate for providing data on particles in the size range 800 μm–20 μm. This range is considered to be of relevance clinically, especially so far as adverse reactions are concerned. A size of 6 μm is normally taken as a critical size. The Coulter counter was used to study the intermediate size range. Likewise a few larger droplets greater than 20 μm may not be sampled by the Coulter counter or have a large effect on the statistics of counting. However, these particles could have a serious effect in clinical practice. The light microscope was used to detect the presence of large particles. Reliance on one method of size analysis can be very misleading as has been shown by Hansrani (1980) in her studies on the sterilization of fat emulsions. Here the mean particle size, as measured by Coulter counter (or PCS), was not changed by autoclaving at 115°C for 20 min but instability was manifested by the presence of a small number of oil droplets (1000 μm and larger) on the surface of the emulsion.

The photon correlation spectrometer (Malvern Instruments) was a system 4300 fitted with a helium-neon layer. The emulsion systems were diluted with filtered distilled water before measurement at 25°C. When laser light is passed through a sample of colloidal particles undergoing Brownian motion the number of photons scattered in a given direction per unit time is a function of the number, size and relative positions of the particles in space. Changes in the position of particles due to Brownian motion changes the rate of photon arrivals at the detector causing a departure in randomness of the times of arrival. Advanced digital processing techniques are used to follow these departures from randomness. Statistically this is handled by the temporal autocorrelation function. For a monodisperse system the autocorrelation function of the scattered light decays exponentially with a time constant proportional to the diffusion coefficient of the particle. The diffusion coefficient is inversely related to particle size (Pusey and Vaughan, 1975).

Each emulsion sample was analyzed twice and for each diluted system 6 size determinations were made. The data are expressed as a mean diameter and polydispersity factor that defines the deviation of the system from a monodisperse distribu-

tion. Polydispersity is related to the standard deviation of the system but not in a simple way.

The Coulter counter (Coulter Electronics) was a model TAII fitted with a 30 μm orifice tube and used to measured fat particles in the size range 0.8–20 μm. The electrolyte (0.9% sodium chloride) had no adverse effect on the particle size measurements (Hansrani, 1980). The instrument was calibrated using polystyrene microspheres of known diameter. Three separate determinations were made on each emulsion sample. The light microscope was a Vickers M152. The emulsions were diluted with 50% v/v glycerin before analysis. The diluted emulsion was placed in a Hawkesley haemocytometer cell of depth 0.1 mm. The presence of particles over 20 μm in size was assessed by examining at least 20 fields of view.

The visual appearance of the emulsion (aggregated, creamed etc.) was also recorded as was the presence of any free oil droplets on the surface.

Electrophoretic mobility

The charge on emulsion droplets was measured using the technique of microelectrophoresis. A Rank Mark II apparatus with cylindrical cell and laser light attachment was used (Rank Bros.). The procedures described by Bangham et al. (1958) were adopted. Measurements were made at 25°C in distilled water and in the appropriate electrolyte, amino acid mixture. 20 particles were examined in each experiment.

Particle aggregation

At high electrolyte concentration emulsion droplets will aggregate and the emulsion will cream rapidly. The critical concentration of electrolyte necessary to bring about aggregation will depend upon the valency of the cation of the electrolyte if the emulsion droplets are negatively charged. The rate of aggregation can be followed in a quantitative way using a technique known as rheoscopy that determines the transmission of light through a sheared sample of emulsion. The principle of the method has been described by Klose et al. (1972) and the experimental set-up, comprising a modified light microscope and photocell arrangement has been described by Hassan (1982).

At low concentration of electrolyte the rate of aggregation of a fat emulsion was too small to be measured but above a critical electrolyte concentration aggregation rate was linearly related to electrolyte concentration. An exact value for the critical aggregation concentration can be found by extrapolation of this linear relation to the concentration axis.

Accelerated stability tests

The stability of fat emulsions can be decreased by processes of shaking and freeze-thaw cycles (Hansrani, 1980) thereby enabling comparative assessments of the effects of additives to be made over short time periods. The following procedures were adopted: (i) shaking emulsion systems at 100 strokes/min at 25°C for 6 h; and (ii) alternative cycles of rapid freezing in a deep freeze at −20°C followed by thawing at room temperature.

Results

Storage of mixtures

The mean hydrodynamic diameter of the particles in Intralipid (20%) was found to be 310 nm (polydispersity 19%) as determined by photon correlation spectroscopy (PCS). This result compares well with previously reported values (Groves and Yalabik, 1975). After 12 h storage at 4°C the mean size of mixtures A, B and C had increased to between 400 and 500 nm (with a polydispersity of 25%) indicating that a decrease in stability had occurred. However, clinically it is the particles outside the range of PCS (2 μm and above) that are of importance when considering adverse reactions and side-effects. Consequently, data from the Coulter counter, which measures particles in the 0.8–20 μm range were given special attention (Table 2).

The changes in mean diameter occurring in 12 h storage at 4°C were not statistically significant. After 48 h the mean size had increased significantly for all systems but was still below 2.0 μm. After 9 days at 4°C mixtures B and C had mean diameters greater than 3.0 μm. For systems C and B the increase in mean diameter was linearly related to time. The emulsions all had a narrow size distribution and the standard deviation (log normal distribution) was in the range 1.2–1.5. The standard deviation increased upon storage. The particle size data can also be expressed in an alternative form as the percentage of particles less than an arbitrary size (here chosen at 1.5 μm). This parameter has been found to be a more sensitive measure of changes in stability (Fig. 1).

In no mixture were particles greater than 20 μm observed using light microscopy.

Storage at 4°C for 12–48 h followed by 24 h at room temperature (as would happen clinically during infusion) was also examined. A very slight increase in the number of particles greater than 5 μm was observed for mixtures B and C, but this did not exceed 1% of particles over 0.8 μm in diameter. As the vast majority of particles in emulsions were less than 0.8 μm diameter, this proportion was a tiny fraction of all particles present.

TABLE 2

STORAGE OF MIXED SYSTEMS AT 4°C

	Mean particle diameter (μm) of particles in 0.8–20 μm range			
	Intralipid	A	B	C
after 12 h at 4°C	0.94	1.05	1.10	1.00
after 48 h at 4°C	0.96	1.35	1.50	1.85
after 9 days at 4°C	1.00	1.55	3.30	3.50

Mean particle diameter of 20% Intralipid (diluted to 7% with water) and mixtures A, B and C (each figure is the mean of 3 measurements on each of 3 samples, the standard error was less than 5%).

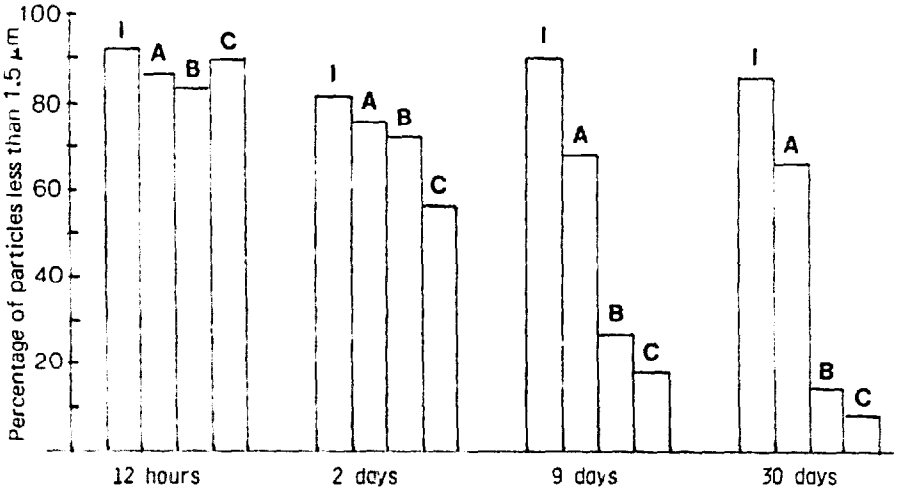

Fig. 1. The change in particle size parameter (% of particles less than 1.5 μm) with storage of emulsion mixtures.

Electrophoretic mobility

The mobilities of emulsion droplets were determined after 12 h storage at 4°C (Table 3). The mobilities of droplets diluted in amino acid–electrolyte mixtures were low and could be attributed directly to the effect of the electrolyte in reducing surface charge. However, when the droplets were removed from the mixtures and diluted with distilled water (effectively washing them free of amino acid, carbohydrate and electrolyte) they had mobilities very similar to the unmixed Intralipid. This indicated that mixing and storage of the emulsion with other nutrients and electrolytes did not produce a permanent change in the nature of the stabilizing lecithin layer.

TABLE 3

ELECTROPHORETIC BEHAVIOUR OF FAT EMULSIONS (AFTER 12 h STORAGE AT 4°C)

System	Mobility (μm/s, V/cm)	
	Distilled water as continuous phase	Feeding mixture as continuous phase
Intralipid	2.1	
Mixture A	1.9	0.4
B	1.9	0.3
C	1.9	0.25

Mean of 20 measurements on individual droplets. Standard error of mean not greater than 15%.

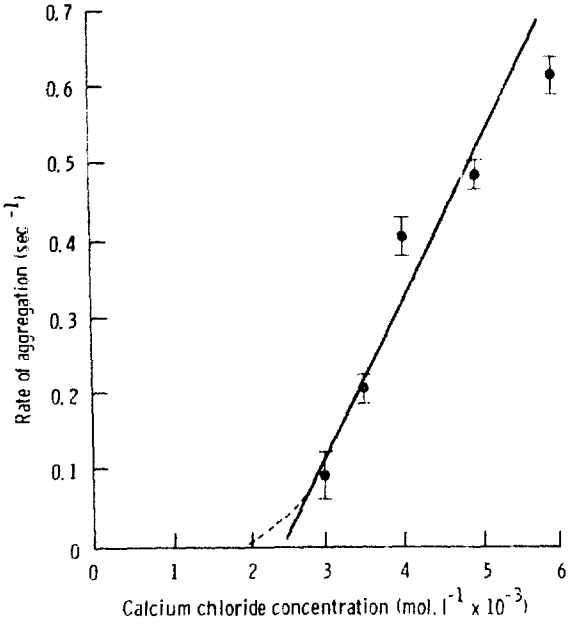

Fig. 2. Effect of calcium on the aggregation of Intralipid (oil concentration 10% 0.6% egg lecithin).

Particle aggregation

The effect of calcium chloride concentration on the aggregation behaviour of Intralipid is shown in Fig. 2. At low concentrations of calcium ion the emulsion was disaggregated but at a critical concentration of about 2.5 mmol·l^{-1} aggregation commenced and the rate increased linearly with concentration. Critical aggregation concentrations for other electrolytes are given in Table 4 together with literature values for silver iodide, a negatively charged colloid.

TABLE 4

CRITICAL AGGREGATION CONCENTRATIONS FOR ELECTROLYTES ADDED TO A DILUTED INTRALIPID SYSTEM (OIL CONTENT 10%, EGG LECITHIN CONCENTRATION 0.6%)

Electrolyte	Critical aggregation concentration (mmol·l^{-1})	
	Intralipid	Silver iodide [a]
NaCl	110	–
$NaNO_3$	–	140
KCl	150	
KNO_3	–	136
$CaCl_2$	2.4	–
$Ca(NO_3)_2$	–	2.4
$MgCl_2$	2.6	–
$Mg(NO_3)_2$	–	2.6

[a] From Overbeek (1952).

Accelerated stability testing

Mixture A with added Addamel and heparin was selected for clinical evaluation and consequently this system was subjected to a wider range of tests including accelerated testing in the form of shaking and freeze-thaw cycles. Diluted Intralipid containing no additive was used as control. In the light of the results shown in Table 2 and Table 4, the amount of Addamel was reduced from 10 ml to 5 ml in order to reduce the concentration of divalent ions and thus confer greater stability. The particle size data have been expressed in terms of the mean particle diameter as well as the percentage of particles less than an arbitrary size of 1.5 μm (Table 5 and Fig. 3). As before mixture A with added Addamel and now heparin was less stable than the unmixed Intralipid product in all tests performed. 12 h at 4°C gave a 10% reduction in the percentage of particles below 1.5 μm and after 7 days this was 30% or more. The accelerated tests also demonstrated the destabilizing effect of mixing Intralipid with the various additives and the effect of different quantities of Addamel. Heparin at a dose of 2000 I.U. has no statistically significant effect on the stability results.

TABLE 5

EFFECT OF STORAGE AT 4°C, SHAKING AT 100 STROKES/MIN FOR 6 h AT 25°C AND FREEZE-THAW CYCLES ON PARTICLE SIZE (MEASURED BY COULTER COUNTER) AND ELECTROPHORETIC MOBILITY OF VARIOUS MODIFICATIONS OF FEEDING MIXTURE A

	Intralipid 7%	A	D (A + 5 ml)	E (A + 5 ml Addamel + Addamel) 2000 I.U. heparin
12 h at 4°C				
Mean size (μm)	1.15	1.10	1.15	1.20
% < 1.5 μm	95.5	90.3	84.0	84.5
7 days at 4°C				
Mean size (μm)	0.94	1.29	1.9	1.5
% < 1.5 μm	92.0	81.1	47.0	62.0
Shaking				
Mean size (μm)	1.20	1.95	1.5	1.5
% < 1.5 μm	71.5	48.2	58.0	63.0
Freeze-thaw 1st cycle				
Mean size (μm)	0.94	2.4	2.3	1.9
% < 1.5 μm	95.5	35.5	42.5	48.0
2nd cycle				
Mean size (μm)	1.15		2.4	2.3
% < 1.5 μm	82.0		32.0	28.0
Electrophoretic mobility in appropriate continuous phase (μm/s/V/s)	2.11	0.4	0.5	0.5

Each figure is the mean of 3 measurements on each of three samples.

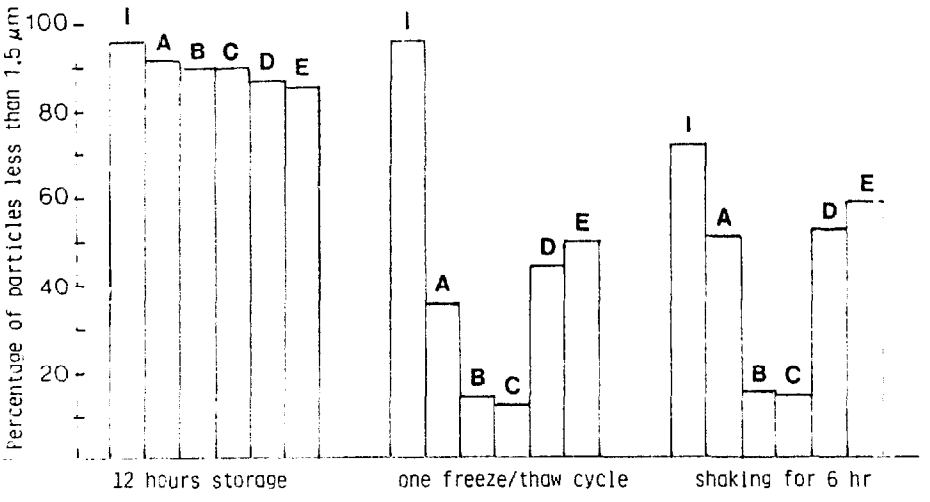

Fig. 3. The change in particle size parameter (% of particles less than 1.5 μm) with accelerated testing.

Discussion

Fat emulsions contain particles that range in size from less than 50 nm to greater than 2 μm and it is impossible to quantify the complete range using one apparatus. Photon correlation spectroscopy is an excellent method for studying particles below 1 μm while the Coulter counter is the appropriate instrument for particles above this size. The mean particle diameter measured will depend upon the population sample being examined and the method used to measure particle size. For instance, with the PCS the mean diameter of Intralipid particles is about 300 nm whereas with the Coulter counter it is close to 1 μm. The Coulter counter as employed in the present work with a 30 μm orifice tube had a lower limit of 0.8 μm and thus ignored particles below this size. However, this lower limit does not prevent the Coulter counter being used successfully to study nutritional mixtures. Large particles are believed to be responsible for adverse effects. The upper size limit is still disputed but many workers take the value of 6.0 μm (Geyer et al., 1951). The natural fat particles, the chylomicra, can have sizes up to 3 μm diameter (Hollberg and Wersall, 1964). The theoretical danger of infusing particles having diameter greater than the red blood cell is that they may cause pulmonary embolism, although it could be argued that lipid particles with diameters greater than 7.5 μm could deform and pass through the pulmonary vasculature without difficulty.

The studies performed in this work indicate that mixture A, comprising fat emulsion, carbohydrate, amino acid and electrolyte in the form of sodium and potassium chloride together with potassium dihydrogen phosphate has acceptable stability when stored at 4°C for as long as 9 days. Mixtures B and C containing supplemental additives, although more useful clinically, are less stable. The destabilizing component is considered to be the calcium and magnesium ions in Addamel (5 mmol and 1.5 mmol, respectively, in one vial of 10 ml). Divalent ions have a

pronounced effect on the surface charge of colloidal particles and thereby reduce greatly the repulsive forces between particles. Coalescence and particle growth is thus favoured. The effects of different electrolytes on particle aggregation are shown clearly by the rheoscopy experiments. Monovalent and divalent ions have effects that can be predicted by the Schultze-Hardy rule which states that coagulation of a colloid is brought about by the ion of opposite charge to that on the colloid and that the efficacy of this ion increases (markedly) with its valence (Alexander and Johnson, 1949). Calcium ions are also known to have an adverse effect on the properties of phospholipids, in particular phosphatidic acid, one of the minor components of egg lecithin that confers both electrical charge and mechanical stability. Complexation between phosphatidic acid and Ca^{2+} will result in the removal of the acid from the interface (Hauser and Phillips, 1979). However, the results from microelectrophoresis indicated that the nature of the interfacial film was not changed permanently by mixture with nutrients and electrolytes since washing droplets in distilled water provided the same mobility characteristics as untreated Intralipid. The reduced mobility of the emulsions in the mixtures is due to the suppression of the surface charge on the particles. At low mobilities (low charge) the particles can aggregate to form large clusters that will give rise to an unstable creamed emulsion system.

The following recommendation can be made concerning the mixture of nutrients for parenteral nutrition and their storage before use. The present study has confirmed and extended previous work indicating that Intralipid emulsions are less stable when mixed with electrolytes, amino acids and dextrose (Black and Popovich, 1981; Frank, 1973; Kawilarang et al., 1980) but that mixed systems do have acceptable stability for storage at 4°C over periods of up to one week and possibly longer. The addition of nutritional supplements leads to a further decrease in stability but even for mixtures B and C, the mean diameter of particles in the 0.8–20 μm range was less than 3 μm even after 48 h storage at 4°C. Furthermore, the percentage of particles over 5 μm diameter was minute compared to the emulsion as a whole when the conditions of 48 h storage and 24 h infusion were simulated. Thus, mixtures B and C may be safely stored at 4°C for 48 h before infusion. The presence of divalent ions such as Ca^{2+} and Mg^{2+} are thought to be the cause of the decreased stability for system B and C. The greater the concentration of electrolyte the more the charge on the droplets will be reduced and the greater the possibility for droplet coalescence. Divalent cations will be far more effective in reducing droplet charge than will monovalent cations. Such effects will be cumulative for a mixed electrolyte system and can be assessed quantitatively by the DVLO (Deryagin-Landau, Verwey-Overbeek) theory which describes the electrostatic contribution to stabilization of emulsion against aggregation (Shaw, 1970). Potential energy curves can be constructed using appropriate formulae for calculating the energies of repulsion and those of attraction for interacting droplets having the same size.

The addition of electrolyte has the effect of reducing the energy barrier for aggregation and it can be shown that the critical aggregation concentration depends on the sixth power of valency (Shaw, 1970). This is a confirmation of the empirical rule of Schultz and Hardy which predicts the critical aggregation concentrations to

be in the ratio:

$$1:(1/2)^6:(1/3)^6:(1/4)^6$$

for mono-, di-, tri- and tetravalent ions, respectively.

$$1:1.6\times10^{-2}:1.4\times10^{-3}:2.4\times10^{-4}$$

The data in Table 4 fit quite well with these theoretical predictions that are based on calculations for monodisperse small spherical particles. Thus for a fat emulsion in the presence of a mixed electrolyte system we can derive an expression that defines the theoretical boundary condition under which aggregation will not occur.

$$x < a + b/1.6\times10^{-2} + c/1.4\times10^{-3}$$

where a, b and c are the concentrations of the mono-, di- and trivalent cations in $mmol\cdot l^{-1}$; x is defined as the critical aggregation number and is the concentration of a monovalent cation (in $mmol\cdot l^{-1}$) required to aggregate the system. For the present work this is taken as $x = 130$ and we can write conditions for stability (Table 4)

$$130 < a + 64b + 729c$$

The value of x will change with the surface charge on the particles which in turn depends on the pH of the system and the presence of additives such as amino acids. However, it provides a convenient rule of thumb for predicting possible states of aggregation and set limits for total electrolyte and the cumulative effect of different cations on emulsion stability.

Emulsions containing added electrolytes (especially divalent ions) are likely to aggregate and mixed systems should always be examined visually before administration to ensure that the system is disaggregated. The aggregation of fat emulsions by electrolyte can be reversed by gentle shaking. However, the reversibility of such aggregation in vivo is not known. The rapid adsorption of blood components onto the surface of lipid droplets and the endogenous Ca^{2+} level of the blood could lead to an enhanced state of aggregation and the aggregates may be broken down only poorly under shear conditions of the circulation. Thus pulmonary emboli could be possible when infusing aggregated systems. These situations will be considered in future work. Other formulation variables will also be considered especially the differences between the various amino acids currently available and the use of different types and quantities of fat. The data reported in the paper refer specifically to the one fat emulsion based intravenous feeding mixture that has been used successfully clinically without any incidence of adverse reaction and side-effects (Burnham et al., 1982). The mixture was given to 20 patients with gastrointestinal disease who required parenteral nutritional support. Positive nitrogen balance was maintained in all but one patient and other parameters of nutrition improved. No abnormalities of pulmonary gas exchange attributable to the infusion of the mixture

were noted. The extrapolation of the stability results to other feeding mixtures should be done with care. However, certain general rules can be formulated taking into account other studies in this area.

(i) Mixed feeding systems containing amino acids, carbohydrates, electrolytes and fat emulsions can be prepared which have acceptable physical stability for two days or longer.

(ii) Electrolytes are the major factor that give rise to instability. The higher the electrolyte content the lower the stability. The valency of the cation is a major determinant and Ca^{2+} and Mg^{2+} contents should be minimized. Monovalent cations cause aggregation at about 150 $mmol \cdot l^{-1}$ whereas divalent cations cause aggregation at about 2.5 $mmol \cdot l^{-1}$. The electrolyte effects are cumulative. Aggregated systems, while not necessarily hazardous should be avoided since they cream rapidly and give rise to enhanced particle interaction and coalescence.

The quantity of soybean oil emulsion in the mixed system would be expected to have only a minor influence on stability. The greater the quantity of fat the greater will be the number of particles and thus the greater the number of interparticulate collisions that can give rise to coalescence. Hansrani (1980) has shown in shaking experiments that the greater the amount of Intralipid in a diluted system the lower the stability. The particle size of the emulsion droplets must also be considered in this context. The mean size of Intralipid (10%) is about 250 nm whereas the mean size of Intralipid (20%) is around 400 nm. Thus the use of an Intralipid system of higher fat content does not necessarily lead to a corresponding increase in the number of fat droplets.

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