Preparation of Fat Emulsions for Intravenous Alimentation[1]

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EMULSIONS of fat given intravenously offer the most promising means of providing abundant calories for patients whose oral intake is not sufficient to meet their needs. The use of high pressure homogenization in the preparation of such emulsions has been reported by a number of investigators (1, 2, 3). In the experience of this laboratory, this method has proved better suited to the production of satisfactory emulsions than ultrasonic vibration or dispersion in a colloid mill.[2] Since publication of an earlier report (4) however, various modifications of equipment, procedure, and composition have been adopted in the light of continued animal experimentation and clinical findings. This paper deals with the preparation of fat emulsions as currently practiced in this laboratory.

A number of extrinsic factors to which they are exposed act adversely on the "status quo" of the emulsions and must be considered when judging their over-all suitability for intravenous use. Hence the term "stable" as applied here means not simply that the preparation was received from the homogenizer in satisfactory form but that no apparent changes of a physical nature occurred in consequence of sterilization in the autoclave, storage, shaking, temperature changes in the range 0-60°C., and admixture with blood in the living subject. It has been our experience that emulsions may be rejected for failure to meet any one or any combination of the above mentioned conditions. Furthermore the primary requirements that an emulsion for intravenous use be non-toxic, sterile, and relatively high in caloric value eliminate many otherwise suitable preparations.

Experimental

Homogenizer Equipment. During the past 12 years a number of different homogenizers with auxiliary equipment have been used in this laboratory for the production of fat emulsions for intravenous use. Homogenizers having three pistons have proved better adapted to the preparation of the kinds of emulsions employed in these studies. For the past four years the equipment shown in Figures 1 and 2 has been used for the preparation of all emulsions administered to patients.

Three types of flow are possible with this equipment: a) the emulsion enters the homogenizer from one tank and returns directly to the same tank (infinite mixing method; b) the emulsion enters the homogenizer from one tank and returns to the other tank (batch method); c) the emulsion enters the machine from both tanks simultaneously and returns to both tanks. The maximum quantities of emulsion which can be made in a single batch for the size tanks used are 30, 30, and 60 liters by methods 1, 2, and 3, respectively.

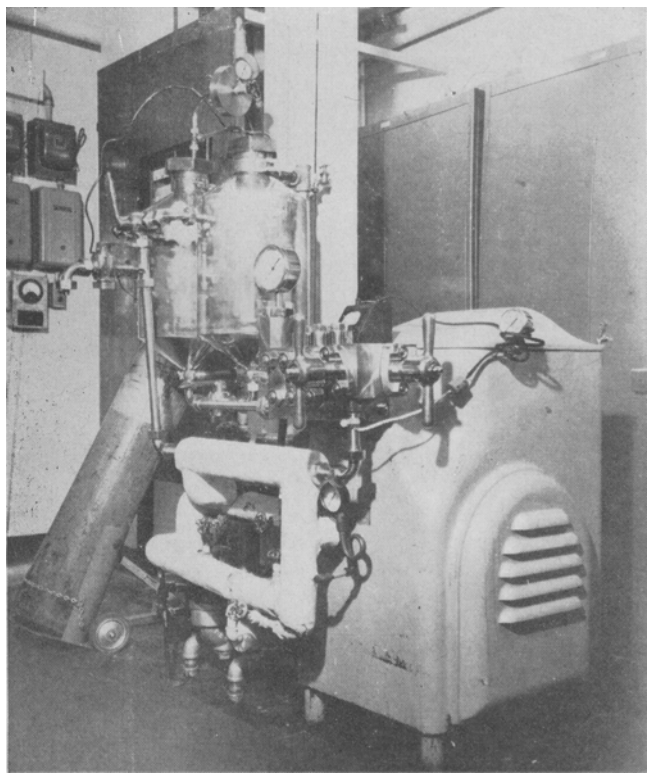

FIG. 1. Homogenizer and accessory equipment used in the preparation of emulsions for intravenous alimentation. The machine illustrated is made by the Manton-Gaulin Company, Everett, Mass. (homogenizer, Type 425E). The two-stage homogenizing valve assembly is in the foremost center of the picture. The first stage adjustment handle is to the right, and the second stage adjustment handle is to the left.

The equipment can be used in two different ways. One, in which the entire equipment is dismantled, cleaned, and reassembled between the preparation of each emulsion, will be described in detail later in this section of the paper. A second is a procedure in which the entire apparatus is kept intact except occasionally for the gauge and gauge well. Cleaning is accomplished by the recirculation of boiling detergent solution followed by hot water rinses and pyrogen-free water rinses. Ethyl alcohol is then added and allowed to circulate while steam is applied to the outer jacket of the heat exchanger. After the air has been vented by the boiling alcohol, the escape valve is closed, and an alcohol vapor pressure of 15 lbs. p.s.i. is developed while the machine remains in operation. After 15 min. the steam and homogenizer are turned off, and the entire equipment is left undis-

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[2] For convenience, we refer to compounds whose main function appears to be that of promoting subdivision of the oil as emulsifiers. Those which tend to prevent reversion we call stabilizers. It is obvious that this distinction, although useful, is somewhat arbitrary and that in practice it can seldom be drawn completely. It is hoped however that, as acquaintance with such systems is extended, improved resolution of the roles played by the several components will become possible.

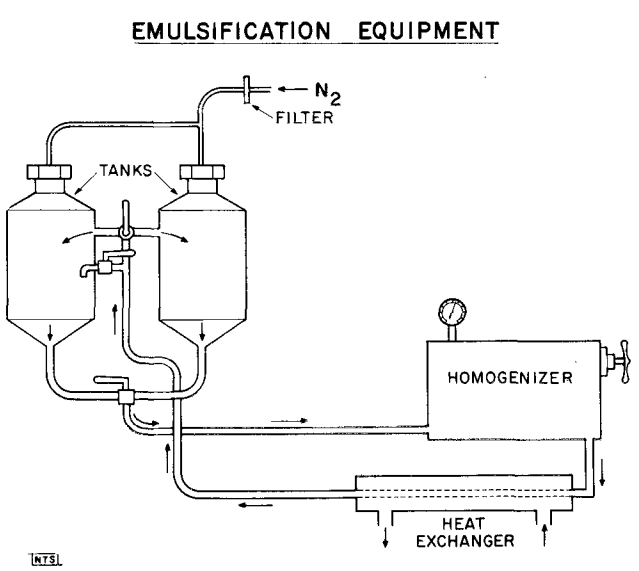

FIG. 2. All parts are of stainless steel. Emulsion flow pipes have a diameter of 1 in., N_2 intake tubing, ½-in. diameter. The heat exchanger is a simple condenser type.

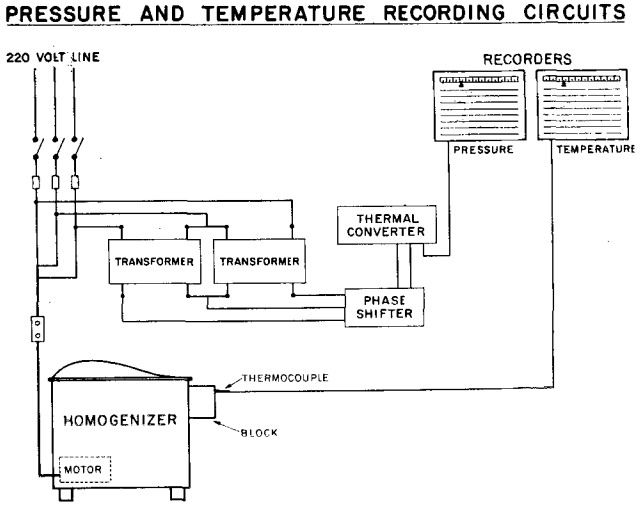

FIG. 3. Transformers: primary, 220 volts; secondary, 110 volts (General Electric, Type E-21). Phase Shifter (General Electric, Type MC-21, Model AA1). Lincoln Thermal Converter (Leeds Northrup Company, Type CW10). Brown "Electronik" Recorders (Minneapolis-Honeywell Company, Chart No. 543-N).

turbed. At the time of the preparation of the next emulsion the alcohol is drained out, fresh alcohol is used for rinsing, followed by pyrogen-free water rinses. This second procedure was used exclusively for one period of eight months in a similar apparatus of earlier date, during which time the only difficulty encountered was the replacement of an occasional gasket or packing. No unusual change was apparent in the clinical reaction rate due to infusion of emulsions made during this period.

Auxiliary Equipment. In the earlier equipment, temperature measurements of the emulsion during preparation were taken by means of thermometers. Later an externally mounted thermocouple and pyrometer were employed to reduce contamination hazards. Finally an externally located iron constantan thermocouple was used in conjunction with a recording potentiometer. A selector switch is interposed between the recorder and thermocouple to allow switching to a thermocouple located in the autoclave. The latter thermocouple is placed in a bottle of emulsion, and all autoclaving is then done on the basis of the temperature of the emulsion itself, not on that of the autoclave. It is therefore possible to have a permanent, continuous record of the temperature of the emulsion from the time the components enter the homogenizer until the emulsion comes out of the autoclave.

Although the measurement of homogenization pressures can be adequately made by means of the gauge incorporated into the machine, an alternative device is also provided (Figure 3). This consists essentially of a method by which the increased power consumption in the armature of the motor under load is used to intensify the signal fed to the electronic chart recorder. The 220 v. three-phase power line leading to the driving equipment is inductively coupled through a pair of step-down transformers to one side of a 110-volt, phase-shifting device, so adjusted that the power factor approaches zero. A proportion of the wattage drawn by the motor is employed in conjunction with suitable resistors to heat a thermopile. The low voltage signal thus generated is fed to the amplifier of the pressure recording chart. With the regular pressure gauge in position the recorder can be calibrated against various pressures. Subsequently the pressure readings can be taken from the recorder chart in an accurate manner since the power utilized by the homogenizer is little affected by such changes as viscosity and interfacial tension. These might well be important if a motor smaller than 7½ horsepower is used. The main advantage of this arrangement, besides furnishing a permanent pressure record, is that the gauge and gauge-well can be replaced with a cap, thereby eliminating the additional dead space which otherwise would accumulate crude emulsion. This is important when the appartus is to be kept intact between the preparations of different batches of emulsion.

Emulsion Components. More than a thousand emulsions of various sorts have been prepared in this laboratory on an experimental basis, but relatively few have reached the stage of clinical testing. In this latter group the principal stabilizer has been a preparation made from soybean phosphatides. In earlier studies a preparation which had been designated BF-2 (5) was used; however it was subsequently found that triply reprecipitated phosphatides prepared from Grade N lecithin were satisfactory and much easier to prepare. Most of the phosphatides used in our clinical emulsions in the past four years have been prepared on a pilot-plant basis. A suitable method for the preparation of this material on a small scale is as follows: 500 g. of Grade N. lecithin are dissolved in 1.5 l. of redistilled petroleum ether (B.P. 65°C.) by means of constant stirring. The solution is then filtered through a bacteria retaining positive pressure filter [3] in order to remove a small quantity of non-ether-soluble material. The clear, brownish-colored filtrate is poured with rapid stirring into 4.5 l. of redistilled acetone to precipitate the phosphatides and leave the oil in solution. The precipitate is collected on a suction or pressure filter, washed with 400 ml. of a petroleum ether-acetone mixture (1.5), and then redissolved in 1 l. of petroleum

[3] F. R. Hormann and Company Inc., Newark, N. J.

ether. The above process is repeated until three precipitations have been effected. The final precipitate is freed of residual solvent by allowing a generous supply of nitrogen to flow over it while on a suction filter. The product is kept in a vacuum desiccator for at least 24 hrs. and then stored in nitrogen-filled bottles at a temperature of —6°C. Although either redistilled diethyl ether or petroleum ether can be used in the procedure, the former has the disadvantage of usually being contaminated with peroxides.

The two principal materials used in conjunction with the phosphatides in the clinical type of emulsions have geen Demal-14 and Pluronic-F68. These materials have a number of important influences during emulsification. One obvious and important effect, noted especially with the Pluronic-F68, is that of greatly reducing the number of particles larger than one micron in diameter when phosphatide is present. That such an effect is not merely due to a greater total concentration of surface-active material is attested by the fact that doubling the phosphatide concentration does not accomplish this, nor does the addition of other emulsifying agents necessarily accomplish the desired end.

Demal-14 [4] has been used in concentrations between 0.5 and 1.0%, and considerable data have been collected using emulsions containing this agent (6). In the last few years this material has been largely replaced with Pluronic-F68,[5] at concentrations varying from 0.2 to 0.5% (w/v) in clinical-type emulsions. It is always added to the water phase since at room temperature its solubility in most oils is limited. The composition of some typical emulsions which have been used in the clinic is given in Table I.

TABLE I

Composition of Typical Emulsions Which Have Been Used Clinically [a]

Oil	Per Cent	Per Cent Phosphatide	Per Cent Demal-14	Per Cent Pluronic-F68
Coconut	15	1.0	1.0	....
Coconut	10	2.0	....	0.2
Coconut / Olive	5 / 5	1.2	....	0.5
Olive	12.5	1.5	1.0	....
Olive	15	1.5	....	0.5
Olive	15	1.2	....	0.3
Olive	10	2.5	....	....
Olive	10	2.5	....	0.2
Olive	10	2.0	....	0.2
Olive	10	1.5	....	0.5
Olive	10	1.2	....	1.0
Olive	10	1.2	....	0.5
Olive	10	1.0	0.5	....
Triolein	10	1.2	....	0.2
Cottonseed	15	1.2	....	0.3
Cottonseed	10	1.2	....	0.2

[a] All percentages are on a weight per volume basis. Five per cent dextrose solution constituted the aqueous phase in all emulsions. From the standpoint of particle size and of shelf life all of these emulsions proved satisfactory for clincial use. They are listed in approximate chronological order as developed and used clinically. The more satisfactory results have been obtained with those emulsions which contained either triolein or cottonseed oil. For details of the clinical results with these preparations the reader is referred to Reference 6.

Present Method for Preparing Emulsions for Clinical Use. Emulsions for clinical use have been prepared on an average of once a week. On the day prior to each "run" the homogenizer (except for driving equipment) is completely disassembled; used gaskets and packings are discarded. All parts, including the heavy cylinder block and storage tanks, are placed in a deep, stainless steel sink and thoroughly scrubbed in hot water plus detergent. For the protection of their precision ground surfaces the stellite homogenizing valves and seats are kept in a separate container. Following the wash, repeated flushing with very hot water is employed to remove the last traces of detergent. The cylinder block and storage tanks remain in the sink during this process, but all small parts excepting valves and valve seats are loosely piled on the drainboard of the sink where for about 10 min. a stream of hot water is played over them from a Tygon hose. While the metal parts are still hot, a final rinse is made with redistilled ethyl alcohol.

The homogenizer is then reassembled. Fresh gaskets are used throughout; plungers are provided with new, untreated leather packings; and a fresh filter is placed between supporting flanges on the nitrogen intake. All orifices are closed and the machine is allowed to stand thus until the following morning when the emulsion itself is prepared.

The entire operation is conducted in a separate room provided with an overhead fan exhaust. Thorough cleansing and sterilization of the reassembled homogenizer are first accomplished in a series of four steps that occupy about 1 hr. Four liters of double-distilled pyrogen-free water are placed in one tank of the machine; valves are adjusted to permit circulation between the cylinder block and both tanks; and the homogenizer is set in motion. At this point a careful check is made for leaks in the system. The contained water, brought to a boil by admission of steam, is shut off. With the machine still running, attention is next paid to the valves that control the flow between cylinder block and tanks. By loosening the body of each valve in its tapered seat, small amounts of water are permitted to escape and in so doing to rinse the external surfaces (annular rings, etc.) of the valve parts. By a similar procedure the gauge well, if present, also is flushed. All water is then drawn from the machine through the delivery valve. The cylinder block is drained by opening a louver plate located at the right hand end of the intake channel, and the small amount of water remaining in the circulating pipes is removed by uncoupling a section of this system at its lowest point.

As a second step in cleansing the machine, the entire procedure described above is repeated with the substitution of redistilled ethyl alcohol for water. The third and fourth steps are identical and consist in a repetition of the first procedure, except that now the temperature of the water is raised by application of pressure to the homogenizing valves rather than by use of steam in the heat exchanger. Steps No. 3 and No. 4 having thus been completed under actual working conditions, the homogenizer is considered ready to receive in order the components of the emulsion.

With valves adjusted to direct flow between the cylinder block and one tank only, 10 liters of redistilled, pyrogen-free water are poured into the machine, which is still in operation. Routinely a total pressure of 3,000 lbs. p.s.i. is placed on the homogenizing valves (Figure 2). This pressure is built up in three steps as follows: a) by advancing the first-stage valve until the indicator records 1,000 lbs.; b) by advancing the second-stage valve until it also registers 1,000 lbs.; and c) by again advancing the first-stage valve until a total pressure of 3,000 lbs. is

[4] Polyglycerol partially esterified with oleic acid. Emulsol Corporation, Chicago, Ill.

[5] Prepared by condensing ethylene oxide with a hydrophobic base formed by the condensation of propylene oxide with propylene glycol. Wyandotte Chemicals Corporation, Wyandotte, Mich.

indicated. When the temperature of the water has reached 85°C., as shown by the automatic recording device, the correct quantity of phosphatide, crudely dispersed in approximately two liters of sterile pyrogen-free water, is added. The fluid system is at once overlaid with nitrogen filtered through a pad [6] supported between flanges fixed above the tanks of the machine. And from this point forward, whenever for any reason, such as the addition of water, oil, etc., the cover of the tank is removed, a fresh volume of nitrogen is introduced. The temperature of the phosphatide dispersion is raised to 100°C. and kept at that point for 3-5 min.

Prior to the addition of oil, the temperature of the phosphatide dispersion is lowered to 85°C. by any or all of the following methods: reduction of pressure, admission of cold water to the heat exchanger, and dilution of the dispersion itself with fresh 2-liter volumes of water. Subsequently for the 40-min. period during which homogenization proceeds, the temperature is carefully maintained in the range 85-90°C. The oil, previously warmed over a water bath to approximately 70°C., is added slowly in order to prevent the formation of a surface film and, under some circumstances, to avoid phase reversal. Some 5 min. later, or when it is judged that the crude emulsion has been sufficiently formed, the Pluronic-F68 is added in a liter of water. There now remain to be added only the dextrose (for tonicity) and the balance of the water. The former is added dry; the latter, in 2-liter volumes at carefully spaced intervals to avoid undue depression of the temperature. Ordinarily a 30-liter batch of emulsion is ready to be withdrawn from the machine within 35-40 min. following the addition of the oil.

The progress of emulsification is checked from time to time by microscopical examination of 1-2 cc. (samples taken from the tank in sterile pipettes). A small drop of the emulsion is placed near the center of a clean glass slide and spread into a uniformly thin film beneath a cover slip. Gross inspection of this film affords a rough idea of how finely dispersed the oil may be. If to the unaided vision it seems chalky white, a majority of the oil particles will be 1 μ. or larger in diameter. A bluish appearance however, especially where the film is thinnest, indicates the presence of many particles whose diameters fall in the range 0.1-1.0 μ. Once the slide has been prepared, it is examined with an oil immersion lens in the customary manner. Illumination is adjusted as for translucent objects. Alternatively, the examination may be made, using phase contrast. Microscopical findings are reported under two headings as they refer to background or foreground. The former comprises the great bulk of the dispersion; the latter consists of the larger particles and represents the right limb of the size frequency distribution. From the standpoint of particle size an emulsion is considered suitable for clinical use when the average diameter of background particles is $\frac{1}{2}$ μ. or less, with only an occasional foreground particle 1-2 μ. in diameter.

When the emulsion has been satisfactorily formed, pressure on the homogenizing valve is reduced to about 1,500 lbs. p.s.i., and a small quantity of emulsion is withdrawn and discarded to flush out the point of discharge. The emulsion is then collected directly into sterile pyrogen-free bottles, which are immediately closed with a rubber cap followed by a Bakelite screw cap.

The bottles are autoclaved at 120°C. for 18 min. and allowed to remain in the unvented autoclave for an additional half hour. Sterility of each batch of emulsion is checked by plating on blood agar. In some instances additional sterility tests have been made, using other media.

The routine animal tests done on each batch of emulsion are as follows:

Rat Test. Three albino female rats weighing approximately 150 g. to 170 g. are each given an injection of 2 ml. of emulsion per 100 g. body weight on two consecutive days. The injections are made into one of the tail veins from a 100-ml. syringe through a No. 24 or 26 needle while the animals are under a light ether anesthesia. The rate of injection is approximately 3 ml. per minute. On the third day the animals are sacrificed by means of ether; they are examined grossly; and the major viscera, occasionally also the brains, are removed and taken for microscopic examination. It should be mentioned that unanesthetized rats may be used if suitably restrained.

Tissues are fixed in 10% neutral formalin. Frozen sections of lungs and spleens, and on occasion other viscera, are stained with Sudan IV. Hematoxylin-eosin stains are used routinely on paraffin embedded tissues. The latter material is examined to detect any morphological lesions relative to the infusions. It should be clearly stated that to date such lesions have been found only in animals receiving emulsions of a distinctly experimental nature and never intended for clinical use.

The frozen sections are used as a check on the intravenous stability of the emulsions. Rats infused on the above dosage-time schedule will often show varying amounts of globular Sudanophilic material within the capillaries 24 hrs. after the second infusion. The quantities of such apparent fat are graded visually according to an arbitrarily established set of standard slides and designated as trace, or 1 to 4+. A "trace" of intracapillary fat represents an occasional intracapillary fat globule per low power microscopic field, "1+," 1 to 2 such globules per low power field, and "4+," many fat globules per low power field. Many clinical preparations show no demonstrable intracapillary fat under these testing conditions. On the other hand, many preparations will show "trace to 1+" intracapillary fat, and such preparations are judged acceptable for clinical use. Any emulsion giving more than "1+" intracapillary fat is discarded.

It is obvious that the entire concept of this screening procedure is arbitrary in nature. It has however been one of the most practical tests of emulsion suitability that we have been able to devise to date. By maintaining its constancy we have been able to amass considerable data on many different experimental and clinical emulsions.

Dog Test. Two dogs each weighing approximately 10 kg. are each given 20 ml. of emulsion per kilogram body weight via a foreleg vein. The rate of infusion is approximately 5 ml. per minute. The dogs are accustomed to the procedure prior to the day of the testing. Throughout the test the dogs are observed for signs of adverse reactions, such as apparent discomfort and nausea or related symptoms. They are also observed intermittently during the subsequent 24 hrs. The dogs are used on a rotation basis so that at

[6] F. R. Hormann and Company, Inc., Newark, N. J.

least 14 days elapse between the tests on any one animal.

All dogs used for testing are eventually sacrificed by intravenous sodium pentathol, and complete autopsies are performed, including examination of the central nervous system. Since these animals receive repeated infusions over periods of months to several years, detailed histologic study of all organ systems, including use of both of the above staining techniques, are carried out in order to detect any long-term morphologic alterations. This type of study is obviously only an over-all screening procedure as each dog may receive a number of different clinical preparations. Hence, should any significant morphologic changes be found, correlation of such changes with specific emulsions would be difficult without additional experimental data.

Rabbit Test. Three albino rabbits weighing 3.5-4.5 kg. are used for pyrogen testing. They receive 10 ml. of emulsion per kilogram of body weight at a rate of 8 to 10 ml. per minute. The animals are confined in boxes and rectal temperatures are taken at 30-min. intervals during a 2-hr. period preceding the injection and at hourly intervals during the 5-hr. period after injection. The emulsion is considered satisfactory if the average temperature rise does not exceed 1.2°F. In the rare instance where this is exceeded, an additional three rabbits are used. If the response is again too high, the emulsion is discarded.

Results and Discussion

The preparation of fat emulsions for intravenous use in patients and experimental animals can be satisfactorily carried out with the equipment shown in Figures 1 and 2. The capacity of both the homogenizer and auxiliary equipment given was chosen to allow sufficient emulsion to be prepared for suitable clinical trials and, at the same time, to permit the preparation of smaller batches whose size might be determined by such factors as the quantity of material available. Since all pipe connections are of a standard sanitary type, modification of the auxiliary equipment can easily be made. The use of disposable neoprene gaskets facilitates obtaining water-tight closures even when true alignment of parts is not achieved.

The use of a nitrogen atmosphere is, of course, dictated by the inherent oxidative instability of unsaturated lipids, especially the phosphatides.[7] This would be particularly true at the elevated temperatures of homogenization and sterilization. It would be naive to believe that the procedures which the phosphatides undergo do not lead to some changes, both hydrolytic and oxidative. The fundamental practical point however is not whether these changes occur, but rather whether or not any adverse physiological reactions result when such changes do occur. If convincing evidence for such a cause-effect relationship can be obtained, then appropriate steps must be taken to circumvent such changes.

It must be emphasized that considerable *in vitro* and *in vivo* testing is done before a given type of emulsion is produced for clinical use. In practice, this preclinical testing requires about a week to 10 days. The multiple animal tests given in the present paper constitute a reasonable safeguard against the possibility that one or more emulsions of a series made with identical ingredients and under identical conditions may differ sufficiently to cause undesirable physiological effects. It is believed such tests on each batch of emulsion are and will be necessary no matter how standardized such emulsions may become. The tests have been made fairly rigorous from the standpoint of dose and rate of administration and appear to be satisfactory (see Table II). However it is likely that these tests will be modified and new ones added as experience dictates.

TABLE II

Relative Rates of Infusion into Various Species

Species	Body Weight [a] (kgs.)	Dosage (ml./kg.)	Infusion Rate [a] (ml./min.)	Infusion [a] Rate on Weight Basis (ml./kg./min.)
Rat	0.15	20	3	20.0
Rabbit	4.00	10	9	2.2
Dog	10.00	20	5	0.5
Man	70.00	20	4	0.057

[a] Values are approximate due to variations in body weight. These figures serve chiefly to show what margin of safety is provided by the screening tests.

From some standpoints, emulsions made entirely of synthetic materials (with the exception of glucose) might be more satisfactory than those containing purified natural products. Progress in this direction has been made by the use of such synthetic triglycerides as triolein and palmitodiolein and by introducing various synthetic agents to supplement the action of the phosphatides. Efforts are being made to find synthetic substitutes for the phosphatides themselves. Besides offering certain practical advantages, the use of such definitely characterized systems appears indispensable to a full understanding of the fundamentals involved in the preparation of fat emulsions and their intravenous application.

A fairly extensive clinical experience has been gained with emulsions given in Table I and forms the basis of another report (6). On an infusion basis emulsions which contained cottonseed oil or triolein caused no reaction in more than 90% of the cases. With emulsions of olive oil a somewhat higher reaction rate was observed. When reactions did occur, they were usually one of the following: a mild pyrogenic reaction, generally not associated with a chill, or a reaction characterized by a transient pain of various degrees of intensity in the lumbar region. The latter reaction has been termed a "colloid reaction" (6) since similar symptoms have been observed with intravenously administered colloidal iron and inulin. Present efforts are being directed towards a better understanding of the causes of these reactions with the hope of being able to eliminate them altogether.

Summary

Descriptions are given of the high pressure homogenization equipment used and of the actual procedure

[7] It is of interest to note that dispersions of phosphatide alone are likely to oxidize rapidly whereas when present in emulsions of either saturated or unsaturated fats, little oxygen uptake can be detected even in a 100% oxygen atmosphere (7). In the present equipment, emulsions can be prepared in the presence of air without appreciable organoleptically detectable rancidity developing. In earlier studies in which a different homogenizer was used, emulsions made in the presence of air acquired a strong odor of rancidity within as little as 5 min. This was probably due to the fact that Monel metal parts present in the homogenizer contributed appreciable copper, which acted as an oxidative catalyst. The phospholipid used in the present emulsion has remained the most satisfactory emulsifying and stabilizing material for preparations of the type made in this laboratory. Its chief disadvantage is its complex composition. It may be possible to overcome this by using newer fractionation methods to obtain fractions which would have a readily definable chemical composition.

followed in the preparation of fat emulsions suitable for intravenous nutrition. Such emulsions contain 10-15% oil (w/v) dispersed in particles less than one micron in diameter. They are made under nitrogen and subsequently autoclaved to ensure sterility.

Procedures are also given for screening each batch of emulsion by means of tests performed on rats, dogs, and rabbits. Emulsions of the type described have found extensive application in the clinic with a low incidence of unfavorable reactions.

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Synthetic Detergents from Animal Fats. V. Esters from Alpha-Sulfonated Fatty Acids and Sodium Isethionate[1]

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ISETHIONATE ESTERS of fatty acids, of the Igepon A type, particularly the ester of oleic acid, $CH_3(CH_2)_7CH=CH(CH_2)_7CO_2C_2H_4SO_3Na$, are well known surface active agents and detergents. The usefulness of this type has been somewhat limited because of instability to hydrolysis.

The presence of an α-sulfo group in esters, such as sodium methyl α-sulfopalmitate and sodium isopropyl α-sulfostearate, has been shown to retard hydrolysis, to a surprising degree, in acid and alkaline solutions (9). It was thus of interest to prepare and evaluate esters from α-sulfonated acids and hydroxyalkanesulfonates, such as sodium isethionate. The esters might be expected to have the desirable surface-active and detergent properties of sodium 2-sulfoethyl oleate and perhaps to be of greater potential usefulness because of greater resistance to hydrolysis.

Preparation of Esters

Esters were prepared from the diacid (α-sulfopalmitic, α-sulfostearic, or α-sulfobehenic acid) and sodium isethionate or sodium 2-hydroxypropanesulfonate, by a method previously described (10), without the use of an esterification catalyst.

α-Sulfopalmitic acid. Stabilized liquid sulfur trioxide, 1.25 moles, was added dropwise in 30 min. to a stirred slurry of 0.78 moles of purified palmitic acid in 500 ml. of carbon tetrachloride. The mixture was stirred and heated 1 hr. at 60-65°, cooled to −15°, and filtered. The diacid was washed with cold carbon tetrachloride and dried in a vacuum desiccator at room temperature to give a gray product in a yield of 85%. Analysis: calculated for $C_{16}H_{32}O_5S$, neutralization equivalent 168.2; found, 167.3.

α-Sulfostearic acid. A diacid was prepared from purified stearic acid in a similar manner in a yield of 88%. Analysis: calculated for $C_{18}H_{36}O_5S$, neutralization equivalent 182.3; found, 183.3.

α-Sulfobehenic acid. Commercial behenic acid was purified by two crystallizations from acetone to give behenic acid, m.p. 79.0-79.6°, neutralization equivalent 340.3 (calculated, 340.6). Reaction with sulfur trioxide gave α-sulfobehenic acid, yield 97%, neutralization equivalent 196.2 (calculated for $C_{22}H_{44}O_5S$, 210.3).

Disodium 2-sulfoethyl α-sulfostearate. A mixture of 0.2 mole of α-sulfostearic acid, 0.207 mole of sodium isethionate, and 250 ml. of toluene was stirred and heated at reflux temperature for 6 hrs., with azeotropic removal of water. The reaction mixture was cooled, diluted with 200 ml. of 95% ethanol and neutralized with 18 N sodium hydroxide. Solvent and water removal left 103 g. of light brown product, which was dissolved in hot water. The aqueous solution was cooled, and unesterified diacid was removed as the sparingly soluble sodium salt. Ethanol was added to give a 75% ethanol solution, which was decolorized with carbon. Two crystallizations from 75% ethanol at −15° gave $C_{16}H_{33}CH(SO_3Na)CO_2C_2H_4SO_3Na$ as a white product in a yield of 66%. Analysis: calculated for $C_{20}H_{38}Na_2O_8S_2$, 46.49% C, 7.41% H, 8.90% Na, 12.41% S; found, 46.36% C, 7.44% H, 8.82% Na, 11.95% S.

Disodium 2-sulfoethyl α-sulfopalmitate. Esterification of α-sulfopalmitic acid with sodium isethionate in a similar manner gave $C_{14}H_{29}CH(SO_3Na)CO_2C_2H_4SO_3Na$ as a white product. Analysis: calculated for $C_{18}H_{34}Na_2O_8S_2$, 44.25% C, 7.01% H, 9.41% Na, 13.13% S; found, 44.12% C, 6.90% H, 9.38% Na, 12.78% S.

Disodium 2-sulfoethyl α-sulfobehenate. Esterification of α-sulfobehenic acid with sodium isethionate gave

[1] Presented at the meeting of the American Oil Chemists' Society, New Orleans, April, 1955.

[2] A laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, U. S. Department of Agriculture.