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Parenteral emulsions for drug delivery

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Abbreviations: AD, anaesthetic dose; AmB, Amphotericin B; body wt., body weight; CT, computerized tomography; EVA, ethylvinylacetate; LD, lethal dose; i.v., intravenous; PFOB, perfluorooctylbromide ($C_{18}F_{17}Br$); PGE_1, prostaglandin E_1; RES, reticuloendothelial system; THC, tetrahydrocannabinol; TPN, total parenteral nutrition; WFI, water for injection.

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Summary

This review presents the current status of drug delivery systems based on parenteral emulsions. When the carrier system contains emulsified lipids, typical production steps may encompass premixing of raw materials including the drug, high-energy homogenization, filtration and filling of bottles followed by heat sterilization. This procedure is defined as drug incorporation de novo, in contrast to extemporaneous addition of a drug to a pre-formed emulsion. Changes in concentration or chemical composition of raw materials, including the pharmaceutically active ingredient, or changes in process conditions, including time, temperature and pressure, may have profound effects on physical properties and stability of the final product. Careful characterization of these properties is essential in order to minimize toxicity of the carrier system and optimize drug efficacy. First-generation drug emulsions, which are either in clinical trials or are being marketed, include Amphotericin B, Diazemuls®, Vitalipid®, prostaglandin E_1 and Diprivan®. Second-generation formulations, which are currently being developed and evaluated, incorporate cytotoxics such as Perilla ketone, Penclomedine and taxol or anesthetics such as halothane or pregnanolone. Other types of drug emulsions under development include perfluorocarbons for oxygen delivery and lipophilic carriers for radiopaque contrast agents. Future trends in this field are outlined, followed by a discussion of potential pitfalls in the evaluation of novel emulsion delivery systems.

I. Introduction

The purpose of this review is to discuss the current status of drug delivery systems which employ emulsions suitable for parenteral administration. The term parenteral is of Greek origin, from para, meaning besides or other than and enteron, meaning the gut [1]. Therefore, any method of drug administration which does not include passage through the gut is correctly referred to as parenteral delivery. An emulsion is a heterogeneous mixture of two or more immiscible liquids, with a third component (emulsifier) used to stabilize the dispersed droplets. Co-emulsifiers and other additives are often used to improve stability.

Lipid emulsions were developed after World War II to serve as an intravenous source of both calories and essential fatty acids. Since that time, fat emulsions have been developed for use in the administration of total parenteral nutrition (TPN).

Pioneering work using lipid emulsions as drug delivery systems began in the early 1970's. For example, R. Jeppsson investigated the incorporation de novo of drugs such as barbituric acid [2], nitroglycerin and cyclandelate [3] into fat emulsions.

Progress in the field of parenteral drug delivery using emulsions has been followed in numerous reviews and monographs. A good review of the literature covering applications of emulsions is provided by S.S. Davis [4]. In 1986, M. Singh and L. Ravin reviewed parenteral emulsions as drug carriers. Their review includes emulsion preparation, drug incorporation and specifically discusses diazepam[reg;] and Amphotericin B as examples of parenteral emulsions under development [5]. Some of the same topics were reviewed in 1987 by S. S. Davis et. al., focusing specifically on lipid emulsions [6]. In 1988, B. Skeie et. al. reviewed the metabolism of parenteral fat emulsions and their effects on lung function [7]. R. Nash, in 1988, wrote a chapter on pharmaceutical suspensions which includes historical references to parenteral emulsions [8].

This review is an update, designed to build upon the work mentioned above by outlining drug emulsion literature from 1986 through 1989. General information will be presented on emulsions, their formation, stability, toxicity and metabolism. The current status of first-generation parenteral drug products will be discussed, followed by a summary of proprietary drugs, water-insoluble compounds and antineoplastic agents which are now being administered in lipid emulsions. Future directions covered in this review include possibilities for second-generation anaesthetic emulsions, ethiodized oil preparations for computer assisted tomography and perfluorocarbon preparations. Newer technology for producing emulsions now permits customizing carrier systems to match more closely the requirements of both the drug and the patient treatment (e.g., see subsection III.1: Amphotericin B).

II. Emulsions

Emulsions fall into two general categories. The heterogeneous system described by a drop of organic liquid immersed in an aqueous solution has been designated an oil-in-water emulsion [9]. Alternatively, the heterogeneous system described by a drop of water in an organic solution has been designated a water-in-oil emulsion [9].

Fat emulsions of the oil-in-water type evolved after World War II [10]. The rationale behind their development is that microscopic, emulsified fat droplets are similar in structure to chylomicrons. Chylomicrons are fat globules ranging from 0.5 to 1 μm in size composed of triglycerides, proteins, free cholesterol and phospholipids. The liver and intestine generate chylomicrons in vivo. There are several commercially available fat emulsions such as Intralipid® 10% and 20% (KabiVitrum), Lipofundin and Lipofundin S (Braun) and Liposyn (Abbott), all of which are essentially non-toxic [11]. For example, Intralipid® 20% has an LD_{50} of 163 ml/kg body wt. in mice [12]. Their relatively low toxicity coupled with their extensive use in TPN has made the lipid emulsion an attractive choice as a carrier system for lipophilic drugs. These drugs may be delivered ocularly, intramuscularly, intraperitoneally, or intravenously [6]. In addition, water-in-oil and gelatin-in-oil emul-

sions have been developed with the ability to incorporate water-soluble or gelatin-soluble drugs. Since their toxicity and metabolism are less well-defined compared to fat emulsions, these preparations offer untested alternative carriers for hydrophilic drugs.

II.1. Emulsion preparation (see Ref. 13)

For all injectable lipid emulsions, oil is the internal phase, dispersed as extremely fine droplets in the continuous phase, usually water. The emulsification process requires addition of surfactant and mechanical energy. The two main functions of surfactant are to lower interfacial tension of the oil and water phases and to prevent flocculation and coalescence of the dispersed phase (see Fig. 3, subsection II.2). While a wide variety of surfactants are available for industrial manufacturing of foods, cosmetics, insecticides, paints, detergents and so forth, relatively few are approved for i.v. administration. Natural phosphatides, principally from egg yolk or soybean, are in most widespread use. However, certain synthetic surfactants which have been approved for oral consumption have been or are being evaluated for i.v. applications at low doses. These include fatty acid esters of sorbitans (Spans) and polyoxyethylene sorbitans (Tweens) as well as block copolymers of ethylene and propylene oxides (Pluronics). Occasionally, secondary or co-surfactants are added in trace amounts, an example being soluble salts of long chain fatty acids.

Typical steps in the production of a lipid emulsion which may contain a pharmacologically active agent are summarized in Fig. 1.

Incorporation of a drug typically occurs during premix formation (steps A and B in Fig. 1). This procedure is defined as incorporation of the drug de novo. If the pharmaceutically active compound is added to a pre-formed, sterilized emulsion, the process is termed an extemporaneous incorporation. Although it is the first stage, premix formation has considerable influence on the quality of the final product. Generally, a uniform premix with a droplet size smaller than 20 μm results in a more monodisperse and physically stable final emulsion.

Following premix formation, a much higher energy emulsification process (step C, Fig. 1) is required to break droplets down to diameters smaller than 1 μm. Although the mechanism of the Gaulin homogenizer is not fully understood, it is thought that rapid changes in velocity occur as liquid is forced through a Gaulin valve system, producing an almost instantaneous pressure drop. This forms imploding bubbles (cavitation) which generates shock waves which in turn shatter the dispersed droplets. As droplets become smaller, greater amounts of energy are required for further break-up. Thus, additional passes through a homogenizer operating at a constant pressure drop narrow the particle size distribution until an equilibrium is reached (Fig. 2). Equipment which is available for emulsification in the U.S.A. includes Gaulin homogenizers (APV Gaulin, Everett, MA) and Rannie homogenizers (APV Rannie, St. Paul, MN) for vols. of 8 l up through large-scale production. For small-scale developmental work, Rannie Model Mini-Lab and Microfluidizer Model M-110 series are examples of widely used bench-top equipment.

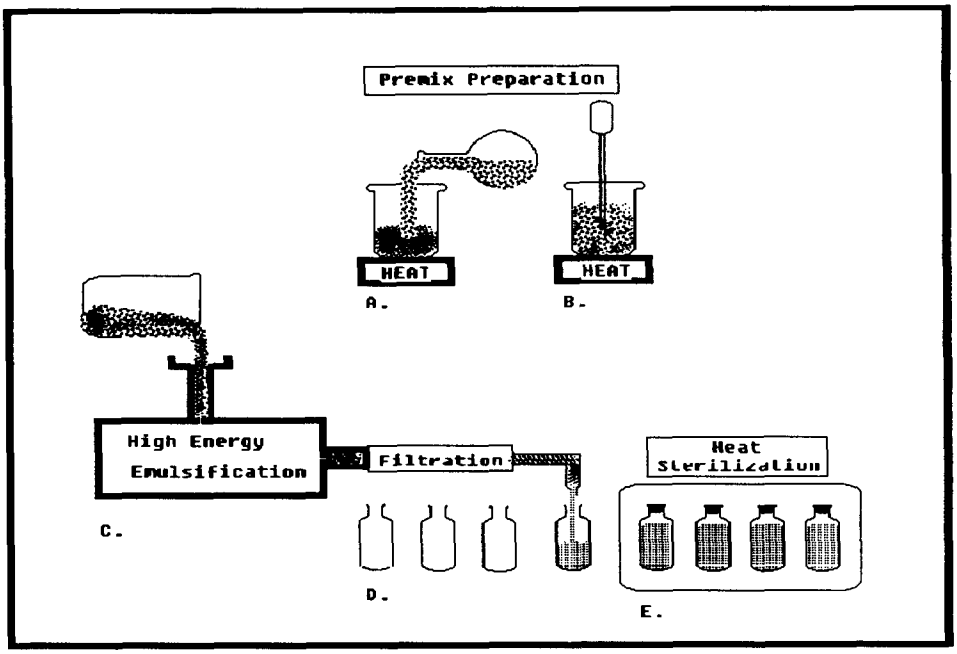

Fig. 1. Major production steps for a lipid emulsion.

A filtration step is commonly included to remove poorly emulsified material from the product (step D, Fig. 1). In pharmaceutical manufacturing, a cartridge-type filter might be used, providing that it is non-pyrogenic, contains no extractables, sheds no particles and possesses a medium pore size (about 1–5 μm). The bottle-filling operation takes place with full gowning under clean room conditions or in a laminar flow hood, followed by heat sterilization (step E, Fig. 1). All process stages depicted in Fig. 1 are carried out in a closed system to prevent both microbial and particulate contamination.

There are a number of important variables inherent in this process. Effects of a moderate *increase* in some of the more easily controlled parameters are summarized below, assuming that a lipid-based drug emulsion is being developed. Of course, specific formulations may not respond exactly as expected. Furthermore, many effects listed above will reach a plateau value at some point which must be determined during process development (see Table I).

II.2. Emulsion characterization (see Refs. 13, 15 and 16)

Physical properties of emulsions which can be readily quantified include particle mean diameter, size distribution, surface ζ-(zeta) potential, interfacial tension, osmolality and phase inversion temperature.

All of these properties are important to predictions of emulsion stability and biocompatibility. For parenteral use, a droplet mean diameter of less than 1 μm is highly desirable. Size distribution is equally important, since a more homogeneous

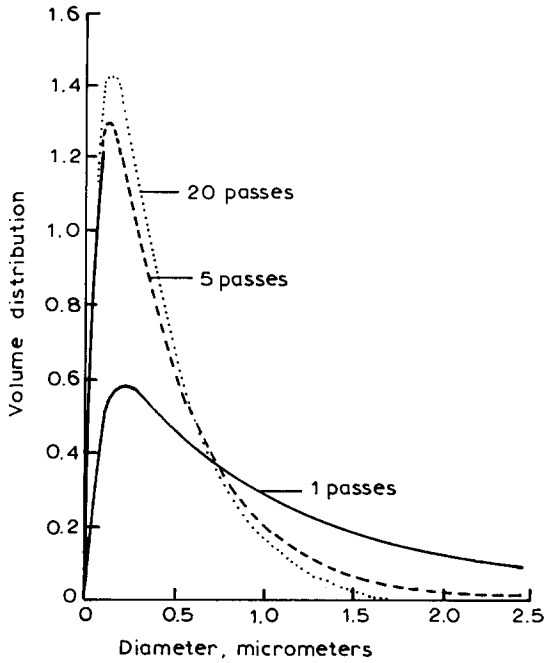

Fig. 2. Multipassing through a homogenizer narrows emulsion drop size distribution but has relatively little effect on mean diameter. The emulsion depicted is 'filled milk' which contains corn oil, non-fat milk solids and water. The emulsion was prepared using a laboratory-size Gaulin homogenizer model 15MR [14]. Reproduced with permission of W. Pandolfe.

TABLE I

VARIABLES AND THEIR EFFECT ON THE FINAL EMULSION

Variable to be increased	Expected effect
Oil concentration	larger droplet size
Salt concentration	wider droplet size distribution (or breakage)
pH	improved physical stability
Drug concentration	unpredictable due to altered surfactant solubility in oil phase
Surfactant concentration	smaller droplet size until optimum, then increased viscosity
Process temperature	smaller droplet size (via reduced viscosity)
Process pressure	smaller droplet size
Homogenizer passes	narrower droplet size distribution

(monodisperse) emulsion tends to exhibit less coalescence and greater resistance to breakage. Furthermore, droplets larger than 5 μm are capable of forming emboli in small capillaries such as in the lungs. Biocompatiblity is also related to net charge on the particle surface, or ζ-potential. In general, a more electronegative surface exhibits reduced tendency to aggregate in the presence of blood proteins. In addition, very low interfacial tension is associated with a more stable emulsion while high surface tension predicts short shelf life due to phase separation.

An ideal, biocompatable emulsion is also isotonic, i.e., containing 280–300 mOsm/kg. In practice, there are few physiologically acceptable tonicity agents which may be incorporated into an emulsion without causing disruption during thermal sterilization.

The phase-inversion temperature is the temperature at which an emulsion inverts from either an oil-in-water form to a water-in-oil form or vice versa. Temperature changes such as those occurring during homogenization or sterilization procedures may cause inversion to occur. There is some evidence to suggest that relatively stable systems are obtained when the phase-inversion temperature of an oil-in-water emulsion is about 20–65° C higher than the storage temperature [15].

There are several physical changes which may occur when a drug is added extemporaneously to a sterilized lipid emulsion (Fig. 3), some of which lead to breakage (free oil: separation of oil and water phases). While creaming and gross oil separation are visible to the trained eye, other changes such as flocculation and coalesence must be detected by either light-scattering instruments or by light microscopy.

III. First-generation drug emulsions

'First-generation' drug emulsions are those which are either in clinical trials or are being marketed in Europe and Japan (Table II). Interestingly, all products in this group are prepared with an egg yolk and soybean oil formulation similar to Intralipid® Manufactured by Kabi, AB

III.1. Amphotericin B

Amphotericin B (AmB) has been incorporated extemporaneously into both Intralipid® 10% and 20%, resulting in decreased acute toxicity without loss of antifungal activity [17]. Decreased toxicity of the polyene macrocycle AmB in an emulsion system may be explained by reduced binding of the drug on cellular membranes [17]. AmB was dissolved at a concentration of 10–14 mg/ml in dimethylacetamide plus sodium deoxycholate. Any undissolved drug was removed by membrane filtration and then 0.6 ml of solubilized AmB was added to 20 ml of Intralipid® 20% under aseptic conditions. This extemporaneous drug emulsion remains stable for 1 year at 4° C when protected from sunlight [18].

Metabolism studies of AmB in Intralipid® 10% (prepared as above for Intralipid® 20%) reveals normal hydrolysis of the triglyceride carrier by lipoprotein lipase. As an emulsion AmB is preferentially taken up by the reticuloendothelial system (RES), a process which may underlie the therapeutic advantage of this

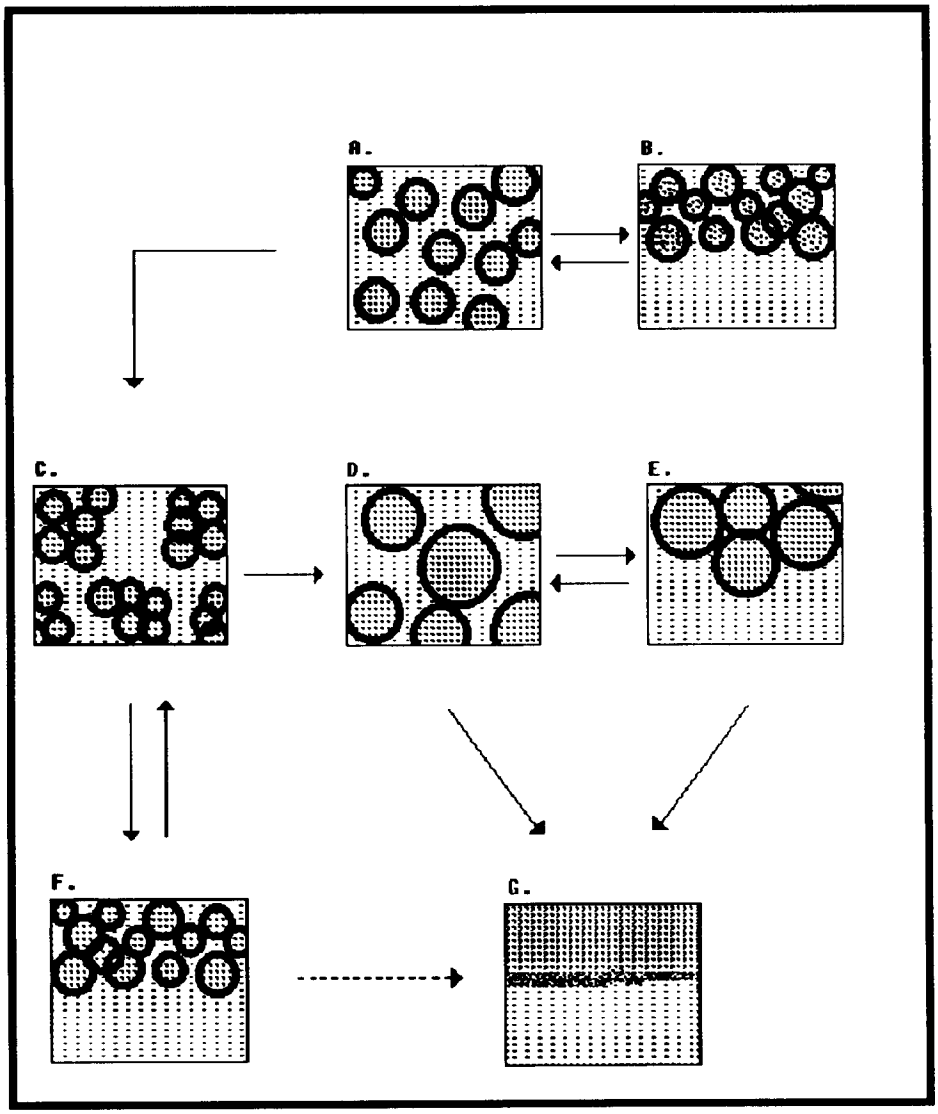

Fig. 3. Physical changes possible in a lipid emulsion. Solid arrows designate reversibility while the dashed arrow suggests uncertainty. (A) Freshly prepared lipid emulsion; (B) *creaming* – readily reversible, slow flotation of lipid droplets on more dense aqueous phase; (C) *flocculation* – aggregated droplets are not readily redispersed by agitation; (D) *coalescense* – irreversible merging of smaller droplets; (E) rapid creaming of coalesced emulsion; (F) rapid creaming of flocculated emulsion; (G) *broken* emulsion – separation of oil and water phases.

delivery system [19]. According to Kirsch and coworkers [17], this formulation has an advantage in that individual components have been approved for clinical use in the U.S.A. by the Food and Drug Administration. They also claim that large scale production is feasible.

TABLE II

FIRST GENERATION DRUG EMULSIONS

Emulsion	Drug	Company	Activity	Method	Status
Intralipid®[a]	Amb	SmithKline	antifungal	extemporenous	pre-clinical trials
Diazemuls®[a]	diazepam	Dumex, Denmark	sedation	de novo	marketed in Europe
Vitalipid®	vitamins	Kabi	nutrition	de novo	marketed in Europe
	PGE_1	GreenCross	vasodilator, inhibits platelet aggregation	de novo	marketed in Japan
Diprivan®[a]	Propofol	ICI, England	Anaesthetic	de novo	marketed in Europe

[a] Manufactured by Kabi.

III.2. Diazemuls® (Dumex, Denmark)

A lipid emulsion containing diazepam (manufactured by Kabi, AB for Dumex, Denmark) is marketed in Europe as Diazemuls®. One ml contains 5 mg of diazepam (Valium), 150 mg of fractionated soybean oil, 50 mg of acetylated monoglycerides, 12 mg of fractionated egg phospholipids, 22.5 mg of glycerol, sodium hydroxide (to pH 8), plus water for injection. This is an oil-in-water emulsion with an 18 month shelf life. Due to the solvents present i.v. administration of conventional preparations of diazepam often causes pain on injection [20]. A study of 2435 patients treated with Diazemuls® showed only 0.4% who experienced such pain. In addition, 99% of these patients showed sedation similar to that from a comparable strength solution of Valium. Interestingly, the distribution and elimination phases after i.v. injection were the same for Diazemuls® as for Valium in conventional solvents.

III.3. Vitalipid® emulsions

Vitalipid® N Adult and Vitalipid® N Infant are mixtures of the following naturally occurring compounds in concentrations corresponding to those commonly absorbed from an adequate oral diet (see Table III).

Vitalipid® N has a 2-year shelf life when stored at 2–8° C, protected from light. The palmitate ester of Vitamin A remains more effectively solubilized [21] than would the acetate derivative. Two major concerns which have been thoroughly investigated are migration of plasticizer from plastic i.v. infusion bags and administration sets into the product [22] and trace element-catalyzed degradation of vitamin A [23]. More recently, plasticizer-free ethylvinylacetate (EVA) bags have eliminated most of these problems.

No pharmacodynamic effects are expected, aside from maintaining or repleting the patient's nutritional status. This product must be infused slowly over several hours in order to minimize rapid increases in blood concentration and thus prevent

TABLE III
COMPOSITION OF VITALIPID® N

Components	Amount	
	adult	infant
Retinol palmitate (corresponding to retinol)	99 mg	69 mg
Ergocalciferol	0.5 mg	1.0 mg
Dl-α-tocopherol	0.91 mg	0.64 mg
Phytomenadione (Vitamin K)	15 mg	20 mg
Fractionated soybean oil	100 mg	100 mg
Fractionated egg phospholipid	12 mg	12 mg
Glycerol	2.5 mg	2.5 mg
Sodium hydroxide to pH	8	8
Water for injection	1 ml	1 ml

excessive urinary loss of nutrients.

In a European clinical trial involving 13 patients, each of whom completed 7 days of continuous i.v. nutrition, the vitamin status of each patient either improved or remained stable across the study period. Vitalipid® N in Intralipid® 20% was administered to mice at a dose of 25 ml/kg body wt. and all animals survived, suggesting a very low toxicity.

III.4. Prostaglandin E_1 emulsion

Prostaglandin E_1 (PGE_1) is a potent vasodilator as well as an inhibitor of platelet aggregation. Undesirable effects of PGE_1 administration include diarrhoea and hypotension. However, incorporation of PGE_1 into a fat emulsion (Green Cross) increases biological activity and reduces side effects [24].

The emulsion is formulated by dissolving PGE_1 in soybean oil (10 parts) and egg yolk phospholipids (1.2 parts), followed by homogenization in water (1:9). The final emulsion is sealed in glass ampoules and sterilized at 121° C for 10 min. PGE_1 concentration in this emulsion is 3 $\mu g\ ml^{-1}$.

Teagarden et al. addressed the issue of PGE_1 chemical stability in a lipid emulsion [25]. Their study of the dehydration kinetics of PGE_1 revealed that, despite potential promotion of acid-catalyzed dehydration of PGE_1 at the oil-water interface, formulation as a lipid emulsion results in an overall improvement in PGE_1 stability at pH 4.5–6.0. These authors concluded that the concentration of hydrogen ions at the interface could be reduced by incorporating cationic surfactants into the lipid emulsion and that this would lead to a reduction in the acid-cata-

lyzed degradation rate. Of course, one must also consider the effects of adding a cationic emulsifier on the stability and toxicity of the final product. This remains to be tested.

III.5. Diprivan® (ICI, England)

Diprivan® an Intralipid®-like emulsion incorporating Propofol (10 mg/ml) manufactured for ICI by Kabi, AB, is currently marketed in several European countries. This short-acting, intravenous anaesthetic agent is suitable for induction and maintenance of general anaesthesia in surgical procedures which generally do not exceed 1 h in duration. There is a swift recovery with little post-operative nausea and vomiting. Using this emulsion formulation, Propofol is distributed rapidly in the patient with a half-life between 1.8 and 8.3 min.

In Belgium, investigators have studied the effects of continuous infusion (18 mg kg^{-1} h^{-1}) of Diprivan® in 15 intact hypoxic and hyperoxic dogs [26]. Their results suggest that Propofol, as an emulsion formulation, does not influence pulmonary vascular tone and does not inhibit hypoxic pulmonary vasoconstriction. It does, however, reduce the systemic vascular tone when venous return or oxygenation is decreased.

Propofol is metabolized in the liver to produce water-soluble glucuronide and sulphate conjugates which are excreted primarily in the urine [27]. Studies with mice involving i.v. infusion of Diprivan® determined an AD_{50} of 6.1 mg/kg body wt. and a LD_{50} of 31 mg/kg body wt. [28].

In 1989, the FDA approved Diprivan® for sale in the U.S. as a new molecular entity. It is currently marketed in 20 ml vials by Stuart Pharmaceuticals. (ICI).

IV. Second-generation drug emulsions

'Second-generation' drug emulsions are formulations which are currently being developed and evaluated. Relatively new developments in the areas of cancer chemotherapy and anaesthetic emulsions are summarized in Table IV.

IV.1. Cancer chemotherapy

Perilla ketone is an investigational lipophilic cytotoxic agent which is typically administered i.v. in 5% dextrose [29]. However, between 20% and 60% of the drug is lost due to high affinity for the plastic administration set. Extemporaneous formulation of Perilla ketone into lipid emulsion appears to eliminate this problem. Perilla ketone (5 mg/ml) solution in 10% ethanol, 40% propyleneglycol and 50% water was prepared and diluted 1:50 with Intralipid®10%. This dilution did not appear to damage the emulsion and there was no apparent change in physical appearance over 2–3 days [29].

Although this is a promising improvement in the Perilla ketone formulation, the chemical and physical stability of this extemporaneous drug emulsion has not been adequately explored. The fact that this formulation appears stable over several days suggests that an emulsion could be prepared de novo from raw materials which would be both stable and active over a sufficiently long period of time.

TABLE IV

SECOND GENERATION DRUG EMULSIONS

Drug	Activity	Method	Comments	Refs.
Perilla ketone	cytotoxic	extemporaneous	in 5% dextrose, ketone rapidly absorbed by plastic administration set; incorporation into Intralipid® prevents this loss	29
Penclomedine	cytotoxic	de novo	most stable emulsion (intralipid-like)	30
Penclomedine	cytotoxic	extemporaneous	drug crystallizes out of Intralipid®	30
Taxol	anti-tumor	de novo	triacetin emulsion; hand-made	32
Halothane	anaesthetic	extemporaneous	intralipid® 20%, useful for short-term anesthesia	34 35
Pregnanolone	anaesthetic	de novo	intralipid-like, similiar in efficacy to diprivian, but with lower toxicity	36, 12, 37

Penclomedine is a novel cytotoxic agent which has been screened at the National Cancer Institute as an aqueous suspension (at about 1 mg/ml), even though it is practically water-insoluble [30]. In order to evaluate the dose range for cytotoxic activity systematically, a formulation containing greater than 5 mg/ml has been developed. Prankered, Frank and Stella [30] found that the extemporaneous addition of Penclomedine to Intralipid® 10% and Intralipid® 20% results in precipitation of drug after several hours while de novo emulsification is more satisfactory. This emulsion is prepared with egg yolk or soy lecithin (0.96 g), glycerol (1.8 g) and double distilled water (69.24 g). The mixture is dispersed by means of a Polytron homogenizer, the pH adjusted to 8.3–8.4 with dilute NaOH and a final emulsion obtained by processing with a Microfluidizer (Microfluidics, Newton, MA). The mean hydrodynamic particle size was 0.24–0.32 μm with no significant change after 12 months of storage. Chemical stability of the emulsion was also monitored as a function of time, with no concentration changes noted after 12 months. Although this is a preliminary assessment, the importance of particle size and emulsion stability in the presence of an incorporated drug are emphasized in the findings.

The emulsion formulation of Penclomedine was tested for antitumor activity in mice by both intraperitoneal and i.v. administration. Preliminary results suggest that this emulsion preparation shows improved cytotoxic activity compared to a suspension of the solid drug in a comparable dosage range [30].

Taxol is a macrocyclic plant product with potent antitumor properties [31]. The current i.v. formulation of taxol includes ethanol, Cremophor EL and isotonic saline. However, not more than 0.6 mg/ml of taxol can be incorporated and the formulation is stable for only 3 h [32]. Emulsions incorporating up to 15 mg/ml of taxol

TABLE V

Identity	AD_{50}	LD_{50}	Ref.
Diprivan®	6.1	31	37
Pregnanolone	5.3	50	37

have been formulated with triacetin, L-α-lecithin, Pluronic F-68, Polysorbate 80, ethyloleate and glycerol. Although particle size and distribution data initially indicated a 1 μm mean diameter with a range of 0.5–5 μm, the mean grew to 2 μm in 1 week and increased to 4 μm in 2 months.

This taxol-triacetin emulsion has a preliminary LD_{50} of 2 ml/kg body wt. in mice (i.v.). Tarr and coworkers [32] attribute the major source of toxicity to the triacetin (50% w/v), but given the unstable nature of this preparation and the fact that no data were provided on the taxol-free triacetin emulsion, assignment of toxicity is unclear. The need for a low toxicity carrier to solubilize taxol is a challenging problem, since this drug is insoluble in Intralipid®. Although, the emulsion prepared for taxol appears unstable, improved stability may be possible with more rigorous homogenization techniques.

IV.2. Anaesthetic emulsions

Halothane is currently administered as an inhalation anesthetic. In view of the success of Diprivan® as an anesthetic emulsion, it is reasonable to ponder other methods of anaesthetic administration for halothane. Undiluted halothane administered by i.v. injection results in severe lung damage [33].

Johannesson and coworkers investigated the extemporaneous incorporation of liquid halothane (5.0 vol.%) into Intralipid® 20% [34]. The admixture was completed by shaking vigorously for 3–4 min. This preparation was stored protected from light; unfortunately no stability data was made available. When administered to rats i.v., this halothane emulsion behaves as a potent anesthetic with fast recovery time [34]. However, the safety margin between effective dose and lethal dose is very narrow for this species. A similar extemporaneous preparation of a halothane emulsion was used in a study comparing effects of inhalation versus i.v. administration in dogs [35]. This study concludes that the latter route would be useful for experimental procedures with animals when a short-term, readily controllable anaesthesia is required.

Pregnanolone, a metabolite of progesterone, was found to have anaesthetic activity [36]. A de novo emulsion formulation of pregnanolone (4 mg), soybean oil (200 mg), acetyltriglycerides (70 mg), egg yolk phosphatides (18 mg), glycerol (17 mg) and water to 1 ml has been prepared [12]. The mean particle size of this emulsion formulation is 0.2–0.5 μm with less than 3% larger than 1.0 μm.

When compared to Diprivan® a commercially available preparation, pregnanolone emulsion exhibits similar efficacy with significantly lower toxicity (as mg/kg body wt.) (see Table V).

Further investigation of this pregnanolone emulsion in rats suggests that it may provide a short acting, less toxic and non-cumulative alternative for althesin [37].

V. Perfluorochemical emulsions

Fluosol-DA® (Green Cross, Osaka, Japan) is the most extensively tested example of a perfluorocarbon emulsion. This preparation is composed of perfluorodecalin (14% w/v) and perfluorotripropylamine (6% w/v) emulsified with a mixture of poloxamer 188 (Pluronic F-68), glycerol, egg yolk phospholipids and potassiumoleate [38]. The particle mean diameter is reported to be as small as 0.12 μm by the manufacturer. The formulation is unstable and must be stored frozen then thawed before use. Another potential limitation of this product is the prolonged tissue retention time for the perfluorinated amine component, in contrast to rapid elimination of perfluorodecalin.

Fluosol-DA has been evaluated clinically as a red cell substitute in acute anemia for patients with religious objections to human blood transfusions [39]. Recently, this preparation has been shown to enhance the ability of radiation to destroy solid tumors by delivering high concentrations of oxygen to relatively poorly vascularized tissue [40]. Another potential application for this product is oxygen delivery to the heart during balloon angioplasty, a surgical technique designed to widen partially occluded coronary blood vessels. Clinical trials for this indication have been completed in the U.S.A. and an NDA submitted to the FDA by Green Cross.

In order to avoid the use of perfluorotripropylamine, S. Davis and coworkers have developed perfluorocarbon emulsions based solely on perfluorodecalin [41]. These new formulations show bioequivalence when compared to Fluosol-DA$^{reg;}$. Adoxx™ (Adamantech, Linwood, PA) is another new perfluorocarbon emulsion containing perfluoromethyladamantane emulsified with egg yolk phospholipids. This preparation manufactured by KabiVitrum (Clayton, NC) has been used in a number of preclinical research studies [42].

A new direction in the development of perfluorocarbon emulsions is the design of surfactants which are partially fluorinated [43], allowing for the preparation of more efficacious and stable emulsions [44]. These surfactants are designed with a hydrophilic sugar head group, a hydrocarbon spacer of 2–11 carbon–hydrogen linkages and a fluorophilic tail. Surfactants of this variety have been used to prepare emulsions which are in the early stages of characterization [44].

VI. Other uses

VI.1. Emulsified contrast agents

Emulsions possessing low toxicity and high oxygen carrying capacity have been prepared using perfluorooctylbromide ($C_{18}F_{17}Br$ or PFOB) with egg yolk lecithin as the emulsifier [45]. PFOB is also radiopaque and this emulsion has been tested as a contrast agent for CT scanning of both liver and spleen [46]. Although toxicity in mice is relatively low (LD_{50} is 45 g/kg body wt.), this strongly lipophilic perfluorocarbon may be retained for several years in adipose tissue. The formulation is reported to be stable and it is currently prepared by Alliance Pharmaceuticals, San Diego, CA.

Iodinated lipid emulsions constitute another class of highly efficient macrophage

TABLE VI

TOXICITY OF CONTRAST AGENT EMULSIONS

Identity	Mean diameter (μm)	LD_{50} (ml/kg body wt.)	Minimum effective dose for CT scan (per kg body wt.)	Ref.
AG60.99	1.3	16[a]	0.3 ml	49
EOE-13	0.98	15.6[a]	0.3 ml	47
Intraiodol	0.31	60[a]	3 ml	47
PFOB	–	45[b]	0.25 g	46

[a] Two rats.
[b] Mice.

imaging agents, with applications for ultrasound, magnetic resonance and CT scanning of liver and spleen. There have been several preparations of iodinated emulsions which have shown promise as contrast agents but exhibit unacceptable side effects (fever, chills, thrombocytopenia, hypotension, respiratory distress and temporary impairment of the liver function) [47]. An emulsion designated AG 60.99 (Laboratoire Guebert, Aulnay-sous-Bois, Seine-St.Denis, France) has been prepared containing 35% iodinated ethyl esters of poppy seed oil, soya lecithin, glucose, disodium phosphate, polyoxyethylene glycolmonostearate and water [48]. The average particle size is 1.3 μm with a broad range from 0.16–7 μm. However, two problems remain: the emulsion is fairly toxic (Table VI) and unstable with a large droplet size.

Similar problems hold true for an ethodized oil emulsion designated EOE-13 (National Institutes of Health, Bethesda, MD); EOE-13 has been shown to have a metastases size detection threshold of 1–1.5 cm using computerized tomography [49]. Previous methods could not detect masses smaller than 3 cm in diameter. The emulsion EOE-13 contains 53 g of Ethiodol (Savage Laboratories, Houston, TX) which is composed of iodinated ethyl esters of mixed fatty acids from poppy seed oil, plus 0.45 g soya lecithin, 10 ml alcohol, phosphate buffer adjusted to pH 7 and water to 100 ml. Although this iodinated lipid emulsion has a smaller particle diameter (0.98 μm) and cannot be autoclaved (like AG 60.99), the preparation has been rejected for clinical trials due to its high toxicity (Table VI) [49].

A new iodinated lipid emulsion called Intraiodol, has been formulated by Wretlind and coworkers [47]. This contains 10 ml Lipiodol UF (Laboratoire Guebert, Aulnay-sous-Bois, Seine-St.Denis, France) which is also composed of iodinated ethyl esters of fatty acids derived from poppyseed oil, plus 2.25 g glycerol, 1.2 g egg yolk phospholipids, 0.1 g L-phenylalanine, sodium hydroxide (to pH 9.3) and water to 100 ml. Intraiodol addresses the problems of particle size and side effects. The mean particle diameter of Intraiodol is 0.31 μm and while the preparation has slightly less contrast ability than EOE-13, the adverse reactions are reduced [47] (Table VI).

VI.2. Flurbiprofen emulsion

Flurbiprofen esters have been incorporated into lipid emulsions [50] and intravenous administration was studied versus i.v. aspirin. At the optimal dose for post-operative pain relief, reduction of plasma prostaglandin ($PGE_{2\alpha}$) levels for aspirin and emulsion patient test groups were similar, but onset of relief was more rapid for the latter.

VI.3. Tetrahydrocannabinol emulsions

Tetrahydrocannabinols (THCs) were incorporated de novo into emulsions to obtain vehicles for administration which would facilitate evaluation of toxicity. Emulsions were prepared by sonicating THC in sesame oil with Polysorbate 80 and isotonic saline to yield a preparation containing 2–4% w/v THC. This preparation was used to determine the effect of administration mode on LD_{50} in rats [51]. The results are as follows (mg/kg body wt.): 36–40 for i.v., 106 for inhalation and 800 for intragastric routes.

VII. Future directions

The future of emulsion-based drug delivery lies in 'fine tuning' the carrier to suit the requirements of both the incorporated drug and the intended therapeutic program. With a wide variety of non-toxic vegetable and marine oils available, this appears to be an achievable goal. For example, medium chain triglycerides from coconut oil and ethyl esters of fatty acids derived from certain vegetable oils may have potential applications in drug solubilization and emulsification.

The essential raw materials of a lipid emulsion, phospholipids and triglycerides may themselves be considered pharmaceutically active under certain conditions. For example, cholesterol mobilization occurs following i.v. infusion of phospholipids into animals or humans. Conceivably, the therapeutic 'drug' being delivered could be the phospholipid emulsifier as a treatment for atherosclerosis [52,53]. As another example, recent reports suggest that dietary alterations in ratios of certain long-chain polyunsaturated fatty acids from marine oils may suppress tumor growth in vivo and/or increase tumor sensitivity to anti-neoplastic agents [54]. Since these effects are mostly due to modulations in prostaglandin biosynthesis, future fish oil emulsions may well serve as adjuvants for cancer therapy.

One recurrent problem with emulsions is shelf life. Although many lipid emulsions are stable for up to 2 years stored at 5° C, a more economical preparation would be stored in dry form and reconstituted just prior to use. The early stages of research into freeze drying and reconstitution of emulsions have begun with the investigation of various cryo-protective agents. Labarquilla and coworkers [55] have studied the effect of incorporating carbohydrates into a lipid emulsion de novo [55] and their results suggest that either sucrose or trehalose may function as cryo-protectants under certain conditions.

The major focus of recent literature has been in the area of i.v. administration, with fewer reports on intraperitoneal and intragastrointestinal delivery. This leaves open the ocular, oral and transdermal delivery routes as new areas of research.

Major investigation into the use of emulsions as ocular delivery systems has already brought to light the advantage of increased residence time for pharmaceutically active agents in the eye [56,57]. Incorporation of lipophilic drugs into a liquid emulsion which can be delivered orally has been studied by Bachynsky and co-workers [58]. This self-emulsifying formulation was encapsulated and found to improve absorption of the lipophilic compound [58]. Similar investigations into transdermal delivery of drugs using emulsions is showing potential utility for delivery of progesterone [59].

A related area of emulsion technology is that of microemulsions [60] which are self-emulsifying and stable formulations requiring very mild preparation methods. Microemulsions offer opportunities for very different solubilization and delivery capabilities. One such preparation under current investigation is in an encapsulated form for oral delivery as discussed above [58].

Multiple emulsions are another alternative which may allow fine-tuning of the delivery system, e.g., for sustained release. Multiple emulsions are easily prepared by re-emulsifying a simple oil/water (o/w) or water/oil (w/o) system to produce o/w/o or w/o/w types. Such systems have been formulated to deliver drugs [61], an example being intramuscular delivery of bleomycin for cancer chemotherapy. One serious problem with multiple emulsions is instability and these formulations must be used immediately after preparation. However, modification of the surfactants being used has the potential to overcome this drawback.

X. Conclusions

While emulsion-based drug delivery is a relatively new field with exciting growth potential, there are several pitfalls to be avoided. Foremost among them is the failure to adequately characterize experimental formulations with respect to emulsion integrity including droplet size distribution, free oil, osmolality and ζ-potential. A second pitfall is failure to measure and minimize toxicity of the carrier system independent of the drug substance. Finally, while extemporaneous incorporation of a drug into a pre-formed emulsion is sometimes possible (e.g., halothane), generally the most satisfactory and reproducible results are achieved by incorporation de novo (e.g., Diazemuls). Extemporaneous systems are often associated with a third pitfall: failure to monitor stability of both the drug and the emulsion as a function of time and storage conditions.

The 'gold standard' for quality of all potential drug emulsions should be a clinically proven nutritional product such as Intralipid® (KabiVitrum) or Liposyn$^{reg;}$ (Abbott Laboratories). A high incidence of untoward and unacceptable physiological side-effects often may be avoided by carefully optimizing oils, solubilizing agents and surfactants to produce a uniform, monodisperse emulsion. The evolution of formulations containing iodinated contrast agents is a prime example.

Currently, emulsion technology may be fine-tuned to meet the unique requirements of each drug. Indeed, this will be essential if these new carrier systems are to achieve their true potential: clinically significant improvements in drug efficacy and reductions in toxicity.

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