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Unexplored Areas and New Findings in Lipid Emulsion Serving as a Potential Drug Carrier for Lipophilic Drugs: A Review

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ABSTRACT

Most of the drugs are poorly water soluble or lipophilic in nature, that's why we are facing the problem of poor solubility of drugs, it also affect the bioavailability of drugs. Lipid emulsion (LE) is one of the best methods to improve the solubility of lipophihc drugs. Since 1962 the improvement of hpid emulsions were observed as intralipid iodinated hpid emulsion, Physostigmine salicylate lipid emulsions Amphotericin B lipid emulsion, tcopherol lipid emulsions, Apomorphine, Lipid emulsion as antidote has been occurred. The lipid emulsions are potential carrier for poorly water soluble drugs. The components which are used in lipid emulsions are oils, emulsifiers, buffering agents, antioxidants, chelating agents and preservatives. Oils and emulsifiers play important role in lipid emulsions.

Key words: Oil, emulsifier, biotransformation, solubility, stability, lipid emulsion

INTRODUCTION

Lipid emulsions are potential drug carrier for lipophilic and amphiphilic drugs with many favorable properties that are biocompatibility, biodegradability, stability and easy of prepare and handling. Lipid emulsions are heterogeneous dispersion of two immiscible liquids (Lundberg, 1994; Igarashi *et al*., 1996; Patlolla and Vobalaboina, 2005; Kandadi *et al*., 2011). Lipid Emulsions are thermodynamically unstable system (Sinko, 2006; Gonyon *et al*., 2007). The basic structure is a neutral lipid core (triglycerides stabilized by a monolayer of amphiphilic lipid (i.e., phospholipids) (MacLaren *et al*., 1997; Carpentier and Hacquebard, 2006), Such emulsions can solubilize considerable amounts of lipophilic drugs monolayer (Davis *et al*., 1987; Lundberg, 1991; Vyas and Khar, 2002; Lundberg *et al*., 1996). Emulsion behavior is largely controlled by the properties of the adsorbed layers that stabilized the oil-water surfaces (Abdurahman *et al*., 2007).

There are three prerequisites to be met by lipid emulsions for designing of a drug carrier system methods of preparation for adequate hpid emulsions, drug should be suitable for incorporation into such systems, hgands attach on to the surface of emulsion globules for targeting to special sites in the body (Vyas and Khar, 2002). After appropriate choice of the emulsifier the lipid emulsions can be performed by applying brief sonication or by pressure homogenization (Redgrave and Maranhao, 1985; Hirata *et al*., 1987; Maranhao *et al*., 1986). Phospholipids are generally weak emulsifier but by addition of a non-ionic detergent like polysorbate 80, emulsions with globule diameter down to 50 nm with good physical stability can be produce (Benita *et al*., 1986; Levy and Benita, 1989; Kellner *et al*., 1951; Weingarten *et al*., 1991; Jumaa *et al*., 1998; Nour *et al*., 2010).

Drugs for effective incorporation in to lipid emulsions should be preferably oil soluble or amphiphilic (Lee and Robinson, 1986; Tamilvanan, 2004). Lipid emulsions are suitable for both passive and active drug targeting (Vyas and Khar, 2002). Especially coarse emulsions are rapidly taken up by the Mononuclear Phagocyte System (MPS) and can thus be used to deliver the drug to macrophages (Jain, 1989; Lundberg *et al.*, 1996), By coating emulsion droplets with a hydrophihc polymer like polyethylene glycol (PEG), modified phosphatidylethanolamine (PEG-PE) the uptake by MPS can be reduced while resulting in prolonged circulating time (Dunn *et al.*, 1994; Lundberg *et al.*, 1996).

Site specific delivery can be designed by attaching Ligands specific for cellular receptors on to the surface of the emulsion globules. The development of new effective ligands for site specific delivery is a challenging task in the future development of lipid emulsions as drug carrier. I V administered emulsion are excellent carrier for hpophilic drugs which otherwise difficult to deliver (Vyas and Khar, 2002).

Rationals for using and developing medicated lipid emulsions (Table 1): Pharmacokinetic advantage in the use of lipid emulsions a low immunogenic and biodegradable drug delivery system (Balamuralidhara *et al.*, 2011). Emulsions can protect the encapsulated drug against hydrolysis and enzymatic degradation it is widely known that ingested lipids in food enhance the absorption and bioavailability of poorly soluble drugs (Tamilvanan, 2004; Carlson and Hallberg, 1963; Hutlin *et al.*, 1995; Liu and Liu, 1995; Song *et al.*, 1996; Spengler *et al.*, 1988; Klang *et al.*, 1996; Stevens *et al.*, 2003).

Disadvantages: The use of lipid emulsions as drug carriers were impeded by two major limitations, i.e., restricted access of delivery system to extra vascular space from systemic circulation and rapid clearance of colloidal particles by Mononuclear Phagocytic System (MPS) (Kandadi *et al.*, 2011). The first limitation, extravasations can be improved by decreasing the size of the colloidal particles or by ligand specific delivery or combination of these two approaches (Vyas and Khar, 2002). Usually colloidal drug carriers after intravenous administration are recognized as foreign bodies by Mononuclear Phagocytic System (MPS) and are rapidly taken up by liver Kupffer cells, macrophages of spleen and bone mar-row and by circulating monocytes and macrophages. Blood coat the hydrophobic surfaces of colloidal carriers and enhance their recognition and uptake by Reticuloendothelial System (RES) (Senior *et al.*, 1991; Kandadi *et al.*, 2011). Among the various methods of avoiding the RES uptake, the simplest way is to increase the hydrophilicity of surface. The hydrophilicity of a lipid surface can be increased by incorporating pegylated lipid (PEG) in the bilayer or sphingomyelins (Papahadjopoulos *et al.*, 1991; Awasthi *et al.*, 2003; Redgrave *et al.*,

Table 1: Rationals for using and developing medicated lipid emulsions

Reason	Example of drug
Solubilization of poor water soluble drugs (Wang *et al.*, 2006)	Diazepam, vit A, vit E, propofol, dexamethasone palmitate
Stabilization of hydrolytically susceptible compounds (Vyas and Khar, 2002)	Lemustin, physostigmine salicylate
Prevention of drug uptake by infnsion sets	Diazepam, perilla ketone
Potential S.R dosage forms (Vyas and Khar, 2002)	Barbiturates, dexamethasone palmitate
Site specific drug delivery to various organs (Jumaa *et al.*, 1999)	Cytotoxic agents
Reduction of irritation pain, toxicity (Shi *et al.*, 2009)	Amphotericin B

1992; Takino *et al.*, 1994; Varshika *et al.*, 2009; Semple *et al.*, 2005). The higher residence of pegylated colloids is attributed to the fact that highly hydrated and flexible PEG chains carry a thin film of aqueous fluid around the colloidal carrier and this steric stabilization of PEG chains results in reduced interactions with plasma proteins and cell surfaces (Blume and Cevc, 1993; Allen *et al.*, 2002).

FACTS OF LIPID EMULSIONS

Physicochemical properties of lipid emulsions: The components used in an emulsions must be chemically and physical stable, Sterilable and endotoxin free. Biologically compatible at a reasonable cost to both the manufacture and patient. Emulsions are visually inspected for creaming coalescence oil separation or colour change and particulate matter monitored by filtration (Carlson and Hallberg, 1963; Hutlin *et al.*, 1995; Liu and Liu, 1995; Song *et al.*, 1996; Spengler *et al.*, 1988; Stevens *et al.*, 2003). The drop size distribution of lipid emulsion is typically between 0-2-0.6 um with 90% of distribution less than 1um by using a dynamic light scattering or equivalent tech. The formulation is usually isotonic and at pH 7-8 for stability of the excipients in the emulsion for applicability in large volume (Chinsriwongkul *et al.*, 2007).

Biotransformation of lipid emulsion and bioavailability: The safety of emulsions as a drug delivery system is inherent to the biodegradables excipients commonly used such as the emulsifier egg and soya lecithin and oleaginous substance examples Soybean, safflower, structured triglycerides or milycol oil (Lenzo *et al.*, 1988). The metabolism of lipid emulsion after absorption and distribution occurs by two pathway. The binding of apoproteins from the blood stream to the surface of the emulsion droplets which promotes metabolism similar to chylomicros (Lenzo *et al.*, 1988). Some of the triglycerides are hydrolyzed by the capillary endothelial enzyme lipoprotein lipase to release glycerol, fatty acid and diglycerides in to the adjacent tissues (Redgrave *et al.*, 1992; Granot *et al.*, 1985; Richelle *et al.*, 1986; Carpentier and Hacquebard, 2006). The reminder of the emulsions particles removed from plasma by the liver. Lipoprotein lipase present in the adipose tissue, heart and skeletal muscle. The other metabolic pathway results in removal of more than 50% of emulsion particles from blood stream in to the extra hepatic tissue with little or no preceding lipolysis (Granot *et al.*, 1994; Peterson *et al.*, 1990; Liu and Liu, 1995).

After having acquired apoproteins (apo) by transfer from HDL, emulsion particles bind to lipoprotein lipase (LPL) at the endothelial site of most extrahepatic tissues. A substantial proportion of core triglycerides (TG) are hydrolyzed, releasing Fatty Acids (FA), which are either immediately taken up by the adjacent tissue or released into the circulation to increase the free FA pool. In the meantime, through exchanges of neutral lipids mediated by the Cholesteryl Ester Transfer Protein (CETP), emulsion particles transfer TG to endogenous cholesterol-rich high density (HDL) and low density (LDL) lipoproteins and, in a reverse manner, acquire Cholesteryl Ester (CE). Remnant particles, enriched with CE and depleted of TG (but having kept a major part of their liposoluble vitamin and w-3 FA content) are largely taken up by the liver but likely also by several extrahepatic tissues (Fig. 1). Liver uptake of TG and CE stimulates the hepatic production of apo B-100 and the release into circulation of Very Low Density Lipoprotein (VLDL), a proportion of which at a later stage of their intravascular metabolism may be converted into LDL (Carpentier and Hacquebard, 2006).

Elimination of lipid emulsion: The clearance of an lipid emulsions from the blood in intrinsic to the relationship between the physicochemical property of the lipid emulsions droplets and a

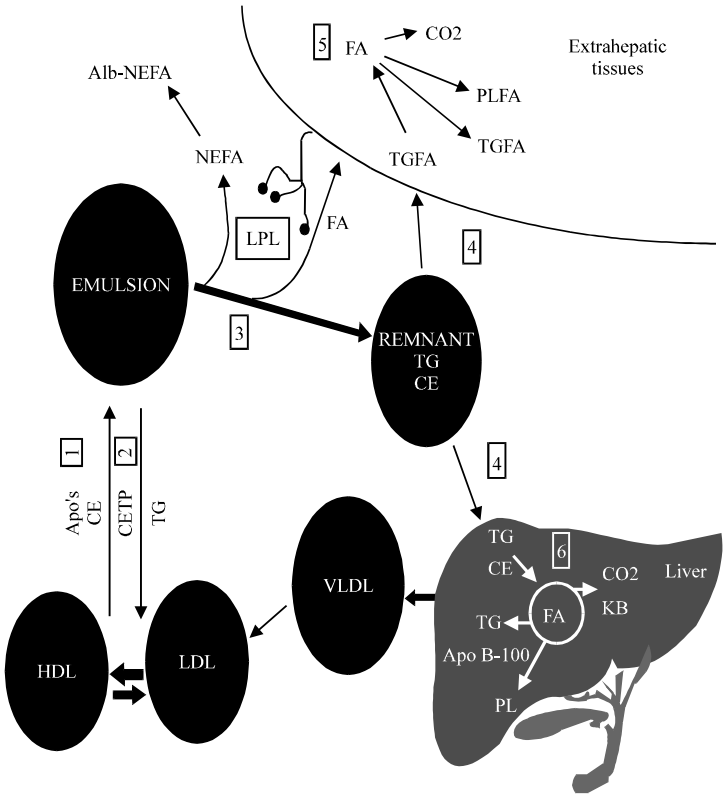

Fig. 1: Metabolism of lipid emulsion particle

physiological response by the reticuloendothelial system (Muller *et al.*, 1992). Small lipid emulsion particles are removed slower than larger droplets and negatively and positively charged emulsifier particles are removed quickly in comparison with neutral lipid emulsion droplets. Lipid emulsions droplet containing larger mol.wt. emulsifier, surfactants or phospholipids containing polyethylene glycol are also found to clear slowly from the bloodstream (Spengler *et al.*, 1988). The liver absorbs 90% of the recognized emulsion particles minor fractions found in the spleen, lung, bone marrow. Diversion from the liver allow passive targeting to the lung, kidneys and areas of inflammation. Active targeting can be achieved by the use of conjugated absorption or vectors to the polyoxyethylene side chains of the emulsifiers (Song *et al.*, 1996; Spengler *et al.*, 1988; Tamilvanan, 2004).

EXCIPIENTS AND FORMULATION CONSIDERATIONS

Parenteral lipid emulsions, topical ophthalmic lipid emulsions, oral lipid emulsions, topical lipid emulsions should be formulated with compatible vehicles and additives. The components of the internal and external phases of lipid emulsions should be chosen to confer enhanced solubility and/or stability to the incorporated active lipophilic drug. This section is a comprehensive presentation of the general considerations concerning excipient selection and optimum concentrations mainly in relation to the oil phase, the aqueous phase and the emulsifiers (Tamilvanan, 2004).

Main excipients used in lipid emulsion: Oils, emulsifiers, aqueous phase, chelating agents, buffering agents.

Oils: The solubility or stability of the drug substance usually drives the oil selection. If the formulation is intended for scale-up, purity and cost must also be considered. To maximize resource utilization and the probability of success, initial studies should focus on the use of Long-chain Triglycerides (LCTs) or Medium-chain Triglycerides (MCTs) (Muller and Heinemann, 1992). Long-chain triglycerides are derived from vegetable sources such as soybean or safflower oil, whereas MCTs are obtained by the re-esterification of fractionated coconut oil fatty acids (mainly caprylic and capric) with glycerin. These are the only oils that have shown long-term commercial acceptability in parenteral emulsions and are found in several FDA-approved products In some commercial fat emulsions, the MCTs are used in combination with LCTs (Lipofundin MCT/LCT 10 and 20%). Crude oils consist of heavy and light crude oil (Anisa *et al*., 2011). For drug solubilization, MCTs are reported to be 100 times more soluble in water than LCTs and to have an enhanced solubilizing capability (Table 2) (Rubin *et al*., 1991).

Yamaguchi *et al*. (2005) was concluded that in the case of steroidal drugs castor oil shows the maximum solubility. In the case of terazepam Jumaa and Muller (2001) was found that the combination of both oils (castor oil and MCT) shows higher solubility. Cohen *et al*. (1996) was studied in Amphotericin B, soy oil shows better solubility.

Emulsifiers: An emulsifier (also known as an emulgent) is a substance that stabilizes an emulsion by increasing its kinetic stability (Anne, 2008). Natural and synthetic agents have been considered for use as possible emulsifying agents because none of the oils typically employed form a spontaneous emulsion when mixed with water (Davis *et al*., 1974). The most commonly used emulsifier is natural lecithin. Natural lecithin is a phosphatide that is found in all living organisms and is either of animal (egg yolk) or vegetable (soy-bean) origin. Although rare, type I allergic reactions to soy-bean lecithin emulsified-lipid solutions have been observed (Weidmann *et al*., 1997). Even after purification, lecithin contains a distribution of related substances (Schneider, 1992). Intrinsically, lecithin is defined as a mixture of the triglycerides of stearic, palmitic and oleic

Table 2: Examples of commonly used oils and recommended concentrations

Excipient	Range (w/w)
General oils	
Soybean oil	10-20%
Safflower oil	10-20%
Sesame oil	10-20%
Corn oil	10-20%
Castor oil	20%
Castor oil: soybean oil (1:1)	Up to 30%
Castor oil: MCT (1:1)	
Coconut oil	Up to 30%
MCTs	10-20%
MCT/LCT mixture	Up to 30%
Altered fatty acid patterns	
Triolein	50%
Iodized ester of poppy	10%
Seed oil	10%
Purified fish oil	
Ethyl oleate	Not available
Squalane	10%

Table 3: Emulsifiers most commouly used in lipid emulsion formulations

Emulsifiers and/or their combinations	Range/ratio
Egg lecithin	1-3% w/w
Soybean lecithin	
Dipalmitoyl phosphatidylcholine: Polysorbate 80:PEG-PE	1:0.4:0.1 (approximately 50% w/w)
Ethylene glycol ether preferred	Not available
Thesit and triton X-100, glycerol/propylene glycol	30-70 w/w individuality
Glyceryl fatty acid esters	3% w/w
Pluronic F68, 88, 108	1.5-10% w/w
Poloxamer 401 (Pluronic L121)	5% w/w
Polysorbate 80	0.4% w/w

acids, linked to the choline ester of phosphoric acid. Other descriptive names include purified egg lecithins, egg yolk phospholipids, phosphatidylcholine and soybean lecithin. It is important to note that the physical properties of lecithin and the resulting emulsion stability can vary greatly, depending on the source and degree of purification of the emulsifier. Deliberate use of auxiliary emulsifying agents can be employed (Venkateswarlu and Reddy, 2001). With combinations of surfactants, in which one is a natural lecithin and the other a synthetic surfactant, formation of lecithin hydrolysis products is minimized and the shelf-life of the product is extended (Table 3) (Riess, 1994).

The formulations with only Tween 80 as an emulsifier showed a noticeable change in the particle size during autoclaving as well as a remarkable erythrocyte membrane damage. In contrast, phospholipids and Synperonic F68 formulations displayed good stability during autoclaving and showed almost no hemolytic activity. Moreover, mixing Tween 80 with either lecithin or Synperonic F68 improved the stability of formulations during the autoclaving process. Simultaneously, this led to a remarkable decrease in the hemolytic effect (Washington, 1990; Jumaa and Muller, 1998a,b, Jumaa *et al*., 1999).

Aqueous phase: The aqueous phase should be augmented by the incorporation of ionic or osmotic agents, antioxidants, buffers and preservatives as required. Because emulsified oil exerts no osmotic effect, isotonic adjustment (280-300 mOsm kg^{-1}) (Sznitowska *et al*., 2002; Foxall *et al*., 2007; Driver *et al*., 1989). IT will be important for large-volume parenterals such as the injectable fat emulsions. Glycerol has been preferred by the manufacturers of commercial soybean oil emulsion (Intralipid) (Travamulsion) and a commercial safflower oil emulsion (Liposyn), while other manufacturers have used sorbitol (Lipofundin) or xylitol. In addition to its contribution to tonicity, glycerol, in combination with propylene glycol has been shown to reduce the globule size and improve the creaming stability of o/w emulsions (Chanana and Sheth, 1993). Ionic agents (sodium chloride) and reducing sugars (glucose) should be avoided because of the potential interaction between reducing sugars and protein contaminants, which results in brown discolouration and/or phase separation of the emulsion.

Various antioxidants can be added to prevent peroxidation of unsaturated fatty acids in the oil as well as oxidation of the drug substance (Levy and Benita, 1989). α-Tocopherol is most commonly selected, probably because of its successful incorporation into two commercial lipid emulsions like Lipofundin and Trive 1000.

All small-volume lipid emulsions should include an antimicrobial agent because the aqueous, external phase is most vulnerable to inadvertent contamination. These agents can be dissolved in

the aqueous phase prior to emulsification. Suggested preservatives include the methyl and butyl derivatives of p-hydroxybenzoic (Levy and Benita, 1989). Quaternary ammonium compounds are useful because of their high aqueous solubility and limited tendency to partition into the oil phase in which they are not needed (Table 4).

Benzalkonium chloride, chlorocresol, parabens etc. are regularly included in ophthalmic lipid emulsions to prevent microbial spoilage of multi-dose ophthalmic lipid emulsions. The presence of components of natural origin like lecithin or oils with high calorific potential render the lipid emulsion a good medium to promote microbial growth when it is packed in multi-dose containers. Sznitowska *et al.* (2002) studied the physicochemical compatibility between the lecithin-stabilized lipid emulsion and 12 antimicrobial agents over 2 years of storage at room temperature. Preliminary physicochemical screening results indicate that addition of chlorocresol, phenol, benzyl alcohol, thiomersal, chlorhexidine gluconate and bronopol should be avoided due to the occurrence of an unfavourable pH change followed by the coalescence of the lecithin-stabilized droplets of the lipid emulsion (Tamilvanan, 2004).

Chelating agents: Chelation is the formation or presence of two or more separate coordinate bonds between a polydentate (multiple bonded) ligand and a single central atom (IUPAC). Usually these ligands are organic compounds and are called chelants, chelators, chelating agents or sequestering agents. The ligand forms a chelate complex with the substrate. Chelate complexes are contrasted with coordination complexes composed of monodentate ligands, which form only one bond with the central atom (Morgan *et al.*, 1920). Examples-Ethanolamine, EDTA (Reitmeier *et al.*, 1940).

Buffering agents: A buffering agent adjusts the pH of a solution. The function of a buffering agent is to drive an acidic or basic solution to a certain pH state and prevent a change in this pH. Buffering agents have variable properties-some are more soluble than others; some are acidic while others are basic (Table 5) (Atkins and Loretta, 2005; Harris, 2003).

Temperature requirements: Temperature is a very important variable in the formation of a stable lipid emulsions. Whereas, an elevated temperature in the 40-70°C range might be necessary to form a stable lipid emulsions, most emulsions cannot withstand these temperatures for more than a couple of hours. Issues to consider in optimizing the temperature and time include: chemical instability of the oils and emulsifiers, the stability of the drug substance and evidence of discolouration or breaking/creaming of the emulsion. The process should be designed to raise the

Table 4: Example of preservatives

Preservatives	References
Benzalkonium chloride, chlorocresol, parabens	Tamilvanan (2004)
Sodium nitrate, sorbic acid, potassium sorbate, potassium nitrate, calcium tartrate	Khairi (2007)

Table 5: Example of buffering agents

Buffering agents	References
Phosphate-buffered saline (PBS, pH 7.4)	Choi *et al.* (2004)
Phosphate buffer	Ivancev *et al.* (1989)
Acetate buffer	Sakai *et al.* (2005)
Borate buffer	Sakai *et al.* (2005)

temperature, mix the ingredients, reduce the globule size, adjust the pH and final volume and cool the emulsion to room temperature, all within a few hours (Floyd, 1999).

Homogenization and globule size reduction: Once the coarse emulsion is formed, it is necessary to reduce the globule size even further by homogenization. Globule sizes of less than 100-200 nm are required. A small globule size also promotes good physical stability because Brownian movement prevents creaming (Davis, 1974). The required globule size can be achieved by using various high-pressure homogenizers or microfluidizers. Their utility on either a laboratory or industrial scale must be evaluated because equipment changes during scale-up could affect the physical and chemical stability of the emulsion and also its pharmacological efficacy (Floyd, 1999).

Equipment considerations: Typically, the physical stability of the lipid emulsion increases in the order of the following mixing methods: standard vortexing, high-shear blade mixing, homogenization, microfluidization (Washington *et al.*, 1989; Washington and Davis, 1988). The processing is based on a sub-merged jet principle in which two fluidized streams interact at ultrahigh velocities in precisely defined microchannels within an interaction chamber. Process pressure can range from 500 to 20,000 psi and the process stream is accelerated to velocities of up to 1500 ft (Jonkman-DE Vries *et al.*, 1996). A combination of shear, turbulence and cavitation forces results in the energy-efficient production of consistently fine droplets with a narrow size distribution, approximately 40-200 nm. Comparison of the microfluidizer with the other methods has suggested that greater lipid emulsion stability is obtained by the microfluidizer's superior ability to decrease the mean globule size and provide a narrower size distribution (Hanna *et al.*, 1992). Centrifugation method can enhance the demulsification of oil-in-water (O/W) emulsion (Abdurahman *et al.*, 2009).

FACTOR AFFECTING STABILITY OF LIPID EMULSION

The emulsifying properties of surface-active agents are of great importance in the formulation of emulsions for pharmaceutical, nutritional and cosmetic applications (Jumaa *et al.*, 1999). The physicochemical properties of the emulsifier molecules at the interface of oil droplets have been shown to have an important impact on the stability and physical properties of a number of lipid emulsions where partial coalescence occurs. Emulsifiers that form thicker and more viscoelastic films at the oil-water interface are more resistant to penetration by fat crystals and so provide greater stability to partial coalescence (Boode *et al.*, 1991, 1993; Dickinson and McClements, 1995; Van Boekel and Walstra, 1981). The formulations with only Tween 80 as an emulsifier showed a noticeable change in the particle size during autoclaving as well as a remarkable erythrocyte membrane damage (Jumaa *et al.*, 1998).

The pH change is expected to influence the interfacial properties of lipid emulsion droplets stabilized by the surfactants and, thus to affect the droplet size and the emulsion stability. Whereas, the physical and chemical stability of emulsions is pH-dependent, buffering agents are not typically added because there is the potential for buffer catalysis of the hydrolysis of lipids. Alternatively, the pH is adjusted with a small quantity of sodium hydroxide. The optimum pH of the finished lipid emulsion is in the general range of 6-7 (Boberg and Hakansson, 1964). The benefits of this pH range are two fold. Initially, this pH range allows for the ionization of the phosphate groups at the surface of the lecithin film, leading to an optimum surface charge for the globules. Low pH (values lower than 5) should be avoided as the electrostatic repulsion between

emulsified oil globules is decreased, resulting in increased globule size and coalescence. Ultimately, the second benefit of this pH range is minimized lecithin hydrolysis. When terminal heat sterilization is employed, however, the pH should be adjusted to approximately 8.0 prior to sterilization. A slightly alkaline pH is preferred in this case because the pH of the emulsion falls on heating and also as a function of time during storage, as a result of glyceride and phosphatide hydrolysis, which liberates free fatty acids (Floyd, 1999). The important parameters affecting the Emulsion Liquid Membrane (ELM) extraction process including external phase concentration, treat ratio (emulsion/external phase), concentration of carrier and agitation speed (Othman *et al.*, 2011). Size of emulsion droplets changes remarkably with temperature and HLB of emulsifiers, the diameter of droplets is very small but less stable towards coalescence close to the Phase Inversion Temperature (PIT), relatively stable O/W type emulsions are obtained when the PITs of respective systems are about 20-65°C higher than the storage temperature, the optimum stability of an emulsion is relatively insensitive the change of the HLB values or PITs of emulsifiers but the instability of an emulsion is very sensitive to the PIT of the system. Since the change in the stability of an emulsion is sensitive to the temperature near the PIT, the selection of an emulsifier according to the PIT may be more accurate and reliable (Shinoda and Saito, 1969).

MARKETED PREPARATIONS OF LIPID EMULSION

Intralipid is a brand name for the first safe fat emulsion for human use, approved in 1962 in Europe and invented by Professor Arvid Wretlind, Sweden. The FDA initially would not approve the product due to prior experience with another fat emulsion. It was approved in the United States in 1972. It is used as a component of parenteral nutrition for patients who are unable to get nutrition via an oral diet. It is an emulsion of soy bean oil, egg phospholipids and glycerin. It is available in a 10, 20 and 30% concentration. The 30% concentration is not approved for direct intravenous infusion but should be mixed with amino acids and dextrose as part of a total nutrient admixture (Driver *et al.*, 1989; Foxall *et al.*, 2007; Litz *et al.*, 2006; Rosenblatt *et al.*, 2006).

Intralipid provides essential fatty acids, Linoleic Acid (LA), an omega-6 fatty acid, Alpha-linolenic Acid (ALA), an omega-3 fatty acid. Some preparations of the anaesthetic drugs propofol and etomidate (the vehicle for etomidate is propylene glycol) are supplied using Intralipid as a vehicle (Driver *et al.*, 1989; Foxall *et al.*, 2007; Litz *et al.*, 2006; Rosenblatt *et al.*, 2006).

Weinberg *et al.* (2003) have published data indicating Intralipid is effective in treating experimental models of severe cardiotoxicity secondary to intravenous overdose of local anaesthetic drugs such as bupivacaine (Picard and Meek, 2006; Weinberg *et al.*, 2003). Recent case reports have been published of the successful use of lipid emulsion in this way save patients who were unresponsive to the usual resuscitation methods. All patients recovered completely shortly after intravenous injections of lipid (Weinberg *et al.*, 2003).

Intralipid is also widely used in optical experiments to simulate the scattering properties of biological tissues (Driver *et al.*, 1989). Solutions of appropriate concentrations of intralipid can be prepared that closely mimic the response of human or animal tissue to light at wavelengths in the red and infrared ranges where tissue is highly scattering but has a rather low absorption coefficient (Table 6, 7) (Driver *et al.*, 1989; Foxall *et al.*, 2007; Litz *et al.*, 2006; Rosenblatt *et al.*, 2006).

Table 6: Marketed lipid emulsions

Trade Name	Drug	Indication	Manufacturer	Market
Diazemuls	Diazepam	Sedative	Pharmacia	Worldwide
Diprivan	Propofol	Anaesthetic	AstraZeneca	Worldwide
Limethason	Dexamethasone palmitate	Steroid	Mitsubishi Pharmaceutical	Japan
Liple	Alprostadil	Vasodilator, platelet inhibitor	Mitsubishi Pharmaceutical	Japan
Ropion	Flurbiprofen Axetil	Non-steroidal analgesic	Kaken Pharmaceuticals	Japan
Vitalipid	Vitamins A, D, E, K	Parenteral nutrition	Fresenius Kabi	Europe

Table 7: Marketed parenteral lipid emulsion for nutrition

Product	Producer
Abbolipid	Abbot
Intralipid	Pharmacia Upjohn
Lipofludin	B. Braun
Lipofundin MCT/LCT	B. Braun
Medialipide/Vasolipid	B. Braun
Medianut	B. Braun
Lipovenos	Fresenius
Ivelip/Salvilipid	Clintec/Baxter
Clinoleic	Clintec/Baxter
Intralipos	Green Gross
Kabimix	Pharmacia-Upjohn
Trive˙ 1000	Baxter SA

RECENT DEVELOPMENTS IN LIPID EMULSION

Lipid emulsion have been administered intravenously to humans for therapeutic purposes since the 17th century (Vinnars *et al*., 2004). Numerous adverse events resulting from lipid use led to the notion that the administration of fat by this route invariably causes severe complications, including fat embolism. The demonstration of a strong link between the presence of malnutrition and the development of post-operative mortality in the 1930s by Studley (1936), was a strong impetus for the exploration of better ways to deliver adequate fuel calories to these patients. After much trial and error (Schuberth, 1961), eventually succeeded in developing a nontoxic lipid emulsion prepared from Soybean Oil (SO) (Intralipid; Fresenius-Kabi, Bad Homburg, Germany) that was introduced in 1961 and 1970s (Edgren and Wretlind, 1963; Hallberg *et al*., 1966; Wretlind, 1972). By contrast, high-osmolar glucose solutions, based on Dudrick's concept of hyperalimentation, remained the sole intravenous nonprotein energy supply for patients in the United States, where lipid emulsions had as yet not been accepted (Dudrick, 2003). This changed when the glucose system was found to cause serious side effects, including hyperglycemia, liver steatosis and deficiencies of Fatty Acids (FAs) and fat-soluble vitamins, whereas lipid infusion was shown to prevent fatty infiltration of the liver and to minimize metabolic stress (Vinnars *et al*., 2004; Wretlind, 1981).

Recent advances indicate a great potential for w-3 FAs incorporated into membrane phospholipids to modulate cell response to various stimuli and to influence several intracellular metabolic processes. Furthermore, some of these FA directly influence the production and the action of important mediators, the eicosanoids. In practical terms, an increased intake of w-3 FAs may reduce inflammatory and thrombotic responses while protecting tissue microperfusion and immune defenses. Such properties may find interesting applications in several types of intensive care unit patients, provided that w-3 FA incorporation takes place promptly. We recently had the opportunity to study *in vitro* and *in vivo*, the metabolism of emulsions made of a mixture of MCT, soybean LCT

and fish oil triglycerides. Plasma elimination of such preparations appeared to be very fast and their infusion was not associated with a prolonged residence of emulsion particles. In addition, uptake of remnants enriched with w-3 FAs and liposoluble vitamins was fairly fast and occurred in several types of cells, leading to an efficient incorporation of w-3 FAs in cell membranes within a few hours. The understanding that remnant uptake plays a significant role in the delivery of components included in lipid emulsions opens new areas of investigation and is likely to find several conditions of applications for new types of preparations (Carpentier *et al*., 1997).

Choi *et al*. (2004) was studied cationic lipid emulsion is the most promising non-viral gene delivery system. Cationic emulsion was formulated and transfection efficiency was evaluated *in vitro* and *in vivo*. The result suggest that cationic emulsion could be a potential gene delivery system in clinical approaches because of enhanced *in vivo* gene transfer with low toxicity. Now lipid emulsion is used as a gene delivery system.

Wang *et al*. (2006) was studied lipid emulsions as Parenteral drug delivery systems for morphine and its ester prodrugs. Morphine and its prodrugs into lipid emulsions retarded their release. The combination of prodrug strategy and lipid emulsions useful for improving analgesic therapy with morphine.

Webb *et al*. (2008) was studied tolerability and safety of olive oil-based lipid emulsion in critically ill neonates The OO-based emulsion (ChnOleic) was well tolerated in critically ill neonates. Soya lipid emulsion contain large amount of PUFA. Exposure to large amounts of PUFA is associated with an increased risk of membrane peroxidation.

Wei *et al*. (2010) was studied impact of lipid emulsion containing fish oil on outcomes of surgical patients. The administration of lipid emulsion containing fish oil to patients undergoing elective major operations improves outcomes. The infectious complications are significantly fewer and length of hospitalization significantly shortened for patients treated with lipid emulsion containing fish oil.

Engels and Davidow (2010) was concluded intravenous fat emulsion to reverse haemodynamic instability from intentional amitriptyline overdose.

Liu *et al*. (2011) was studied nano-sized lipid emulsions were also used as carriers for apomorphine and its prodrugs. Diester prodrugs exhibited superior skin permeation compared to the parent drug when formulated into the emulsions. DAA and DIA fluxes from lipid emulsions were 3-fold higher than that of apomorphine HCl.

Kandadi *et al*. (2011) was concluded Brain specific delivery of pegylated indivir submicron lipid emulsions pegylated SLEs improved brain specific delivery of indinavir and will be useful in treating chronic HIV infection.

CHARACTERIZATION OF LIPID EMULSION

Measurement of droplet size: Particle size distribution is one of the most important characteristics of an lipid emulsion. For example, the stability of an lipid emulsion can be conveniently monitored by measuring the changes in the droplet size distribution. The mean droplet size of most of the lipid emulsions prepare is find to lie between 150-800 nm. Photon Correlation Spectroscopy (PCS) is the appropriate method for studying particle sizes below 1 μm. In the present study, the mean droplet size and size distribution is determine by means of a computerized laser light scattering apparatus. Each emulsion sample is dilute to the appropriate concentration with a filtered isotonic solution (2.5% w/v glycerol in water) before measurement at 25°C. Each lipid emulsion system in analyse twice (Davis and Galloway, 1986). Coalescence rates of water droplets have been studied in the presence of chemical demulsifier (Abdurahman and Yunus, 2009). Elaboration of the lipid emulsions are presented in Table 8.

Table 8: Elaboration of drugs in lipid emulsion

Drug	Class	Oil	Emulsifier	Route of administration	Result	Reference
Latanoprost	Antihypertensive	MCT	Polyvinyl alcohol	Ocular	Enhanced stability	Sakai *et al.* (2005)
Difluprednate	Steroidal	Castor oil, olive oil	Polysorbate 80	Ocular	Enhanced solubility	Yamaguchi *et al.* (2005)
Cyclosporine	Antibiotic	Castor oil, soya oil	Phospholipids, Tween 80	Ocular	Enhanced ophthalmic bioavailability	Tamilvanan (2004)
Azithromycin	Antibacterial	MCT	Poloxamer 188, Soybean lecithin	Ocular	Enhanced solubility, bioavailability and stability	Liu *et al.* (2009)
Amphotericin B	Antibacterial	Soybean oil	Egg yolk	Ocluar	It showed better tolerability	Cohen *et al.* (1996)
Flurbiprofen axetil	NSAID	Castor oil	Tween 80	Ocular	Low irritancy and improved anti-inflammation property	Shen *et al.* (2001)
Piroxicam		MCT	Poloxamer 188	Ocular	Improved stability	Klang *et al.* (1996)
Apomorphine	Antiparkinson	Mineral oil, myverol	Pluronic F68	TDDS	Enhanced permeability	Liu *et al.* (2011)
Insulin	Antidiabetic	Soybean oil	Tween 80	Nasal delivery	Enhanced insnhin absorption	Mitra *et al.* (2000)
Prostaglandin E 1	Autocoid	Soybean oil, Oleic acid	Egg yolk, Phosphatidylcholine	Intravenously	Enhanced rate of release and retentivity	Yamaguchi *et al.* (1995)
Lysophosphatidylcholine	-	Long chain Acylglycerols	-	Intravenously	Inhibitory effect of lysophosphatidylcholine on pancreatic lipase	Tsuzuki *et al.* (2004.)
Amphotericin B	Antibacterial	Soybean oil	Egg yolk	Intravenonsly	Enhanced tolerability	Sundar *et al.* (2000)
Physostigmine salicylate	Cholinesterase inhibitor	Soybean oil, Phospholipids, oleic acid	Poloxamer 188	Oral	Enhanced stability and bioavailability	Pathak *et al.* (1990
Dexamethasone palmitate	Anti-inflammatory	Soybean oil	Egg yolk	Intravenonsly	Provide better anti-inflammatory property	Seki *et al.* (2004)
Morphine	Analgesic	Squalene	Pluronic F68, cholesterol	Parenteral	Showed prolonged analgesic effect	Wang *et al.* (2006)
Indinavir	Anti-HIV agent	Soyabean oil, oleic acid	Egg phospha choline, cholesterol	Parenteral	Improved brain specific delivery	Kandadi *et al.* (2011)

Table 8: Continued

Drug	Class	Oil	Emulsifier	Route of administration	Result	Reference
Tetrazepam	Anti-anxiety	Castor oil, sesame oil, Soybean oil	Triethylenglycol-monobutylether	Parenteral	Enhanced solubility	Jumaa and Muller (2001)
Amphotericin B	Antibacterial	Soybean oil	Egg yolk	Intravenously	Improved safety and efficacy	Joly *et al.* (1996)
Trans-retinoic acid	Antioxidant	Soybean oil	Egg yolk phosphatide, cholesterol	Intravenously	Inhibition of liver metastasis	Chansri *et al.* (2006)
Nalbuphine	Analgesic	Egg phospholipid Brij 30, Brij 98, stearylamine	Squalene	Parenteral	Increased analgesic duration and potency	Wang *et al.* (2006)
Eicosapentaenoic and Docosahexaenoic acid	Dietary supplement	Triacylglycerol	Egg yolk lecithin	Intravenously	Increased liver fatty acid	Tashiro *et al.* (1998)
Indomethicin	NSAID	Coconut oil	Phosphatidylcholine	Oral	Improved oral absorption	Simovic *et al.* (2010)
Caproic acid	Antifibrinolytic	Soybean oil, sesame oil	Egg yolk phosphatides	Parenteral	Increased solubility	Sakaeda and Hirano (1998)
Docetaxel	Anticancer	Oleic acid, oleum neutral, capric triglyceride	Poloxamer 188	Intravenously	Enhanced solubility	Gao *et al.* (2008)
2 (Allylthio) Pyrazine	Antitubercular	Soybean oil, MCT	Soya lecithin	Parenteral	Enhanced stability and liver targeting	Jang *et al.* (2009)
Palmitoylrhizoxin	Antitumor	MCT, dioctanoyl-decanoyl-glycerol	Polyoxyethylene-(60)	Intravenously	Improved solubility	Kurihara *et al.* (1996)
Flurbiprofen	Anti-inflammatory	Soybean oil, coconut oil	Egg lecithin, stearylamine, deoxycholic acid	Topical	Increased rate of release and skin permeation	Fang *et al.* (2004)
Iodine	Radiological agent	Poppy seed oil	Soya lecithin	Intravenously	Showed site specific contrast media	Ivancev *et al.* (1989)
Lorazepam	Antianxiety	Soya oil Poloxamer 188	Soybean lecithin,	Intravenously	Enhanced physical and chemical stability	Su *et al.* (2011)
Vinorelbine	Antineoplastic	MCT	Egg yolk lecithin, Poloxamer 188	Parenteral	Increased efficacy, safety and decreased toxicity	Su *et al.* (2011)

Table 8: Continued

Drng	Class	Oil	Emulsifier	Route of administration	Result	Reference
Lipid emulsion	-	Soybean oil	Egg yolk phosphatide	Intravenously	Showed better bioavailability	Ueda *et al.* (2001)
Oleic acid	Dietary supplement	Olive oil	Egg yolk phosphatide	Intravenously	Improved tolerability	Pontes-Arruda(2009)
Intralipid emulsion	Dietary supplement	Triglycerides, fatty acids	Egg phosphatides, Na-oleate	Intravenously	Showed antimalerial activity	Deharo *et al.* (1995)
Olive oil	Dietary supplement	Olive oil	Egg phosphatidates, Sodium oleate	Parenteral	Increased tolerability and safety	Webb *et al.* (2008)
MCT and fish oil	Fatty acids	Soybean oil, fish oil	Egg yolk phospholipids	Intravenously	It provide TPN for recovery of ill patients	Mimi *et al.* (2005)
Triacylglycerol	Fatty acid	Soybean oil, coconut oil	Phosphatidylcholine, Phosphatidylethanolamine.	Intravenously	Increased tolerability and safety	Rubin *et al.* (2000)
Olive oil	Fatty acid	Soybean oil, olive oil	Egg yolk lecithin	Intravenously	Safe and efficacious use in inchronic intestinal failure	Thomas-Gibson *et al.* (2003)
Maltodextrin	-	Corn oil	Tween 80	Intravenously	Enhanced stability of maltodextrin	Klinkesorn *et al.* (2004.)
Lipid emulsion as antidote	-	20% intra lipid emulsion	Egg yolk phosphatide	Intravenously	Improved antidote property	Zapatero *et al.* (2011)
Lipid emulsion	-	Fatty acid	Egg yolk phosphatide	Intravenously	It provide TPN for recovery of ill patients	Sane *et al.* (1999)
Cationic lipid emulsious	-	Squalene oil	1,2-dioleoyl-sn-glycero-3-trimethylammonium-propane	Parenteral	Better stability	Yoo *et al.* (2004)
Cationic lipid emulsion	-	Squalene oil	1,2-dioleoyl-sn-glycero-3-trimethylammonium-propane	Parenteral	Provide stable and biocompatible non-viral gene carriers	Kwon *et al.*, 2008.
Fat emulsion as antidote	-	Soybean oil,	Egg Yolk Phospholipids	Intravenously	Showed better antidote property	Engels and Davidow (2010)
Cinnarazine	Antihistamicnics	MCT	Egg lecithin	Intravenously	Increased physical and chemical stability	Shi *et al.* (2009)

Zeta potential of lipid emulsion: The charge on lipid emulsion droplets (z potential) is measure by using a Zeta Sizer 3 (Malvern Instruments, Malvern, U.K). The electrolyte solution use for the dilution consist of double distille water with a conductivity of 50 mS cm^{-1} adjusted by NaCl (0.5 mM). 500 mL of each lipid emulsion formulation is dilute with 20 mL of the electrolyte solution. Phospholipid, poloxamer 188 and chitosan-poloxamer emulsions have 255, 210 and 124 mV potential-values, respectively (Jumaa *et al*., 1998, 1999).

Emulsion rheology: The stress viscometry measurements is use. A Paar Physica M300 controlled stress rheometer at 20°C with a double-gap (DG26.7) geometrical arrangement. Measurements are make immediately after a 5 min equilibration in the rheometer (Day *et al*., 2007; Issaka *et al*., 2010). The emulsions are three categories on the basis of both rheological properties and visual appearance: stable; mesostable and unstable.

Acid-base titration: The buffering capacity of the lipid emulsion with various co-emulsifiers is determine by acid-base titration. The lipid emulsion is titrate with increasing volumes of 10-8 mol HCl or NaOH and the pH is measure by the pH meter at every point (Hung *et al*., 2005).

Temperature stability: The influence of temperature on lipid emulsions stability is examine using two approaches: (i) emulsions (pH 5.5) are subject to thermal treatments and then their pH is adjuste (pH 2.9) (ii) the pH is adjust (pH 2.9) and then emulsions are subject to thermal lipid treatments. The thermal treatments involve placing lipid emulsions in glass test tubes, incubating them in a water bath set at a fixed temperature (30, 90°C) for 20 min and then cooling them to room temperature by placing the tubes in ice water (Tokle and Mcclements, 2011).

Optical characterisation of emulsion creaming: The emulsion stability to creaming is measured by the optical characterisation of the liquid emulsion dispersion using a light scattering optical analyser. The freshly prepared lipid emulsion sample (6 mL) is place in a transparent cylindrical glass measurement cell and completely scanned by a light source. The back scattering of light over the whole height of the sample is recorded every 40 mL along the sample tube. The optical scanning of the emulsion sample is carry out every minute over 1 h. A pattern of the light flux as a function of the sample height is obtained, giving a macroscopic fingerprint of the sample at a given time. The superimposed light scatting fingerprints characterise the stability or instability of the emulsion (Day *et al*., 2007).

Determination of total drug content: A High-performance Liquid Chromatography (HPLC) system consisting of a LC-10 AT vp solvent delivery system containing double reciprocating plunger pump (Shimadzu, Kyoto, Japan), a SPD-10A vp UV-visible variable wavelength detector with deuterium lamp (Shimadzu) and a 250×4.6 mm, 5~m, C-18 reverse phase analytical column (Lichrospher, Merck, Mumbai, India) is use to determine total drug content and entrapment efficiency of the formulations. The mobile phase consisted of 68 parts of phosphoric acid solution pH adjusted to 5.5 with triethylamine and 32 parts of acetonitrile. The flow rate was 1 mL min^{-1} and detection is perform (Kandadi *et al*., 2011).

The entrapment efficiency: It is determined by ultracentrifugation using a Hitachi ultracentrifuge and the sample is centrifuge at 50,000 rpm for 2 h at 10°C. The entrapment efficiency is calculate using the equation:

$$\text{Entrapment efficiency (\%)} = \frac{(W_{total} - W_{aqueous})}{W_{total}} \times 100$$

W_{total} is the amount of drug present initially in the formulation and $W_{aqueous}$ is the estimated amount from the aqueous phase of the formulation (Kandadi *et al*., 2011).

***In vitro* drug release studies of LE formulations:** The drug release is study by dialysis method using cellulose membrane (molecular weight cut off of 12,000-14,000), Himedia, Mumbai, India. Initially, the dialysis tubing is hydrated overnight in phosphate buffer pH 7.4 at room temperature. The optimized LEs (1 mL) are place in dialysis tubing, tied at both ends and then suspend in 100 mL of 30% ethanol phosphate buffer pH 7.4 mixture in 250 mL beakers as dialysis medium, which is stirre continuously on a magnetic stirrer. At different time intervals during dialysis 1 mL of samples is withdraw from the beaker and replace by equal volume of fresh medium for analyzing the drug content. The amount of drug in collecte samples is calculate by using the linear calibration curve plot with known concentrations of drug by measuring the absorbance on a UV-visible spectrophotometer. The release pattern of the drug from different formulations is calculate by plotting cumulative percentage drug release versus time (Kandadi *et al*., 2011).

CONCLUSIONS

The lipid emulsions are potential carrier for poorly water soluble drugs. The components which are used in lipid emulsions are oils, emulsifiers, buffering agents, antioxidants, chelating agents and preservatives. Oils and emulsifiers play important role in lipid emulsions. In the review, we have given some details regarding the emulsifying agents used for lipid emulsion, along with the physicochemical properties, advantages and disadvantages of lipid emulsion. The marketed products and recent advances are also included which give acknowledgement about the lipid emulsions.

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