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Preparation And Characterization Of Nano Emulsions Of Lipids Components In Total Parenteral Nutrition Of Neonates

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Abstract

Parenteral nutrition (PN) is how nutrients are delivered intravenously or directly into the veins in those with Intestinal Failure. The components within PN are also important, as overfeeding due to the volume of glucose and lipid components is also related to developing liver dysfunction. Lipid emulsions are oil in water emulsions containing one or more triacylglycerol oil, a phospholipid emulsifier, and glycerol. Presently, medium-chain triglycerides (derived from coconut oil), olive oil, Soybean oil, and fish oil are used in lipid emulsion formulas. Being thermodynamically stable mixtures of two incompatible liquids that function as a cosurfactant and a surfactant, and with a particle size less than a micron, nano emulsions represent efficient drug carriers.

Numerous drug delivery objectives can be accomplished with the use of nanobiotechnology. It is achieved using nanoparticles and nanodevices. The duration of a particle's circulatory residence is dictated by its size and capacity to bind to plasma, which considerably affects therapeutic efficacy. Nanoparticle technology has a plethora of therapeutic and diagnostic applications.

Keywords: Nano emulsions; Total parenteral nutrition; Lipids; Neonates.

- **Introduction**

Parenteral nutrition (PN) is how nutrients are delivered intravenously or directly into the veins in those with Intestinal Failure. Parenteral nutrition is indicated when it is impossible to attain nutrition through the oral or enteral route, enteral nutrition being the delivery of nutrients through a tube directly into the gut. For individuals with Intestinal Failure, PN is deployed in both acute and chronic episodes[1].

Indications of TPN in Neonates[2]:

1. Surgical:
    1) Major Gastro-intestinal tract surgery in newborns
    2) Gastrointestinal fistula
    3) Ischemic bowel
- Medical:
    1) Pre-term newborn
    2) Protracted infantile diarrhea
    3) Small bowel obstruction

4) Feeding tube malfunction
5) Malnutrition
6) Diverticulitis
7) Ileus.
8) Pancreatitis
9) Crohn's disease

- **Long-term consequences of PN**

Compared to healthy subjects, children who require long-term PN different body composition, are shorter, and have a larger fat mass [3]. Body composition measurements, which include information on fat mass, lean body mass, muscle mass function, and functional status [2,3], should be used to assess the success of PN support. Additionally, the long-term effects of PN therapy in children who require PN because of short bowel syndrome or low birth weight newborns include cholestasis infections, catheter-related bloodstream, metabolic syndrome, and IFALD [2,3,4]. The pathophysiology is multifaceted, and associations have been identified with amino acid imbalances, PN duration, and constant (non-cyclical) PN provision [5].

Furthermore, the composition of intravenous lipid emulsions (ILEs) is strongly linked to the development of cholestasis or IFALD. Although there is no evidence that different ILEs affect bilirubin or cholestasis levels during short-term PN use, multicomponent ILEs (including fish oil) have been shown to decrease cholestasis bilirubin levels during long-term PN use[6]. Additionally, composite ILEs outperform pure soybean ILEs in preventing cholestasis and IFALD[6], immune-modulatory properties, anti-inflammatory properties, and antioxidant content. No study, however, has assessed the pro-and anti-inflammatory effects of these various ILEs in severely ill children[7]. Pure soybean ILEs should not be used to treat PN that lasts more than a few days; instead, composite ILEs containing or not containing fish oil should be used[8].

In the short term, pure soybean oil ILEs can be investigated to determine whether they provide a more complete nutritional profile than composite ILEs. Thirteen studies examined children who required long-term PN and their long-term neurocognitive development [9]. The prevalence of normal neurocognitive development has been reported to range between 29 and 100%, with 80–90% of students in mainstream schools participating[5]. There was no evidence that precise timing (cyclic or continuous) or other PN-related characteristics, such as duration, had a long-term beneficial effect on neurocognitive development [8].

As a result, PN must satisfy each patient's nutritional demands while the long-term consequences of PN components, such as intravenous lipid emulsion, are assessed for their potential role in developing IFALD [9].

- **Formulation of TPN Parenteral nutrition**

Trace elements, vitamins, protein, electrolytes, and water are all found in solutions, complex formulations comprising dextrose and fat. These components are frequently tailored to each patient's chronic diseases, acid-base status, fluid-electrolyte balance, primary diagnosis, and specific parenteral nutrition goals. The amounts and composition of intravenous nutrition solutions may vary significantly depending on the patient's nutritional status and underlying medical or surgical condition[10]. The following is a list of components that can be used with TPN [9,10].

- **Proteins**

Nitrogen, the primary goal of parenteral nutrition, is to provide the malnourished patient with enough utilizable nitrogen to re-gain nitrogen balance, in which the supplied nitrogen supplied is roughly equal to the amount excreted (mainly as urea)[11].

The relative requirements of the different amino acids in the body are estimated to be as follows: Essential, in that humans cannot produce it. The eight necessary amino acids are present in variable quantities in all commercially accessible solutions. Non-essential amino acids are those that the body can produce synthesis routinely. These amino acids boost the quantity of nitrogen available from the solutions, and workers have yet to determine the best essential-to-non-essential amino acid ratio[11].

Semi-essential amino acids are those that, while the body is capable of producing them theoretically, may occasionally require supplementation in the TPN solution because of the disease state or the patient's age[8].When amino acids are oxidized for energy, they produce four kcal/g. In general, sufficient total or non-protein calories should be provided to maximize amino acid utilization for protein synthesis[12]. Parenteral amino acid products are classified into customized and standard amino acid formulations. Standard amino acid products are given to patients with normal organ function and dietary requirements[11,12].

Table (1) Supplying of amino acids in parenteral nutrition[11].

Amino acid dose	**Newborn with birth weight above 1500g**	**Newborn with birth weight under 1500g**
Output/Initial dose	2 g/kg of body weight/24h	2.5 g/kg of body weight/24h
Final dose	3.5 g/kg of body weight/24h	4.0 – 4.1 g/kg of body weight/24h

Table (2) Neonatal and Pediatric Amino Acid Products Source[12].

	Troph Amine 6% (McGraw)	**Aminosyn-PF 7% (Abbott)**
L- Amino acid content (g/100ml)	6	7
Nitrogen (g/100ml)	0.93	1.1
Essential Amino acids (mg/100ml)		
Isoleucine	490	534
Leucine	840	831
Lysine	490	475
Methionine	200	125
Phenylalanine	290	300
Threonine	250	360

Tryptophan	120	125
Valine	470	452
Non-essential Amino acids (mg/100ml)		
Alanine	320	490
Arginine	730	861
Histidine	290	220
Proline	410	570
Serine	230	347
Tyrosine	140	44
Glycine	220	270
Cysteine	< 14	-
Electrolytes (m Eq/100ml)		
Sodium	5	3.4
Potassium	-	-
Magnesium	-	-
Chloride	< 3	-
Acetate	56	33
Phosphorus (mM/L)	-	-
Osmolarity (mOsm/L)	525	586
Amount Supplied	500	250 & 500

Lipids

Fats are high-energy substrates. The supply of lipids in parenteral nutrition should cover from 25 to 40% of the extra-cerebral energy needs [13]. Newborns born prematurely, especially those with diminished birth weight less than 1500 g, are susceptible to a deficiency in nutrition because they have less fat than newborns [14]. In premature babies, the two or 3-day limitation of fat supply causes the emergence of a clinical condition known as a deficiency of essential fatty acids. To avoid this disorder, premature babies should receive fat from the first day of life [15]. The total fat supply should be about 3-4 g/kg of body weight per day (Tab. 3).

Phospholipid concentrations in higher preparations may increase the risk of hyperlipidemia[14, 15]. Three varieties of lipid emulsions are recognized in the market for children[16]. The first is entirely composed of soybean oil. It is characterized by an abundance of polyunsaturated omega-6 fatty acids and a deficiency of omega-3 fatty acids. This composition may raise the risk of pro-inflammatory cytokine overproduction and oxidative stress[17]. Soybean oil has been shown to inhibit immune cells, and the phytosterols in it have been shown to contribute to the development of cholestasis, one of the problems of parenteral nutrition18. In the second form of lipid emulsion, soybean oil and olive oil are used. Olive oil contains double the amount of tocopherol and significantly fewer polyunsaturated fatty acids than soybean oil[18].

The third emulsion is a blend of soybean and MCT oils (medium-chain triglyceride fatty acids derived from coconut oil). MCTs are more easily extracted from plasma because of their increased solubility and more effective intravascular metabolism[19]. MCTs are more easily extracted from plasma because of their increased solubility and more effective intravascular metabolism[18, 19]

Pediatric patients receiving fat emulsions should regularly monitor their serum triglyceride levels[14].Additionally, it is recommended to avoid excessive lipid administration in infants diagnosed with acute respiratory failure, as emulsion administration may impair the child's respiratory efficiency[20]. However, lipids should not be avoided entirely in parenteral nutrition because abruptly discontinuing their administration can result in a deficiency of free fatty acids[18]. The use of lipid formulations containing omega-3 fatty acids from fish oil has been shown to considerably lower the incidence of cholestasis and hepatic problems in children who require parenteral nutrition[21].

Table (3) Supplying of lipids in parenteral nutrition[18].

Lipids dose	**Newborn with birth weight above 1500g**	**Newborn with birth weight under 1500g**
Output/Initial dose	0.5 g/kg of body weight/24h	
Final dose	3 -4 g/kg of body weight/24h	2.5 – 3 g/kg of body weight/24h

The addition of lipids to parenteral solutions provides essential fatty acids and a dense source of calories, being ~ 9 kcal/g. To prevent the development of essential fatty acid deficiency, a relatively small dose of parenteral lipids (0.5 g/kg/day) can be given. Parenteral lipid comprises triglycerides, free fatty acids, glycerol, and phospholipids (Fresenius Kabi®). Parenteral lipid enters the bloodstream as lipid droplets <5µm in size, like chylomicrons and classified as chylomicron-like particles. However, parenteral lipid bypasses the major physiological processes commonly involved with dietary lipid digestion[22]. Normal enteral lipid digestion begins with the emulsification of fat globules using bile salts (Figure **1**). These are then further broken down into free fatty acids and monoglycerides thanks to pancreatic lipase. These are then packaged into micelles allowing transport of monoglycerides and free fatty acids across the unstirred layer, and then they diffuse to the epithelial layer of the intestines[23]. Intracellular addition of Apo-proteins (ApoB-48, Apo E, and Apo C-11) converts the micelle to chylomicrons, then transported to the lymphatic system. From here, the chylomicron is transported to the capillaries, where Lipoprotein Lipase (LPL) works to remove the triglycerides and free fatty acids from the chylomicron. Once the chylomicron is depleted of the triglycerides and free fatty acids, the remnant particle is transported to the liver to be converted into very-low-density lipoprotein (VLDL)[24].

In contrast, the primary site of digestion of parenteral lipid bypasses the gastro-intestinal tract directly to the circulation and liver. As mentioned above, lipids from parenteral solutions are labeled chylomicron-like

particles. However, unlike intestinal-derived chylomicrons, these particles undergo lipolysis prior to uptake into the hepatocytes[23, 24]. The suggested pathway for absorption is that chylomicron-like particles bind transiently to the vascular endothelium, where lipoprotein lipase removes some of the triglycerides. This process occurs several times before remnant receptors in the liver accept the triglyceride low lipid droplet. Then the hepatocytes endocytose the lipid droplet and then degrades it[25].

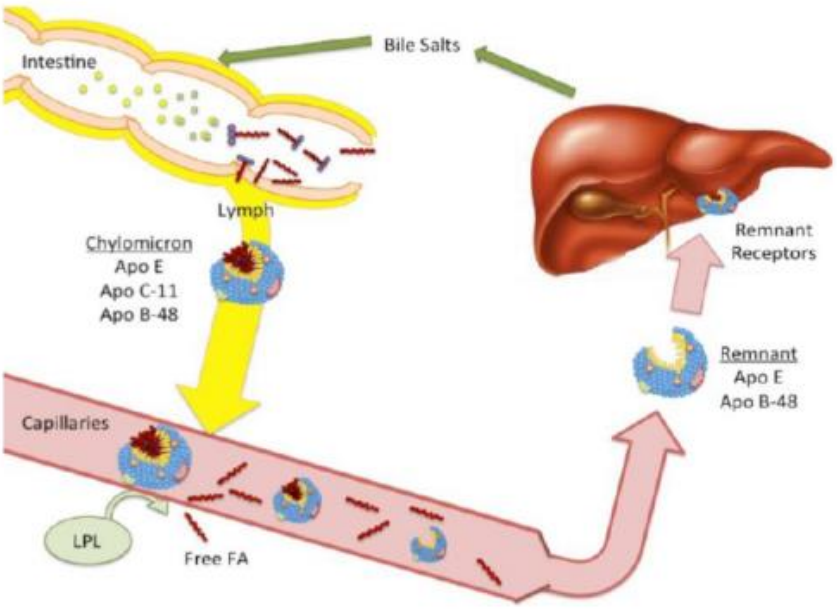

Figure 1 Enteral lipid absorption[24]

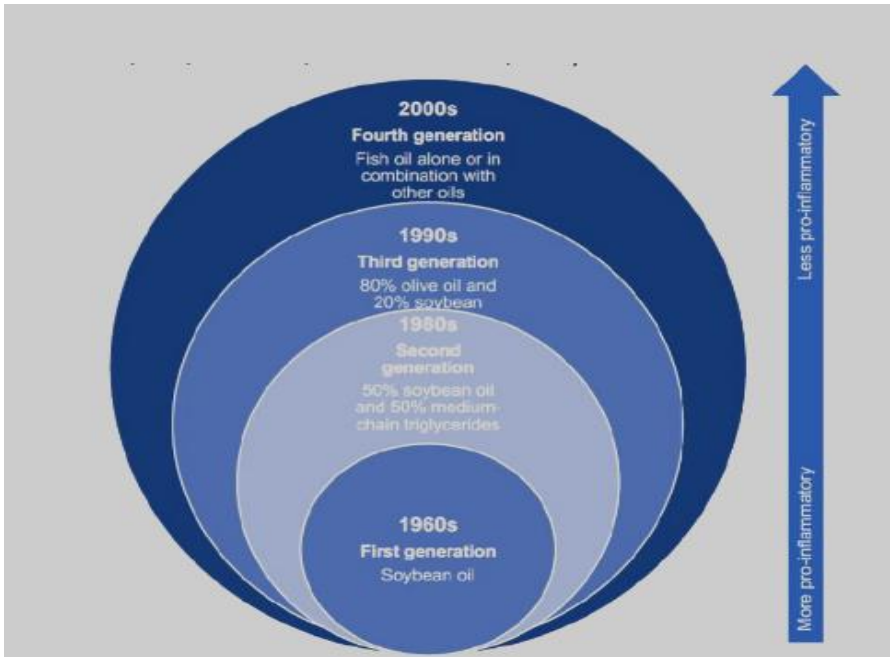

Figure 2: Evolution of intravenous lipid emulsions[24].

Carbohydrates in parenteral nutrition

Carbohydrates are the primary energy source and should account for 40%–60% of a child's energy requirements[26]. Carbohydrate administration supplies energy, inhibits gluconeogenesis, and ensures adequate amino acid consumption for protein synthesis and fat metabolism regulation[26]. Glucose is the most common carbohydrate utilized in parenteral feeding. It provides energy to all human tissues, particularly the brain, spinal cord, kidneys, and erythrocytes[15]. It should give between 60% and 75% of non-protein calories in parenteral nutrition. Parental nutrition should aim to maintain normoglycemia27. The length of TPN therapy was revealed to be a significant risk factor and an independent predictor of developing hyperglycemia in TPN patients[26]. When patients on TPN for less than two weeks were compared to those on TPN for more than two weeks, the percentage of patients with hyperglycemia more than quadrupled (23.5 percent–56 percent). Additionally, each additional day of TPN duration was expected to increase the risk of hyperglycemia by 10%[27].

Another important risk factor for hyperglycemia has been identified as a surgical etiology for TPN therapy. Mona Al Chaer et al. 2020 discovered that surgical TPN patients have a threefold increased risk of developing hyperglycemia than those receiving TPN for medical reasons[28].

Obesity and the risk of developing hyperglycemia are related because obese people have a higher percentage of visceral fat in their bodies, associated with a variety of health problems, including insulin resistance and metabolic syndrome. Furthermore, obese patients experience physiological alterations that can impede their capacity to adapt to intense disease-induced stress[13].

Corticosteroids are known to cause hyperglycemia as a side effect. those who used steroids had a six-fold increased risk of developing hyperglycemia compared to those who did not use steroids[28]. Pleva et al. had previously identified a similar association between hyperglycemia and steroid use in TPN patients[29].

Table (4) Supplying Carbohydrates in parenteral nutrition[13].

Glucose dose	Output/Initial dose	Output/Initial dose
Newborn	8 – 10 g/kg of body weight/24h	17 g/kg of body weight/24h

Vitamins

Vitamin supplementation is generally required for patients receiving long-term TPN therapy. Vitamin preparations commercially available, as well as recommended daily requirements that appear to vary according to the most recent recommendations:[30]

· K Phytomenadione

· E Tocopherol acetate

· D Calciferol

· C Ascorbic acid

· B6 Pyridoxine

· B2 Riboflavin

· B12 Cyanocobalamin

· B1 Thiamine

· B Pantothenic acid

· B Nicotinamide

· B Folic acid

· B Biotin

· A Retinol

Vitamins are a critical component of a patient's daily parenteral nutrition plan due to their impact on normal metabolic and cellular function. The Nutrition Advisory Group of the American Medical Association has established recommendations for the 13 essential vitamins (four fat-soluble and nine water-soluble) in adult and pediatric patients.31 The thirteen vitamins required for adult and pediatric patients are listed in Table 5[32]. Individual parenteral vitamins are indicated when multivitamin products are unavailable. Vitamins A, D, E, K B12 (cyanocobalamin), B1 (thiamine), B6 (pyridoxine), B2 (riboflavin), B9 (folic acid), B3 (niacin), and C are all available as parenteral preparations containing single-entity parenteral preparations (ascorbic acid). Oral multiple vitamins may also be used to treat vitamin deficiency if the patient can absorb the recommended doses orally30.

Table (5) Supplying of Vitamins in parenteral nutrition[32].

Vitamins	A	D	E	K
Newborn	500-1500 IU /kg of body weight/24h	160IU /kg of body weight/24h	2.8 – 3.5 mg/kg of body weight/24h	Newborn with birth weight under 1500g 0.3mg/kg of body weight/6 weeks
				Newborn with birth weight above 1500g 0.5mg/kg of body weight/6 weeks

Mineral ingredients in parenteral nutrition

Minerals are necessary for the human body to function correctly. They perform a variety of critical roles, primarily in metabolic processes. When their homeostasis is disturbed, alterations and aberrant cell function result. Due to the importance of specific mineral components, they are classified as microelements and macro elements [33, 34, 35].

Macro Elements

The final trimester of pregnancy is characterized by rapid growth and mineralization of the fetal skeleton. The fetus acquires minerals at a rate of approximately 90-150 mg/kg/day of calcium (Ca) and 50-85 mg/kg/day of phosphorus (P) during this period (P). This is associated with an increase in the child's weight35.Calcium requirements are as follows: 400-600 mg/day for newborns, about 800 mg/day for

children, 1200 mg/day for adolescents, and approximately 800 mg/day for adults over 25. It is approximately 1200 mg/day in pregnant and lactating women (Tab.5). The fetal development period and an adequate dose of calcium and phosphorus are used as a reference point in parenteral nutrition34. The more amino acids supplied and thus the projected increase in body mass, the more calcium and phosphates should be supplied. Calcium supplementation should begin at one year to prevent early hypocalcemia, while phosphate supplementation should begin from 2-3 days of age. Calcium and phosphate are absorbed most effectively when their ratio in meals is - Ca:P = 1.3-1.7:1. Lactose and a few amino acids are present. Vitamins A, D, E, and K 500-1500 IU/kg of body weight/24h 160 IU/kg of body weight/24h 2,8-3,5 mg/kg of body weight/24h for newborns under 1500g – 0,3 mg/kg of body weight/every six weeks for newborns over 1500g – 0,5 mg/kg of body weight/every six weeks improve calcium absorption, whereas excess fats, phytates, and oxalates inhibit this process[30. 35] .

Magnesium (Mg) is the second most prevalent cation found within cells. It serves a variety of critical functions in the human organism. Intracellular magnesium can bind to the nucleus, ribosomes, cell membranes, and macromolecules found in the cell's cytoplasm due to its physicochemical features. Magnesium activates around 300 enzymes and participates in a variety of metabolic functions, including glycolysis, -oxidation, the Krebs cycle, and the transfer of ions across cell membranes, all of which are critical for a developing organism, such as a newborn baby[34. 35]. Due to the critical role magnesium plays in controlling mitochondrial function and ATP production, symptoms of magnesium insufficiency in infants might include muscle and lung dysfunction and problems in the cardiovascular and gastro-intestinal systems. The magnesium need for babies is 40-60 mg/day, while the requirement for children is 80-170 mg/day (Tab.5)[35].

Potassium (K), sodium (Na), and chlorine (Cl) are electrolytes that help the body maintain its fluids, electrolytes, and acid-base balance. They play a critical role in parenteral nutrition. They should be used following daily requirements and serum concentrations at the time of administration. Their content in the blood serum of premature infants should be monitored daily for the first three to seven days of life or more frequently. Sodium is the predominant electrolyte present in extracellular fluids, whereas potassium is mainly found within cells. These elements are involved in the interchange of substances across the cell membrane and the transmission of electrical stimuli through nerve fibers [15, 34, 36].

The potassium cation is the predominant cation in the intracellular space because it is a sodium antagonist. Its antagonistic function is based on decreasing the volume of extracellular fluids, which aids in controlling the body's water balance. Potassium, which is also a calcium antagonist, regulates the potential of cell membranes and the excitability of nerve and muscle cells. The dietary potassium need increases with age and is constant: 400-1200 mg/day for newborns, 550-2500 mg/day for children under 7, and 1000-4500 mg/day for older children (Tab.5)[34. 35].

The most abundant extracellular cation is sodium. It is in charge of controlling the acid-base balance and maintaining the osmotic pressure. Sodium is involved in regulating cell membrane permeability and is required to maintain proper neuromuscular excitability. It is primarily eliminated through the urine and the skin. Daily requirements for this element vary by age and range from 120-750 mg for babies to 320-1350 mg for children under seven and 600-2700 mg for older children (Tab.5)[35. 36].

Chlorine is an extracellular anion found primarily on extracellular fluids (including blood plasma), the stomach as a component of hydrochloric acid, and saliva. Additionally, it is present in the skin, subcutaneous tissue, and bone[33. 34]. Chlorine, like sodium and potassium, regulates the electrolyte and acid-base balance in the body, activates salivary digestive enzymes (including salivary amylase), and contributes to the stomach's generation of hydrochloric acid[35].

Microelements

The term "trace elements" refers to substances that combined make up less than 0.01 percent of the total body weight. Iron, iodine, chromium, zinc, copper, selenium, molybdenum, manganese, and fluorine are among them. These are critical components that participate in a variety of metabolic processes. Trace elements should always be added to nutrition mixes daily in children who are fed parenterally. When deficits in certain elements are detected, such as those caused by severe diarrhea or gastro-intestinal fistulas, the nutrient combination is enhanced with increased amounts of those elements in the form of different preparations[33. 34]. Chromium (Cr) is a critical element for carbohydrate and lipid metabolism. This molecule is a glucose tolerance factor (GFT-Glucose Tolerance Factor) component required for normal glucose metabolism and improves insulin action. With age, its daily dietary requirement increases from 10-60 mg in babies to 50-200 mg in adults (Tab.6).

Copper (Cu) is a critical component of many enzymes. It is a component of superoxide dismutase, an antioxidant enzyme that guards against free radical damage to cell membranes. Copper is required for the creation of red blood cells, it is involved in the synthesis of connective tissue, and it is a critical component in prostaglandin synthesis, which affects the heart's function and blood pressure. Copper deficiency can decrease energy generation, alter glucose and cholesterol metabolism, increase oxidative damage, and increase iron (Fe) accumulation in the tissues. The dietary need increases with age and varies between 0.4-0.7 mg/day for babies and 1.5-3 mg/day for adults (Tab. 6) [30. 33.34.35].

Iodine (I) is a critical element that contributes to the thyroid hormones thyroxine and triiodothyronine. Both hormones are important for the body's metabolism to function correctly. Its nutritional requirements vary according to age and the degree of metabolic processes. It is around 40-50 mg per day in newborns and approximately 150 mg in adults (Tab. 5)[35, 36].

Manganese (Mn) is a component of numerous enzymes, including superoxide dismutase, and is required to activate some hydrolases, kinases, and transferases. The dietary need for this element varies with age and health status. In babies, it ranges between 0.3 and 1.0 mg/day (Tab. 5) [34, 35, 37].

Molybdenum (Mo) enhances the function of enzymes and enzymes involved in DNA metabolism. The daily requirement increases with age, ranging from 15-40 mg in babies to 75-250 mg in adults (Tab. 5)[34, 35].

Selenium (Se) is a component of several enzymes, including glutathione peroxidase, an antioxidant that shields cell membranes from the oxidative damage caused by oxygen free radicals. Selenium is required for the effective synthesis, activation, and decompression of thyroid hormones. The dietary requirement for this element varies between newborns and adults, ranging from 10-15 mg/day to 40-70 mg/day (Tab. 5) [38].

Zinc (Zn) affects all fundamental life processes, including protein, carbohydrate, and fat metabolism. It is involved in energy metabolism, and nucleic acid metabolism is a component of numerous enzymes required for bone mineralization, wound healing, and immune system function. Premature infants require more of this mineral than those born normally[39, 40]. Zinc requirements are as follows: 5-10 mg/day for neonates, 12-15 mg/day for adults. Increased to 19 mg/day in women during nursing (Tab. 5)[38].

Premature infants are at a greater risk of deficit of the microelements above because of the shorter gestation duration and the increased demand for these chemicals, particularly during the latter stages of pregnancy. When long-term parenteral feeding is used, trace elements should be provided, and the child's body regularly monitored [38, 39] .

Table (6) Supplying of amino acids in parenteral nutrition[35, 39].

Macro elements	**Ca^{+2}**	**Mg^{+2}**	**Na^{+}**	**K+**

Dose	400-600 mg/day		40-60 mg/day	120-750 mg/day		400-1200 mg/day	
Microelements	**Cr^{+2}**	**Cu^{+2}**	**I^{+}**	**Mn^{2+}**	**Mo^{2+}**	**Se^{+2}**	**Zn^{+2}**
Dose	10 mg/day	0.4-0.7 mg/day	40-50 mg/day	0.3-1.0 mg/day	15-40 mg/day	10-15 mg/day	5-10 mg/day

Nanobiotechnology provides the following solutions to the problems of drug delivery:

• Particle size is lowered to the nanoscale range to improve the surface area, which increases by dissolving rate, e.g., Nano edge technology (Baxter)[41].

• Enhancing the drug's solubility[41].

•By utilizing noninvasive modes of delivery, the requirement for injection-based administration of medications is eliminated[42].

• Developing new nanoparticle formulations to extend the shelf life and stability of existing nanoparticles[41,42].

• The development of nanoparticle formulations for the enhanced absorption of insoluble chemicals and macromolecules offers increased bioavailability and release rates, thereby lowering the dose necessary and boosting safety through fewer adverse effects[40].

• Manufacturing nanoparticle formulations with precisely controlled particle size, shape, and surface qualities would be more effective and cost-effective than current approaches[41].

• Nanoparticle formulations that give sustained-release profiles for up to 24 hours can help patients adhere to their medication regimens[42].

• Nano systems enable the coupling of medications and newly discovered disease-specific targets[41].

Nano emulsion

Nano emulsions are ultra-fine emulsions with a diameter of less than a micron that act as delivery systems to improve the delivery of medicinal medicines. They are thermodynamically stable mixtures of two immiscible liquids that contain an adsorbent and a cosurfactant[43].

Nano emulsions can be classified as emulsions with droplet sizes ranging from 50–1000 nm or oil-in-water (o/w) emulsions[44]. The typical droplet size ranges between 100 and 500 nm, and the terms mini emulsion and Sub-Micron Emulsion (SME) are interchangeable. It is classified as water-in-oil (W/O) or an oil-in-water (O/W) mixture, or as a bi-continuous mixture (Fig. 3)[45,46]. The composition of the emulsions can be changed to switch between these three types. Suspensions of nanoparticles are not synonymous with nanoparticles.

A nanosuspension overcomes a drug's low solubility, bioavailability, and pharmacokinetics, thereby improving the drug's safety and efficacy. O/W nano emulsions are frequently employed as starting points for forming different types of structured nanoparticle dispersions (Fig. 4)[47].

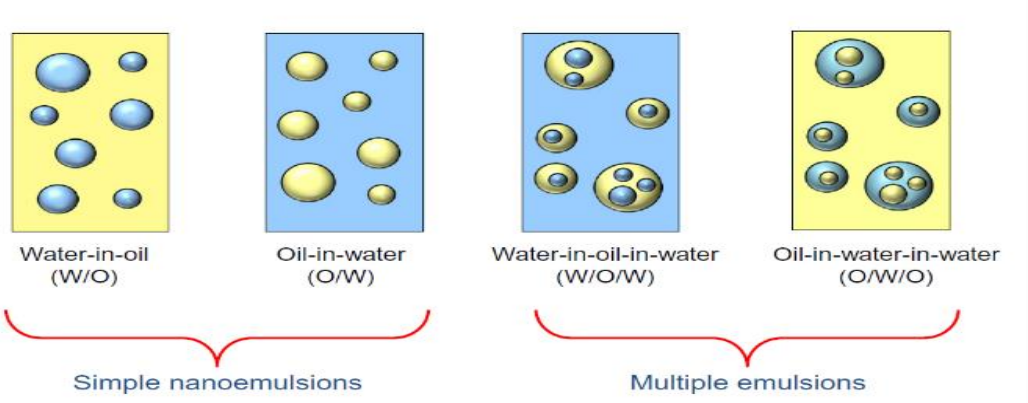

Figure (3): Nano emulsions may have several different structures depending on the relative location of the oil and water phases[46].

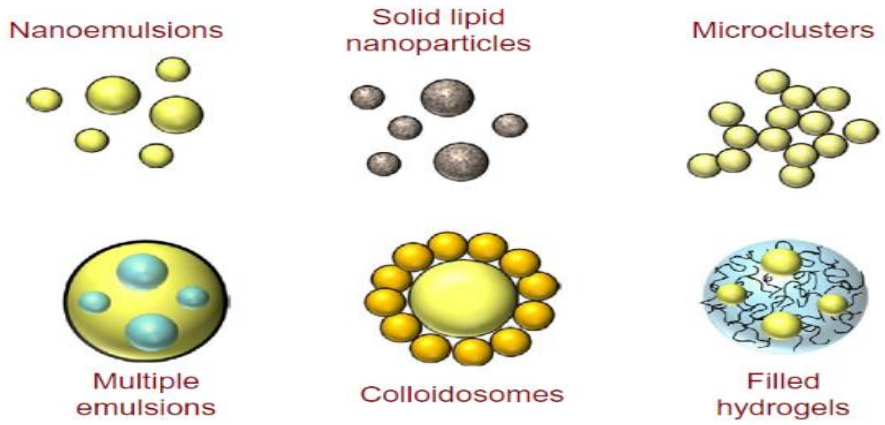

Figure (4): Lipid nano-droplets can be used to create a variety of different structures, including filled hydrogel particles, colloidosomes, multiple emulsions, micro lusters, solid lipid nanoparticles, and nanoemulsions[47].

Typically, an O/W nano emulsions is formed by the homogenization of a high-melting lipid with a water phase comprising a hydrophilic surfactant at a temperature greater than the melting point of the lipid[46]. Following that, the system is cooled below the lipid phase's melting point, leading to the crystallization of the oil droplets. The solidified lipid phase in SLNs and NLCs retards molecular diffusion processes, impeding chemical degradation or regulating the release of encapsulated compounds[47]. Additionally, the physical state of the lipid droplets influences their refractive index and density, thereby affecting the nano emulsions' optical properties and creaming stability[46].

Additional structures, such as multiple emulsions of the type oil-in-water-in-oil (O/W/O) or water-in-oil-in-water (W/O/W), are created by nano emulsions (Fig.3)[46].

Additionally, nano emulsions can be used to create a variety of different structures, including filled hydrogels (Fig. 4). In this situation, an O/W nano emulsion is combined with a biopolymer solution able to form a hydrogel. Then, the filled hydrogels are generated in two steps: particle formation and particle gelation [47]. After creating a particle with tiny lipid droplets trapped within a larger biopolymer-rich water droplet, the system parameters are adjusted to cross-link the biopolymers in the water droplet[48]. It is possible to encapsulate, protect, and release bioactive molecules by adjusting filled hydrogels' size, internal content, or structure[46].

Additionally, nano emulsions can be employed to form various structures, including micro clusters or colloidosomes (Fig. 4). A micro cluster is a collection of smaller particles held together by attraction forces. In contrast, a colloidosome is made up of a large core particle with smaller particles adsorbed on its surface. These structures can be created using nano emulsions to alter stability, optical, or the rheological properties of materials or for controlled release applications.

Various techniques for fabricating nano emulsions have been found, loosely classified as low- and high-intensity techniques. Low-intensity techniques depend on the random formation of tiny droplets in specific surfactant-oil-water mixtures when the system's composition or external factors (such as temperature) are changed[50]. Low-energy approaches such as phase inversion temperature, spontaneous emulsification, and emulsion inversion point are the most frequently used. High-intensity technologies are the frequently used approach in manufacturing nano emulsions in industrial applications.

These techniques separate and mix the water, oil, and phases by producing high-shear, turbulent, and cavitation flow profiles. Devices such as high-pressure valve homogenization, micro fluidization, and sonication are commonly used to create nanoemulsions[46]. Membrane emulsification is another novel technique for producing nano emulsions. While it is frequently referred to as a high-energy emulsification method, it is a mechanical process that consumes low energy. The method used to create a nano emulsions is determined by the components that need to be homogenized. Scientists and technicians must be familiar with the various manufacturing processes available to choose the most suitable.

Due to the fact that nano emulsions typically contain various sizes of droplets, particle size distribution, defines their dimensions (Fig. 6)[46]. Particle dimensions are commonly reported in terms of polydispersity index and mean droplet diameter. The mean droplet diameter is expressed in various forms, the most common of which are as surface-, volume, or number-weighted values denoted by d S (or d32), V (or d43), and d N (or d10). Additional measurements, like the intensity-weighted (Z-average) diameter determined via dynamic light scattering, are used. When providing particle size statistics for nano emulsions, it is essential to specify the used mean diameter type, as their values can vary considerably based on the distribution width[46].

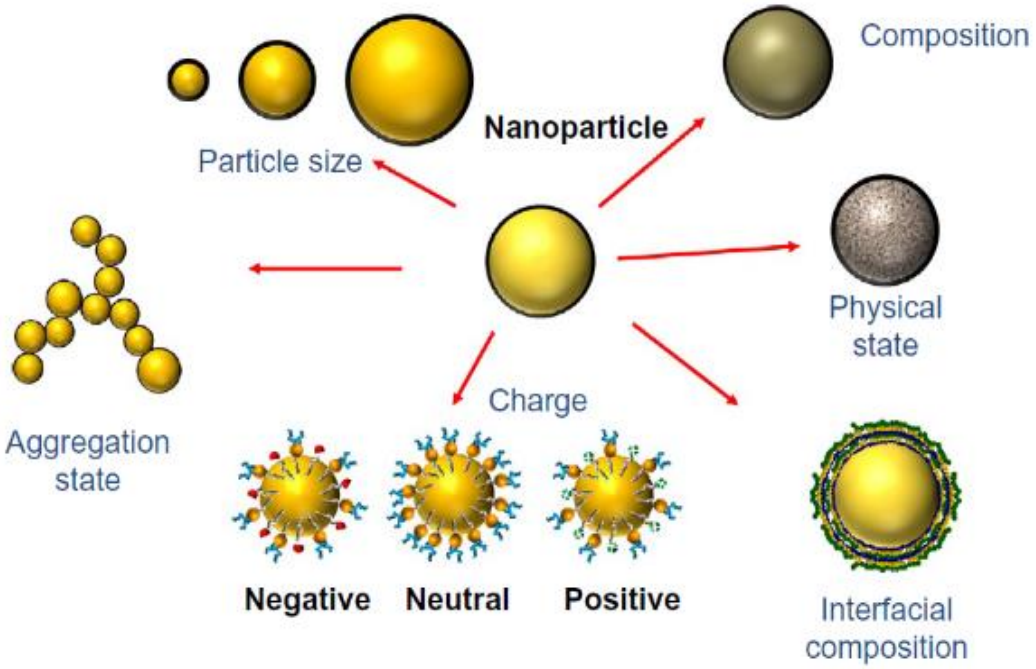

Figure (5): Nano emulsions can have a wide range of particle properties, including size, composition, and charge[46].

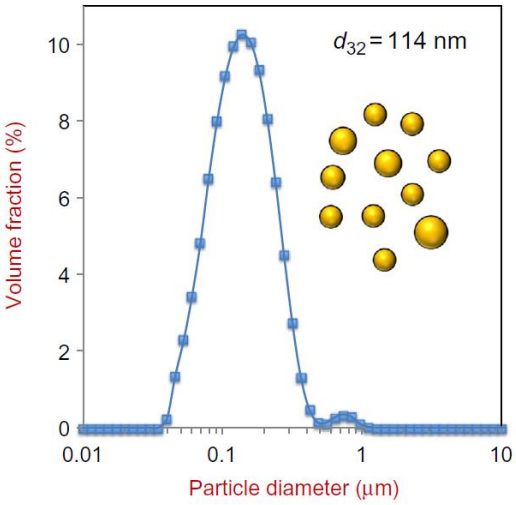

FIGURE (6): Particle size distribution of a nano emulsion generated utilizing Tween 80 as the surfactant and MCT as the oil phase in a low-energy approach. Static light scattering was used to do the measurement[46].

Nano emulsions and conventional emulsions differ in droplet size. Both systems are unstable thermodynamically. Moreover, nano emulsions have a mean droplet diameter of less than 200nm. On the other hand, conventional emulsions have a larger mean droplet diameter. This is a somewhat subjective criterion, as droplet diameters smaller than 200nm have no discernible effect on physical, chemical, or biological properties. Rather than that, as the droplet size decreases, the properties of the droplet typically change very gradually.

Nano emulsions, on the other hand, exhibit unique physicochemical properties in comparison to emulsions[50]:

(1) Nano emulsions may be optically transparent because of the weak light scattering caused by microscopic droplets.

(2) Due to the presence of weak gravitational forces and Brownian motion, nano emulsions are more resistant to gravitational separation.

(3) Nano emulsions may have a higher bioavailability than emulsions because of their rapid digestion.

(4) Because nano emulsions have a larger oil-water interfacial surface, they may exhibit greater chemical reactivity.

- **THE PARTICLE PROPERTIES OF NANOEMULSIONS**

The physicochemical characteristics and functional properties of a nano emulsion are significantly influenced by particle properties such as composition, size, charge, aggregation state, physical state, and interfacial composition (Fig.5). Due to the fact that nano emulsions typically contain a range of droplet sizes, their dimensions are determined by a particle size distribution (Fig.6). It is simpler to express particle dimensions in terms of mean droplet diameter and polydispersity index. The mean droplet diameter can be described in a variety of ways, the most common being through the use of number-, surface-, and volume-weighted

values, specifically dN (or d10), dS (or d32), and DV (or d43). Occasionally, other diameter measurements, such as the intensity-weighted (Z-average) diameter determined via dynamic light scattering, are used.
Emulsion droplet electric properties are primarily determined by the ionic composition of the surrounding solution and the nature of any surface-active chemicals attached to them[48]. The electric potential can range from extremely positive to significantly negative depending on the solution conditions and the emulsifier type. Oil droplets Electric properties in a nano emulsion are critical for their physical and chemical stability, besides their ability to form more complex structures and gastro-intestinal fate (Fig.4)[46]. The liquid cores of the lipid droplets may be solid (as in emulsions) (as in NLCs or SLNs) or liquid (as in nano emulsions). The droplet interior physical state is determined by the utilized oil phase properties like melting properties, crystallization, and the temperature history of the system.
By manipulating the lipid droplets' physical states, it is possible to optimize several encapsulated bioactive chemicals' stability and release properties. Additionally, the droplets' physical state may affect their density and refractive index, thereby altering the system's optical properties and creaming stability.
The emulsifier used in the nano emulsion preparation significantly affects the interfacial parameters like chemical reactivity, hydrophobicity, thickness, and charge[47].

Advantages of Nano emulsion could be summarized into:

1) Due to their increased surface area and free energy, they have an efficient transportation system[46].

2) Versatile formulation capability, including creams, sprays, foams, and liquids[48].

3) They are irritant-free and non-toxic, making them suitable for use on the skin[46].

4) If the formulation contains biocompatible surfactants, they can be taken orally[51].

5) They do not cause harm to healthy human or animal cells, making them suitable for medicinal or research purposes in humans and animals[50].

6) They promote the uptake of oil-soluble nutrients, which allows for the testing of the toxicity of oil-soluble medications and promotes the growth of cultured cells[51].

It is suitable for liposomes and vesicles, and lamellar liquid crystalline phases wrap the nano emulsion droplets.

- **NANOEMULSION STABILITY**

Nano emulsions are thermodynamically unstable due to the unfavorable molecular interactions at the oil-water interface caused by the hydrophobic effect. As a result, there is a thermodynamic incentive to reduce the area of contact between the water and oil phases[50]. As a result, nano emulsions can degrade through a variety of mechanisms, such as Ostwald ripening, coalescence, flocculation, and gravitational separation (Fig.7)[46]. Gravitational separation occurs when droplets move downward (sedimentation) or upward (creaming) according to the density in relation to the surrounding liquid. With increasing aqueous phase viscosity, density contrast, and droplet size, the rate of droplet movement due to gravitational separation increases[51].

small droplets large curvature, unlike large droplets with a small curvature, can better solubilize the dispersed phase, creating a concentration gradient that leads to droplet formation. Incorporating a water-insoluble oil phase or by adding ripening inhibitors can control Ostwald ripening. Understanding the primary mechanisms of instability in a nano emulsion is critical for generating systems with maintained stability[46].

Nano emulsions have a sufficiently extended kinetic stability for commercial purposes by wisely manipulating their structure and composition. It is critical to choose the appropriate aqueous phase, oil, and any necessary additives such as weighing agents, ripening inhibitors, texture modifiers, and emulsifiers[51].

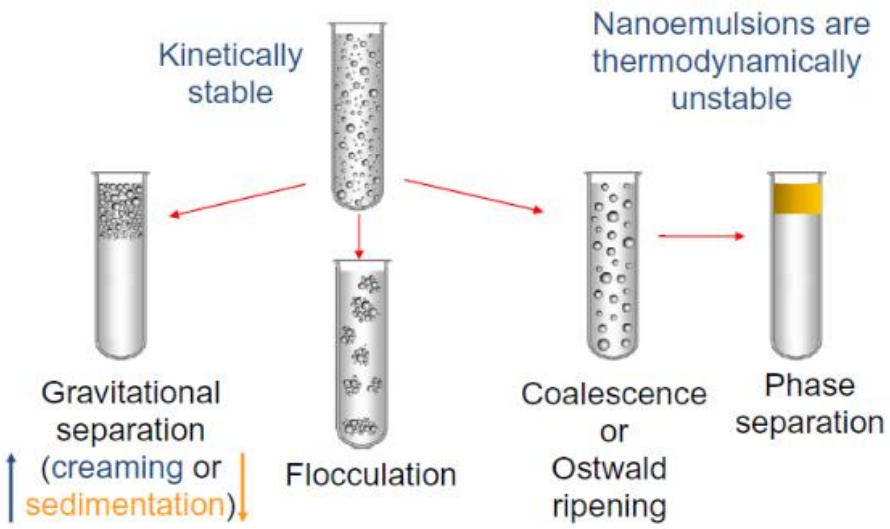

Figure (7): Nano emulsions degrade in a variety of ways, based on their structure and composition, as well as their exposure to specific environmental conditions[46].

- **Formulation Factors affecting the Stability of Nano emulsions**:

While nano emulsions enhance pharmaceuticals' physical and chemical stability, drug product stability is one of the concerns associated with developing nanoemulsions[52]. The stability of nano emulsions is investigated for months by storing them at room temperature and in the refrigerator. The droplet size, refractive index, and viscosity are determined during this storage period[52,53]. When the fluctuations in these parameters exhibit little variation, formulation stability is approved[51]. Accelerated stability experiments are also possible with nano emulsions. The nano emulsion preparation is maintained at elevated temperatures in this case, and samples are taken at consistent intervals, and the drug content is determined using the stability-indicating assay method. The amount of medication destroyed and lasting in the nano emulsion is evaluated at each time interval of 100. The stability of nano emulsion formulations can be improved by controlling factors such as process variables, procedures used, type of oil phase, the type and concentration of surfactant and co-surfactant, and the addition of additives[53,54]. Nano emulsion formulations, in general, may be considered a patient-compliant, safe, and effective method of medication delivery[51].

The following are some of the factors to consider when preparing a nano emulsion:

a) surfactants must be selected well to achieve extremely low interfacial tension at the oil-water interface[50].
b) For nano-droplet stabilization, the surfactant concentration should be enough to deliver the required number of surfactants molecules[54].
c) The interface should be malleable to allow the nano emulsion to develop more easily[50,52].

Nano emulsions are prepared in a variety of ways for medication administration as they demonstrate oral and skin toleration[51].

- **Nano emulsion preparation**

Because nano emulsions represent non-equilibrium systems of structured liquids, their synthesis requires a significant amount of energy, surfactants, or a combination of the two. As a result, they may be synthesized through both low- and high-energy methods. Mechanical devices are used in producing disruptive forces that diffuse the water and oil phases into nanoscale droplets in the high-energy approach. This can be accomplished using high-pressure homogenizers, microfluidizers, and ultrasonicators[50].

The particle size distribution varies according to the equipment used, the operating conditions such as time and temperature, and the sample characteristics and composition. This approach enables more precise control over particle size and composition, affecting the emulsion's stability, rheology, and color[54]. While high-energy emulsification technologies generate nano emulsions with desirable properties and are industrially scalable, they may be incompatible with macromolecules such as proteins, nucleic acids, and enzymes, and thermostable pharmaceuticals such as retinoids[50].

- **Lipid Emulsions with Nanoparticles**

Lipid emulsions are emulsions of oil and water that comprise one or more triacylglycerol oils, a phospholipid emulsifier, and glycerol[55]. Since its inception, the varieties of lipid emulsions accessible in PN formulas have evolved. Now, lipid emulsion formulations are composed of four different oils: medium-chain triglycerides (derived from coconut oil), soybean oil, olive oil, and fish oil. The idea of 'generations' of lipids distinguishes lipid formulations depending on the fatty acid derivative and the inflammatory response elicited by the lipid infusion. (Table 7)[50,54].

Table 7: Oil sources and percentage of the fatty acid content of commercial lipid emulsions[70].

Component	SOF 100%	SO 50% MCT 50%	SO 64% MCT 36%	OO 80% SO 20%	FO 100%	MCT 50% SO 40% FO 10%	SO 30% MCT 30% OO 25% FO 15%
Lipid generation	**First**	**Second**	**Second**	**Third**	**Fourth**	**Fourth**	**Fourth**
Commercial name	**Intralipid®**	**Lipofundin®**	**Structolipid®**	**ClinOleic®**	**Omegaven®**	**Lipofus®**	**SMO Flipid®**
Soybean Oil (%)	100	50	64	20	0	40	30
Coconut Oil (%)	0	50	36	0	0	50	30
Olive Oil (%)	0	0	0	0	0	0	25
Fish Oil (%)	0	0	0	0	100	10	15
ω3-ω 6	7:1	7:1	7:1	9:1	1:8	2.7:1	2.5:1
Linoleic acids (%)	44-62	27	35	18.5	4.4	25.7	21.4
α-Linolenic acid	4-11	4	2	2	1.8	34	25

(%)							
Eicosapentaenoic acid (%)	0	0	0	0		3.7	3
Docosahexaenoic acid (%)	0	0	0	0	12.1	2.5	2
Arachidonic acid (%)	0.18	0.19	0.24	0.16	1.47	0.52-0.66	0.27-0.5
Phytosterols (mg/L)	348	N/A	0	327 +/-8	0	N/A	47.6

The advantages of the lipid nanoparticle technology are:

• In contrast to conventional bilayer liposomes, nanoparticles do not spontaneously merge or interact with other membranes.

• The charge and chemical composition of the surface can be easily adjusted.

• They demonstrate high stability and ease of fabrication in terms of their spherical assemblies.

• When small-molecule ligands are presented on nanoparticles multivalently, the ligand's performance is significantly enhanced.

• Besides attaching ligands/antibodies multivalently to the surface, nanoparticles can deliver a large payload of imaging, chemotherapeutic, or radiation agents to the target cell.

• Due to the nanoparticle's larger size compared to antibodies or small-molecule ligands, the complex does not rapidly leak from the blood vessel. As a result, the biodistribution and safety profile of the drug can be significantly improved[56].

Injectable Lipid Emulsions

Emulsions based on long-chain triglycerides (LCT) (e.g., safflower oil and soybean oil) have been applied in the clinical setting for over 40 years. These lipids are an excellent source of calories[57], critical fatty acids such as linolenic acid (-3 PUFA) and linoleic (-6 polyunsaturated fatty acids (-6 PUFA), as well as vitamins K and E[58].

Nevertheless, the increased concentrations of -6 PUFA in safflower oil (77%) and soybean oil (52%–54%) have raised concerns about their use as the sole source of lipids in critically ill patients and those with trauma, sepsis, or impaired immune function[58]. Elevated arachidonic acid synthesis leads to an increase in potent pro-inflammatory mediators' synthesis, such as interleukin-6 and tumor necrosis factor. Additionally, increased -6 PUFA concentrations have been associated with immunosuppressive effects such as impaired reticular endothelial system function and suppression of neutrophil, macrophage, and lymphocyte activity[59], although the evidence is slightly contradictory. Moreover, because -3 PUFA and -6 PUFA contain a high number of double bonds, they are prone to lipid peroxidation[60].It has been demonstrated that the generated lipid peroxides damage proteins, lipids and DNA, and cause cell death[57,59].

Furthermore, another component of soybean oil and a cholesterol isomer called phytosterols is linked to adverse effects on liver function[58]. To overcome the disadvantages of long-chain triglycerides (LCTs; derived from coconut oil), an emulsion composed of a 1:1 physical mixture of soybean oil and medium-chain triglycerides (MCTs; derived from coconut oil) was initially developed. This emulsion (Lipofundin®) contains 50% fewer -6 polyunsaturated fatty acids than conventional emulsions[61]. Additionally, MCTs have resistance to peroxidation, a faster clearance rate, a greater solubility effect, and a low concentration in adipose and

hepatic tissues. Additionally, unlike LCTs, MCTs have been shown to enhance immunological function by inhibiting the synthesis of pro-inflammatory mediators[61,62]. MCTs, oxidize more quickly and completely than LCTs, making them a more readily available source of energy[62].

Additionally, because MCTs are rapidly metabolized, they should be avoided in patients with diabetes mellitus or in cases where ketosis or acidosis can aggravate a clinical. On the other hand, MCTs are almost always used in conjunction with LCTs, as MCTs lack essential fatty acids[62]. MCT oxidation increases body temperature, increases energy expenditure, and is toxic to the central nervous system[62,63].

Olive oil has also been investigated as a possible soybean oil substitute for lowering -6 PUFA levels. ClinOleic® (80% olive oil, 20% soybean oil) appears to be an excellent choice for immunocompromised patients or those at risk of immune suppression, as it has a neutral immunological effect, making it more tolerable to the liver than MCT/LCT emulsions[64]. Nevertheless, large-scale clinical trials in target populations will be required to establish its superiority to LCT- and MCT-based emulsions and obtain global approval[65].

The most recent development is emulsions containing fish oil. Fish oil is now found in three parenteral nutrition emulsions: SMOFlipid®(30 MCT: 30 soybean oils: 25 olive oil: 15 fish oil), Lipoplus® (50 MCT: 40% soybean oil: 10% fish oil), and Omegaven® (pure fish oil emulsion).Omega-3 polyunsaturated fatty acids (PUFAs) are abundant in fish oil, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)[65,66].

These -3 PUFAs are significantly less vasomotor and inflammatory and can have antagonistic effects[65]. Furthermore, -3 PUFAs inhibit pro-inflammatory cytokines production (TNF-, IL-6, and IL-1) while increasing anti-inflammatory cytokines (IL-10). Moreover, -3 PUFAs may assist in the prevention of cardiac arrhythmias. These characteristics of fish oil make it an ideal constituent of lipid emulsions for critically ill patients suffering from various disorders[65,66,67].

While adverse effects of large volume lipid administration have been stated in parenteral nutrition, their potential adverse effects can be less acute when used in medication delivery due to the minute amounts used. For instance, a 70-kg adult should consume no more than 175 g of Intralipid® 20% daily[68,69].

CONCLUSION

The importance of design and development of emulsion nanocarrier systems aimed at controlling and improving required bioavailability levels of lipids especially when used in Parenteral nutrition cannot be overemphasized. Reducing droplet sizes to the nanoscale leads to some very interesting physical properties. Nano emulsions are developed to encapsulate high amounts of hydrophobic drugs and are also effective delivery approach for poorly water-soluble Drugs. Nano emulsions hold great promise as useful dispersions of deformable nanoscale droplets. Moreover, it is very likely that nano emulsions will play an increasingly important role commercially since they can typically be formulated using significantly less surfactant than is required for nanostructured lyotropic micro-emulsion phases. Finally, nano emulsions are considered as promising nanocarriers for delivering various drugs with different hydrophobic/ hydrophilic ratios and thus have wide applications in drug delivery.

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- **Authors' information and Authors' contributions:**

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Hatem Sarhan : Co-author and shared in the data supply.

Amal Hussein: Co-author and shared in the data supply.

Soad A. Mohamad: Writing the manuscript and design of Figures and Tables.

Sayed I. Abdel-Rahman: Shared in editing and rephrasing and Ideas.

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References:

1- Duggan, C.P. and Jaksic, T., 2017. Pediatric intestinal failure. New England Journal of Medicine, 377(7), pp.666-675.
2- Pierro, A., Hall, N.J. and Chowdhury, M.M., 2006. Gastrointestinal surgery in the neonate. Current Paediatrics, 16(3), pp.153-164.
3- Pichler, J., Chomtho, S., Fewtrell, M., Macdonald, S. and Hill, S., 2014. Body composition in paediatric intestinal failure patients receiving long-term parenteral nutrition. Archives of disease in childhood, 99(2), pp.147-153.
4- Goulet, O., Abi Nader, E., Pigneur, B. and Lambe, C., 2019. Short bowel syndrome as the leading cause of intestinal failure in early life: some insights into the management. Pediatric gastroenterology, hepatology & nutrition, 22(4), pp.303-329.
5- Franca Anzmann, A.L., 2021. Harnessing the Power of-Omics to Uncover Novel Targets of Investigation in Mitochondrial Disorders (Doctoral dissertation, Johns Hopkins University).
6- Goulet, O.J., Cai, W. and Seo, J.M., 2020. Lipid emulsion use in pediatric patients requiring long-term parenteral nutrition. Journal of Parenteral and Enteral Nutrition, 44, pp.S55-S67.
7- Baker, M.A., Cho, B.S., Anez-Bustillos, L., Dao, D.T., Pan, A., O'Loughlin, A.A., Lans, Z.M., Mitchell, P.D., Nosé, V., Gura, K.M. and Puder, M., 2019. Fish oil–based injectable lipid emulsions containing medium-chain triglycerides or added α-tocopherol offer anti-inflammatory benefits in a murine model of parenteral nutrition–induced liver injury. The American journal of clinical nutrition, 109(4), pp.1038-1050.
8- Cober, M.P., Gura, K.M., Mirtallo, J.M., Ayers, P., Boullata, J., Anderson, C.R., Plogsted, S. and ASPEN Parenteral Nutrition Safety Committee, 2021. ASPEN lipid injectable emulsion safety recommendations part 2: Neonate and pediatric considerations. Nutrition in Clinical Practice.
9- Deshpande, G.C. and Cai, W., 2020. Use of lipids in neonates requiring parenteral nutrition. Journal of Parenteral and Enteral Nutrition, 44, pp.S45-S54.
10- Plauth, M., Bernal, W., Dasarathy, S., Merli, M., Plank, L.D., Schütz, T. and Bischoff, S.C., 2019. ESPEN guideline on clinical nutrition in liver disease. Clinical Nutrition, 38(2), pp.485-521.
11- Dudrick, S.J. and Palesty, J.A., 2011. Historical highlights of the development of total parenteral nutrition. Surgical Clinics, 91(3), pp.693-717.
12- Hoffer, L.J., 2016. Human protein and amino acid requirements. Journal of Parenteral and Enteral Nutrition, 40(4), pp.460-474.

13- Sobolewska-Samorek, A., Zarzycka, D., Trojanowska, A., Brodowicz-Król, M., Dońka, K., Szewczyk, M., ... & Łuczyk, M. (2020). New insight of parenteral nutrition in children–short review. Journal of Education, Health and Sport, 10(6), 56-67.
14- Nandivada P, Fell GL, Gura KM, Puder M. Lipid emulsions in the treatment and prevention of parenteral nutrition
15- Mehta NM, Corkins MR, Lyman B, Malone A, Goday PS, Carney LN, Monczka JL, Plogsted SW, Schwenk WF; American Society for Parenteral and Enteral Nutrition Board of Directors. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. JPEN J Parenter. Enteral. Nutr. 2013 Jul;37(4):460-81.
16- Gura KM, Lee S, Valim C, Zhou J, Kim S, Modi BP et. al.: Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition- associated liver disease. Pediatrics 2008;121: 678-686.
17- Druyan ME, Compher C, Boullata JI, Braunschweig CL, George DE, Simpser E, Worthington PA; American Society for Parenteral and Enteral Nutrition Board of Directors. Clinical Guidelines For the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients: applying the GRADE system to development of A.S.P.E.N. clinical guidelines. JPEN J Parenter. Enteral. Nutr. 2012 Jan;36(1):77-80.
18- Savini S, D'Ascenzo R, Biagetti C, Serpentini G, Pompilio A, Bartoli A: The effect of 5 intravenous lipids emulsions on plasma phytosterols in preterm infants receiving parenteral nutrition: a randomized clinical trial. Am J Clin. Nutr. 2013;98:312-318.
19- Forchielli ML, Bonoli A, Preite I, Stancari A, Maselli S, Guarguaglini AM, et. al. Parenteral nutrition admixtures for pediatric patients compounded with highly refined fish oil- based emulsion: assessment of physicochemical stability. Clin. Nutr. 2014 Dec;33(6):1127- 1131.
20- Kao LS, Morris BH, Lally KP, Stewart CD, Huseby V, Kennedy KA. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. J. Perinatol. 2006;26:730- 736.
21- Premkumar, M. H., Carter, B. A., Hawthorne, K. M., King, K., & Abrams, S. A. (2013). High rates of resolution of cholestasis in parenteral nutrition-associated liver disease with fish oil-based lipid emulsion monotherapy. The Journal of pediatrics, 162(4), 793-798.
22- Reber, E., Neyer, P., Schönenberger, K. A., Saxer, C., Bernasconi, L., Stanga, Z., ... & Mühlebach, S. (2021). Physicochemical Stability and Compatibility Testing of Voriconazole in All-in-One Parenteral Nutrition Admixtures. Pharmaceutics, 13(9), 1447.
23- Zhu, X., Ye, A., Verrier, T., & Singh, H. (2013). Free fatty acid profiles of emulsified lipids during in vitro digestion with pancreatic lipase. Food chemistry, 139(1-4), 398-404.
24- Josephson, J. K. (2014). Effects of Dose and Parenteral Lipid Composition on Liver Function in Neonatal Piglets on Total Parenteral Nutrition.
25- Cohen, D. E., & Fisher, E. A. (2013, November). Lipoprotein metabolism, dyslipidemia, and nonalcoholic fatty liver disease. In Seminars in liver disease (Vol. 33, No. 04, pp. 380-388). Thieme Medical Publishers.
26- Ziegler E. Meeting the nutritional needs of the low-birth weight infant. Ann. Nutr. Metab. 2011;58(suppl 1):8-18.
27- Książyk J. European recommendations for parenteral nutrition of children, Contemporary Pediatrics. Gastroenterology. Hepatology and Child Nutrition 2006;8(3):19- 200.
28- Alchaer, M., Khasawneh, R., Heuberger, R., & Hewlings, S. (2020). Prevalence and risk factors of total parenteral nutrition induced hyperglycemia at a single institution: retrospective study. Metabolic syndrome and related disorders, 18(5), 267-273.
29- Pleva M, Mirtallo JM, Steinberg SM. Hyperglycemic events in non-intensive care unit patients receiving parenteral nutrition. Nutr Clin Pract 2009;24:626–634.

30- Hulst J, Joosten K, Zimmermann L, Hop W, van Buuren S, Büller H et al.: Malnutrition in critically ill children: from Israelite J. Pediatric Parenteral Nutrition- Associated Liver Disease. J. Infus. Nurs. 2017 Jan/Feb;40(1):51-54.
31- Mulla S, Stirling S, Cowey S, Close R, Pullan S, Howe R, Radbone L, Clarke P. Severe hypercalcaemia and hypophosphataemia with an optimised preterm parenteral nutrition formulation in two epochs of differing phosphate supplementation. Arch. Dis. Child Fetal Neonatal. Ed. 2017 Sep;102(5):451-455.
32- Wong T. Parenteral trace elements in children: clinical aspects and dosage recommendations. Curr. Opin. Clin. Nutr. Metab. Care. 2012 Nov;15(6):649-656.
33- Bechard LJ, Parrott JS, Mehta NM: Systematic review of the influence of energy and protein intake on protein balance in critically ill children. Journal Pediatric. 2012; 161:333−339.
34- Arrowsmith F, Allen J, gaskin k, Somerville H, Clarke S, OlLoughlin E. The effect of gastrotmy tube feeding on body protein and bone mineralization in children with cerebral palsy. Dev Med Child Neurol, 2010, 52, 1043-1047.
35- Szlagatys-Sidorkiewicz A, Popińska K, Toporowska-Kowalska E, Borkowska A, Sibilska M, Gębora-Kowalska B at all. Home enteral nutrition I children - 2010 nationwide survey of the Polish Society for Clinical Nutrition of Children. Eur J Pediatr. 2011 Dec 15.
36- Merritt RJ, Goldsmith AH. Scientific, economic, regulatory, and ethical challenges of bringing science-based pediatric nutrition products to the U.S. market and ensuring their availability for patients. JPEN J Parenter Enteral Nutr. 2014 Nov;38(2 Suppl):17S-34S.
37- Simmer K., Rakshasbhuvankar A., Deshpande G. Standardised parenteral nutrition. Nutrients. 2013 Mar 28;5(4):1058-1070.
38- Paltrinieri AL, Cheng I, Chitrit M, Turnock K. Parenteral nutrition is not a fluid! Arch. Dis. Child Educ. Pract. Ed. 2016 Oct;101(5):252-257.
39- Toporowska-Kowalska E, Gębora-Kowalska B, Jabłoński J, Fendler W, Wąsowska- Królikowska K: Influence of percutaneous endoscopic gastrostomy on gastro-oesophageal reflux evaluated by multiple intraluminal impedance in children with neurological impairment Dev Med Child Neurol. 2011; 53:938-943.
40- Gallagher K, Flint A, Mouzaki M, Carpenter A, Haliburton B, Bannister L at all. Nutrition Diet Study: Feasibility, Clinical, and Microbiome Outcomes of Providing Blenderized Feeds Through a Gastric Tube in a Medically Complex Pediatric Population. JPEN J Parenter Enteral Nutr. 2018 Jan 16.
41- Sun, J., Wang, F., Sui, Y., She, Z., Zhai, W., Wang, C., & Deng, Y. (2012). Effect of particle size on solubility, dissolution rate, and oral bioavailability: evaluation using coenzyme Q10 as naked nanocrystals. International journal of nanomedicine, 7, 5733.
42- Gratieri, T., Kalaria, D., & Kalia, Y. N. (2011). Non-invasive iontophoretic delivery of peptides and proteins across the skin. Expert opinion on drug delivery, 8(5), 645-663.
43- Singh, Y., Meher, J. G., Raval, K., Khan, F. A., Chaurasia, M., Jain, N. K., & Chourasia, M. K. (2017). Nano emulsion: Concepts, development and applications in drug delivery. Journal of controlled release, 252, 28-49.
44- Bhatt, P., & Madhav, S. (2011). A detailed review on nanoemulsion drug delivery system. International Journal of Pharmaceutical sciences and research, 2(10), 2482.
45- Kushwaha, S. K., Rastogl, A., Rai, A. K., & Singh, S. (2012). Novel drug delivery system for anticancer drug: a review. Int J PharmTech Res, 4(2), 542-553.
46- McClements, D. J., & Jafari, S. M. (2018). General aspects of nano emulsions and their formulation. In Nano emulsions (pp. 3-20). Academic Press.
47- Shewan, H. M., & Stokes, J. R. (2013). Review of techniques to manufacture micro-hydrogel particles for the food industry and their applications. Journal of Food Engineering, 119(4), 781-792.

48- Mokhtari, S., Jafari, S. M., & Assadpour, E. (2017). Development of a nutraceutical nano-delivery system through emulsification/internal gelation of alginate. Food chemistry, 229, 286-295.
49- Katouzian, I., Esfanjani, A. F., Jafari, S. M., & Akhavan, S. (2017). Formulation and application of a new generation of lipid nano-carriers for the food bioactive ingredients. Trends in Food Science & Technology, 68, 14-25.
50- McClements, D. J. (2015). Characterization of emulsion properties. In Food Emulsions (pp. 648-701). CRC Press.
51- Shah, P., Bhalodia, D., & Shelat, P. (2010). Nano emulsion: A pharmaceutical review. Systematic reviews in pharmacy, 1(1).
52- Rai, V. K., Mishra, N., Yadav, K. S., & Yadav, N. P. (2018). Nano emulsion as pharmaceutical carrier for dermal and transdermal drug delivery: formulation development, stability issues, basic considerations and applications. Journal of controlled release, 270, 203-225.
53- Parveen, R., Baboota, S., Ali, J., Ahuja, A., & Ahmad, S. (2015). Stability studies of silymarin nano emulsion containing Tween 80 as a surfactant. Journal of pharmacy & bioallied sciences, 7(4), 321.
54- Sharma, N., Bansal, M., Visht, S., Sharma, P. K., & Kulkarni, G. T. (2010). Nano emulsion: A new concept of delivery system. Chronicles of Young Scientists, 1(2), 2-6.
55- Abbas, Q., Liu, G., Yousaf, B., Ali, M. U., Ullah, H., Munir, M. A. M., & Liu, R. (2018). Contrasting effects of operating conditions and biomass particle size on bulk characteristics and surface chemistry of rice husk derived-biochars. Journal of analytical and applied pyrolysis, 134, 281-292.
56- Lavington, S., & Watts, A. (2020). Lipid nanoparticle technologies for the study of G protein-coupled receptors in lipid environments. Biophysical Reviews, 1-16.
57- Chambrier, C., Lauverjat, M., & Bouletreau, P. (2006). Structured triglyceride emulsions in parenteral nutrition. Nutrition in Clinical Practice, 21(4), 342-350.
58- Hippalgaonkar, K., Majumdar, S., & Kansara, V. (2010). Injectable lipid emulsions—advancements, opportunities and challenges. Aaps Pharmscitech, 11(4), 1526-1540.
59- Wang, M., Ma, L. J., Yang, Y., Xiao, Z., & Wan, J. B. (2019). n-3 Polyunsaturated fatty acids for the management of alcoholic liver disease: a critical review. Critical reviews in food science and nutrition, 59(sup1), S116-S129.
60- Chauhan, P. S., Satti, N. K., Sharma, V. K., Dutt, P., Suri, K. A., & Bani, S. (2011). Amelioration of inflammatory responses by chlorogenic acid via suppression of pro-inflammatory mediators. Journal of Applied Pharmaceutical Science, 1(4), 67.
61- Reiter, R. J., Tan, D. X., & Galano, A. (2014). Melatonin reduces lipid peroxidation and membrane viscosity. Frontiers in physiology, 5, 377.
62- Xu, Z., Li, Y., Wang, J., Wu, B., & Li, J. (2012). Effect of omega-3 polyunsaturated fatty acids to reverse biopsy-proven parenteral nutrition-associated liver disease in adults. Clinical Nutrition, 31(2), 217-223.
63- Hippalgaonkar, K., Majumdar, S., & Kansara, V. (2010). Injectable lipid emulsions—advancements, opportunities and challenges. Aaps Pharmscitech, 11(4), 1526-1540.
64- Alexandrou, E., Herzberg, G. R., & White, M. D. (2007). High-level medium-chain triglyceride feeding and energy expenditure in normal-weight women. Canadian journal of physiology and pharmacology, 85(5), 507-513.
65- Lima, S., Pontes-Arruda, A., Martins, L., & Pinheiro, M. (2010). Effects of an olive oil-based lipid emulsion (ClinOleic) versus LCT/MCT-based lipid emulsions upon the inflammatory markers of critically ill patients (EPICOS Study). Critical Care, 14(1), 1-1.
66- Calder, P. C., Adolph, M., Deutz, N. E., Grau, T., Innes, J. K., Klek, S., ... & Singer, P. (2018). Lipids in the intensive care unit: Recommendations from the ESPEN Expert Group. Clinical Nutrition, 37(1), 1-18.

67- Novak, F., Vecka, M., Meisnerova, E., Sevela, S., Vavrova, L., Rychlikova, J., ... & Novakova, O. (2019). Fish oil supplementation with various lipid emulsions suppresses in vitro cytokine release in home parenteral nutrition patients: a crossover study. Nutrition Research, 72, 70-79.
68- Gostyńska, A., Stawny, M., Dettlaff, K., & Jelińska, A. (2019). Clinical nutrition of critically ill patients in the context of the latest ESPEN guidelines. Medicina, 55(12), 770.
69- Rea, I. M., Gibson, D. S., Mc Gilligan, V., McNerlan, S. E., Alexander, H. D., & Ross, O. A. (2018). Age and age-related diseases: role of inflammation triggers and cytokines. Frontiers in immunology, 9, 586.
70- Cai, W., Calder, P. C., Cury-Boaventura, M. F., De Waele, E., Jakubowski, J., & Zaloga, G. (2018). Biological and clinical aspects of an olive oil-based lipid emulsion—A review. Nutrients, 10(6), 776.