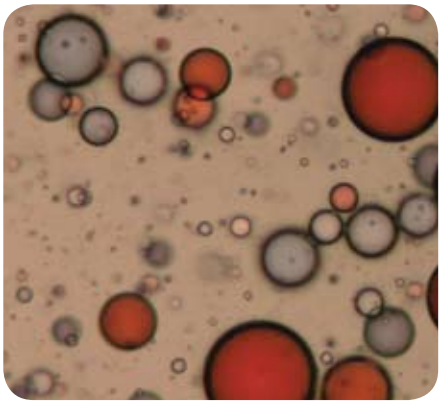
Emulsions - established and promising drug carriers for parenteral administration

Emulsions are in general heterogeneous systems in which one immiscible liquid is dispersed as droplets in another liquid (simplified definition).



Normally one of the two immiscible liquids is water, and the second is an oily substance, often a long chain triglyceride (e.g. soybean oil). Hence, an emulsion in which the oil is dispersed as droplets throughout the aqueous phase is termed an oil-in-water (O/W) emulsion. All pharmaceutical emulsions designed for parenteral administration are of the O/W type. Emulsions do not form spontaneously. Energy input through shaking, stirring, homogenising or spray processes are needed to form an emulsion.

Over time, emulsions tend to revert to the stable state of the phases comprising the emulsion. Surface active substances (surfactants or emulsifiers) can increase the kinetic stability of emulsions greatly so that, once formed, the emulsion does not change significantly over years of storage.

Emulsions – Fundamentals - Composition

Normally one of the two immiscible liquids is water, and the second is an oily substance, often a long chain triglyceride (e.g. soybean oil). The most frequent emulsifiers used in parenteral emulsion formulation are phospholipids (generally from egg yolk sources). The main functions of the emulsifiers are to form a thin film in the interface and lower the surface tension, thus preventing flocculation and coalescence of the dispersed phase. Additives are needed to adjust to physiological pH and tonicity. Glycerol is most recommended as an isotonic agent, and can be found in almost every parenteral emulsion. The pH is adjusted to the desired value with an aqueous solution of NaOH or HCL. The pH of an emulsion should generally be adjusted between 7 and 8 to allow physiological compatibility and maintain emulsion physical integrity by minimising hydrolysis reactions of the components.

Reason	Drug Sample
Solubilisation of low water-solubility drugst	Diazepam, vitamin A, vitamin E, propofol, dexamethasone palmitate, progesterone
Stabilisation of hydrolytically susceptible compounds	Lomustine, physostigmine salicylate
Prevention of drug uptake by infusion sets	Diazepam, Perilla Ketone
Reduction of irritation, pain, or toxicity of intravenously administered drugs	Amphotericine, diazepam, propofol
Potential for sustained release dosage forms	Barbiturates, dexamethasone palmitate, physostigmine salicylate
Possible directed drug delivery to various organs	Cytotoxic agents

Table 1: Reasons for using medicated emulsions.

Emulsions – History

Lipid emulsions were developed after World War II to serve as an intravenous source of both calories and essential fatty acids. The first approved IV-emulsion, Intralipid®, was developed more than 40 years ago for parenteral nutrition. It consists of an O/W-emulsion of 10 or 20% soybean oil droplets (70-400nm in size) stabilised by a monolayer of egg yolk mixed with phospholipids (1.2%) and glycerol (2.25%) as an osmotic agent.



The wide and clinically well-accepted usage of this emulsion for parenteral nutrition later raised the possibility of using the internal oil core of this emulsion for solubilising water-insoluble drugs. The past decade has seen enormous activity in drug delivery and targeting research using emulsions as carriers of a wide variety of drugs.

Emulsions – Relevance in today´s medicine

Intravenously administered emulsions are today excellent carriers for lipophilic drugs which are often difficult to deliver (e.g. diazepam, vitamin A, vitamin E, propofol, dexamethasone palmitate, progesterone).

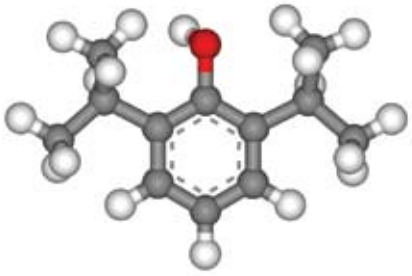




Type	Pre-filled syringes	Ampoules	Vials	Bottles	IV-bags	Multi-chamber bags	Speciality Devices
Size	1-50ml	1–20mL	1–100mL	50–1,000mL	40–5,000mL	100–5,000mL	1mL–200L
Material	Glass Plastic	Glass Plastic	Glass Plastic	Glass Plastic	Non-PVC	Non-PVC	Various

Emulsions - Example:

Propofol (2,6 di-isopropylphenol) is not soluble in water.



It is presented as an oil-in-water-emulsion with 1ml of emulsion containing 10mg propofol (1%) or 1ml emulsion containing 20mg propofol (2%), respectively. Propofol is a highly effective short-acting hypnotic without analgesic properties. It is used for induction and maintenance of general anaesthesia and for sedation of mechanically-ventilated intensive care patients. Propofol emulsion appears as a highly opaque white fluid due to the scattering of light from the tiny (~150nm) oil droplets that it contains. It resembles milk, and is jocularly called "milk of amnesia" by medical professionals.

Emulsions – Relevance in medicine

Emulsions are able to control the in vivo disposition of incorporated drugs, and deliver drugs selectively to a target site. Emulsions are promising to improve the therapeutic index of drugs by increasing their efficacy and/or reducing their toxicity. Fat emulsion drug delivery systems offer today a wide variety of possibilities for preparing better-tolerated intravenous formulations of selected drugs, while either maintaining the same characteristics concerning pharmacokinetics and tissue distribution, or enhancing the site-specific delivery in targeted organs.

Emulsions – Outlook

If emulsions are carefully designed with respect to the target and route of administration, they may provide one solution to some of the delivery problems posed by new classes of active molecules, such as peptides, proteins, genes, and oligonucleotides. They may also extend the therapeutic potential of established drugs.

Emulsions – Manufacturing – The Challenge

Intravenous emulsions, like all parenteral products, are required to meet pharmacopoeial requirements. The emulsion must be sterile, isotonic, non-pyrogenic, non-toxic, biodegradable and stable. Furthermore, the particle size of the droplets has to be controlled accurately and needs to be within certain limits. To comply with these requirements, careful selection of the excipients and of the manufacturing process needs to be performed.

Emulsions – Manufacturing - Fresenius Kabi

Intensive research efforts at Fresenius Kabi for more than 30 years have been concentrated on the design of special injectable emulsion formulations that led to sucessful marketed products such as the emulsion of 1% propofol, a highly effective anaesthetic agent.

Emulsions – Manufacturing – Preparation process

In Graz emulsions are produced in state-of-the-art equipment under full cGMP-conditions, utilising batch sizes ranging from 5 litres to 6000 litres and fully automated high pressure homogenisers. In the first step the drug substance is dissolved in the oily component (e.g. soybean oil). This oily phase is then dispersed together with the emulsifier (e.g. Lecithin) in water for injection using an Ultra-turrax mixing device. The excipients (e.g. Glycerol and sodium oleate) are added under constant heating and stirring, forming the so called pre-emulsion.The pre-emulsion is afterwards homogenised via high pressure homogenisers.

Emulsions – Manufacturing – Filling

For filling the emulsions into the final container the production unit runs different filling lines, which are adapted to a wide range of container types and formats.

Emulsions - Summary

Emulsions are today well-established drug delivery systems of poorly water-soluble drugs. Fat emulsions are established and promising drug delivery systems which can solubilise considerable amounts of lipophilic drugs, control the in vivo disposition of incorporated drugs, and deliver drugs selectively to a target site. If emulsions are carefully designed with respect to the target and route of administration, they may provide one solution to some of the delivery problems posed by new classes of active molecules, such as peptides, proteins, genes, and oligonucleotides. They may also extend the therapeutic potential of established drugs. ■



Copyright © Fresenius Kabi



Anton Gerdenitsch, Master degree in Chemistry followed by Master degree in Economics. His main areas are Biotechnology and Biochemistry. Joined Fresenius Kabi in 2008 as Director Contract Manufacturing, from Sanochemia Pharmazeutika AG where he was Director Supply Chain Management and Logistics. Email: anton.gerdenitsch@fresenius-kabi.com