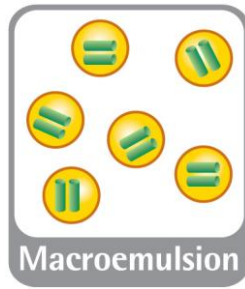


PHYSICAL FORM:**TECHNOLOGY TYPE:****1. What is a macroemulsion?**

A macroemulsion is an optically clear solution comprising a poorly water soluble drug, oil and surfactant, generally without water. When added to water, the optically clear pre-concentrate easily disperses (or 'self emulsifies') to form a milky macroemulsion with oil droplets containing the oily components. The oil droplets can be seen under a light microscope. Macroemulsion formulations are broadly described as lipid based delivery systems. More specifically, the pre-concentrates are known as 'Self Emulsifying Drug Delivery Systems' (SEDDS).

Using the Pouton lipid formulation classification system, macroemulsion pre-concentrates are categorized as Type II formulations.

2. Which administration route is our Macroemulsion technology suitable for?

Commercially, these formulations can only be administered orally. They are unsuitable for intravenous administration due to the toxic nature of the components after systemic administration.

3. Which types of compound are suited to macroemulsions?

Solubilization by macroemulsion pre-concentrates is suitable for poorly soluble compounds which have a high solubility in the lipid based components and easily transfer from the oil phase into the gastro intestinal (GI) tract epithelium. Generally, the compound should not precipitate out into an insoluble form upon contact with the aqueous media of the GI tract, otherwise the benefit is usually lost.

4. How do macroemulsions increase bioavailability?

After oral administration, dissolution is NOT required because the drug should remain dissolved in the pre-concentrate which self emulsifies with gastric fluid without drug precipitation. The solubility of the insoluble drug in the macroemulsion is also increased compared to water alone. Depending upon the type of components used, some digestion of the excipients may be needed for release of the poorly soluble drug from the formulation in the small intestines. The droplets containing drug may be further emulsified by the bile/lecithin micelles in the intestinal fluids and digested by enzymes and further emulsified into smaller lipid particles. The digestion process greatly increases the surface area of the poorly soluble drug for transfer to the intestinal epithelium.

5. Which Phares services use the Macroemulsion technology?

During Survey, we identify whether this technology is suited to the poorly soluble compound.

For our Speed tox service, macroemulsions are generally less suitable for poorly soluble compounds with a wide therapeutic index because of the possible background toxicity of the oils and surfactants at very high doses.

If a sufficiently high drug load can be reached, during Icebreaker a clinical dosage form will include the development of a liquid or preferably a pre-concentrate which is stable and compatible for gelatin encapsulation (soft or hard gel). Furthermore, if the poorly soluble drug is sufficiently potent then conversion into a solid dosage form may be feasible. Third party patents may restrict freedom to operate for specific formulations. Phares can advise on this.

6. The advantages and disadvantages of macroemulsions

Advantages

- The pre-concentrates are relatively easy to manufacture
- As with all lipid based formulations, the liquid form avoids dust formation thereby enabling highly potent or cytotoxic poorly soluble compounds to be encapsulated within individual dosage units. This minimizes the risk of cross contamination during production, dispensing and patient administration

Disadvantages

- Low drug load may limit suitability if single unit doses are essential for the indication
- The degree and reproducibility of absorption of the poorly soluble drug may be dependent on the dispersion and digestion in the Gastro intestinal (GI) tract and may be subject to a food effect
- Some of the excipients are from natural sources and can be variable making formulation validation more demanding

7. Scale-up of macroemulsions

Manufacturing of the pre-concentrate is relatively straight forward. However, capsule filling requires special equipment and needs some optimization to ensure performance of the fill is maintained upon storage.

8. Phares macroemulsion expertise

Phares has developed decision and test systems to identify if a particular lipid based delivery system is the most suitable method to deliver a poorly soluble compound. Lead formulations can be identified rapidly. Optimization is supported by *in vitro* characterization and dissolution behaviour in biorelevant intestinal media along with precipitation studies in simulated intestinal fluids.

9. Macroemulsion products

An example of a poorly soluble drug in a macroemulsion is Menatetrenone (Glakay®, Eisai) in propylene glycol esters of fatty acids and glyceryl mono-oleate which contain 15 mg/capsule.

KEY SERVICES:

