

PHYSICAL FORM:**TECHNOLOGY TYPE:****1) What are emulsions?**

Emulsions are described as milk-like, oil-in-water (o/w) formulations which contain homogenized oil droplets dispersed in an aqueous medium. For intravenous applications, the oil droplets are reduced down to submicron sizes suitable for administration of high volume total parenteral nutrition. In addition to the excipients which must be suitable for injection purposes, injectable emulsions differ from cream emulsions because they have been processed using high shear forces to reduce the average particle size to around 200 nm with only some larger particles up to 5 micrometers.

2) Which administration route is our Emulsion technology suitable for?

The formulations can be administered topically, parenterally or orally. However, intravenous delivery is the administration route of choice for clinical applications. Emulsions for oral administration are not frequently used due to low drug load and patient compliance. The most common pharmaceutical form is a liquid. Conversion of emulsions into powders is limited to experimental research applications.

3) Which types of compound are suited to emulsions?

Poorly soluble lipophilic compounds which are oils, or which have very high oil solubility or miscibility in oils, are suited to emulsions. Highly crystalline compounds or poorly soluble compounds which destabilize emulsified droplets are unsuitable for incorporating into emulsions. The final drug concentration is limited by the maximum oil content for a stable emulsion which is ca. 20 % w/v.

4) How do emulsions work to increase bioavailability?

After oral administration, the emulsion readily disperses. No dissolution of the poorly soluble compound is required before absorption because the drug is dissolved in the oil of the emulsion. The solubility of the poorly soluble drug in the oily solution is also increased compared to water alone. However, digestion of the oil droplets may be necessary to release the drug.

Poorly soluble drugs which are lipophilic are usually more soluble in oil than water. For this reason, higher doses and concentrations can be administered parenterally in emulsions. Due to solubilization in the oil droplets, aggregation of insoluble drug at the injection site and emboli formation in the bloodstream can be avoided. If a compound is well suited to an emulsion, the typical concentration of an insoluble drug is between 1 mg/ml to 10 mg/ml for intravenous administration. For compounds

that readily transfer and distribute *in vivo*, the pharmacokinetics after intravenous administration are similar to other solubilized forms (such as co-solvents and mixed micelles).

5) Which Phares services use the Emulsion technology?

Emulsions are explored during the Survey and Icebreaker services.

Occasionally, Emulsion technology can be used in our Speed tox form service but only if the drug is sufficiently potent and can easily and stably be incorporated in an emulsion to a very high degree. However, since most poorly water soluble drugs in such emulsions are not very soluble in oils, the required dose and high drug concentrations may not be achieved for tox studies. Clinical dosage forms may be more feasible because the requirements for the dose and drug concentration are considerably lower.

6) Advantages and disadvantages of emulsions

Advantages

- The low parenteral toxicity of o/w emulsions is to be expected as supported by the extensive use of intravenous (iv) parenteral nutrition in man. Intravenous emulsions have been used clinically to replace enteral nutrition for more than 30 years
- Potential to reduce pain and irritation compared to co-solvent formulations

Disadvantages

- In practice, very few poorly soluble compounds can be successfully delivered as emulsions because of low oil solubility- it is mainly limited to oily materials that are miscible with oils
- Re-crystallization and particle size growth of the emulsion can be difficult to identify, particularly in low dose formulations. High opacity of the milk-like liquid prevents a straightforward visual check. Many pre-clinical formulations are unknowingly tested where the drug is finely suspended as insoluble crystallites which accumulate in capillaries after injection

7) Scale-up of emulsions

Manufacturing formulations *de novo* requires specialist processing equipment and sterilization equipment.

8) Phares emulsion expertise

Phares has experience in the production of these types of formulations and we have the specialist equipment for laboratory and in-house pilot production.

Phares has developed techniques to identify insoluble particles amongst the emulsion droplets and test long term physical stability.

9) Emulsion products

Propofol (Diprivan[®], AstraZeneca) and Diazepam (Diazemuls[®], Actavis) are examples of emulsions for parenteral injection.

KEY SERVICES:

