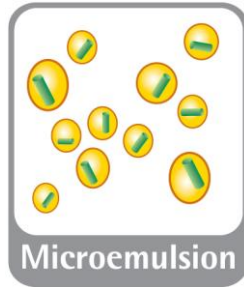


**PHYSICAL FORM:****TECHNOLOGY TYPE:****1. What is a microemulsion?**

A microemulsion is an optically clear pre-concentrate containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves a poorly water soluble drug. Upon contact with water, the formulations spontaneously disperse (or 'self emulsifies') to form a very clear emulsion of exceedingly small and uniform oil droplets containing the solubilized poorly soluble drug.

Compared to macroemulsion pre-concentrates, microemulsion pre-concentrates remain optically clear after dilution and usually contain a higher amount of water soluble surfactant and a higher content of a hydrophilic solvent.

Using the Pouton lipid formulation classification system, these formulations fall into either Type IIIA formulations or Type IIIB formulations. Type IIIB formulations contain more surfactant and hydrophilic solvents than Type IIIA.

The formulations are broadly referred to as lipid based delivery systems. More specifically, these types of pre-concentrates are referred to as 'Self (Micro) Emulsifying Drug Delivery Systems' (SMEDDS).

**2. Which administration route is our Microemulsion technology suitable for?**

These formulations are only administered orally due to the nature of the excipients.

**3. Which types of compound are suited to microemulsions?**

Solubilization using microemulsion pre-concentrates is suited to poorly soluble lipophilic compounds that have high solubility in the oil and surfactants mixtures.

**4. How do microemulsions increase bioavailability?**

After oral administration, no dissolution is required as the poorly soluble drug is maintained in a fully solubilized state after the microemulsion pre-concentrate self emulsifies on contact with gastric fluid in the stomach. The already small droplets containing poorly soluble drug may be further emulsified by the bile/lecithin micelles in the intestinal fluids and digested by enzymes and converted into even smaller lipid particles. This process of digestion greatly increases the surface area of the poorly soluble drug for transfer to the intestinal epithelium.

## **5. Which Phares services use the Microemulsion technology?**

During Survey, we identify whether this particular technology is appropriate for the poorly soluble compound.

During our Speed tox service, microemulsion approaches are only suitable in cases where the drug is sufficiently potent. In most situations, it is unsuitable if the drug has a wide therapeutic index or has a low drug load.

It is more amenable for use in our Icebreaker service as a clinical dosage form will employ significantly lower excipient levels than in tox. The pharmaceutical form will be a liquid or preferably a liquid encapsulated in a stable compatible gelatin capsule (soft or hard gel). If the poorly soluble drug is sufficiently potent, conversion into a solid dosage may be feasible. However, third party patents may restrict freedom to operate for certain formulations and compositions. Phares will be able to offer guidance on this.

## **6. The advantages and disadvantages of microemulsions**

### **Advantages**

- The pre-concentrates are relatively easy to manufacture
- Well developed microemulsion pre-concentrates are not normally dependent upon digestion for drug release. Therefore, optimal bioavailability and reproducibility can be also be expected without co-administration of food (i.e. the fasted state)

### **Disadvantages**

- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent
- The tolerability of formulations with high levels of synthetic surfactants may be poor in cases where long term chronic administration is intended
- Formulations containing several components become more challenging to validate

## **7. Scale-up of microemulsions**

Manufacturing of the micro-emulsion pre-concentrate is straightforward. However, the encapsulation step generally requires soft gelatin capsules and therefore requires special equipment and contract manufacturers. Development of stable capsules requires extensive compatibility and stability testing (possibly for each capsule strength) because the fill can change the stability upon long term storage.

## **8. Phares microemulsion expertise**

Phares has long-term practical experience in developing and optimizing microemulsion formulations. Rational screening of the composition is performed to find an optimal pre-clinical formulation. We have developed decision and test systems to identify whether a particular lipid based delivery system is the most suitable to deliver a poorly soluble compound. Therefore Lead formulations for your

poorly soluble compound can be identified rapidly. Optimization is supported by *in vitro* characterization and precipitation studies in simulated biorelevant intestinal media.

### 9. Microemulsion products

Examples of poorly soluble compounds that use micro-emulsion pre-concentrates are the HIV protease inhibitor tipranavir (Aptivus® capsules, Boehringer Ingelheim GmbH) and the category defining immunosuppressant cyclosporine A, USP modified (Neoral® capsules, Novartis AG).

#### KEY SERVICES:

