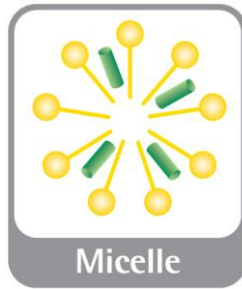


PHYSICAL FORM:**TECHNOLOGY TYPE:****1) What are micelles?**

Micelles are aggregates of one type of surfactant which self assemble above a specific concentration in water. The surfactant molecules have both lipophilic and hydrophilic properties which arrange into very small colloidal particles in water. An example of such a surfactant is polysorbate 80 (Tween® 80). Although oil (lipid) free, this formulation approach is commonly referred to as a lipid based drug delivery system for orally administered drugs. It fits into Type IV formulations based on Pouton's lipid formulation classification system.

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

This formulation technology can be administered orally and parenterally (particularly intravenously). However, upon administration or dilution, the surfactant concentration decreases and the insoluble drug may precipitate. For clinical formulations, unless the drug is extremely toxic, compounds are nowadays rarely administered orally in neat surfactant. If used, this approach is often combined with co-solvents.

If employed parenterally, the administration form is always liquid. For oral administration, the form is liquid or semi solid. Occasionally, these forms can be solidified.

3) Which types of compounds are suited to micelles?

Poorly soluble lipophilic compounds which fit snugly into the micelle structure are most suited. This enables the amount of surfactant to be kept to a minimum. Occasionally, and surprisingly, quite hydrophobic crystalline compounds with less lipophilic characteristics can also be used in such systems, particularly in combination with co-solvents.

Suitability is usually dictated by potency and therapeutic index of the individual poorly soluble drug. As a market form, the approach is mainly reserved for intravenous compounds which are highly potent or toxic and the limiting factor is the drug, not the surfactant.

4) How do micelles increase bioavailability?

Micelles behave in a similar way to washing up liquid (detergents) in water. They soak up greasy and lipophilic material by solubilization within the lipophilic region of the structures. No dissolution of the poorly soluble compound is needed before absorption because the drug is solubilized.

The solubility of the poorly soluble drug is also increased compared to water alone and when administered orally, the movement of the poorly soluble drug (compared to a solid particle) is

facilitated towards the surface of the intestines. In some situations, a very high surfactant concentration may also transiently interfere with the body's intestinal efflux pump mechanisms, thereby indirectly increasing the bioavailability of poorly soluble drugs.

5) Which Phares services use the Micelle technology?

Micelle is explored during the Survey and Icebreaker services.

Micelle is usually less attractive for routine use in Speed tox studies, because of the poor tolerability of most surfactants in many species.

6) Advantages and disadvantages of micelles

Advantages

- Comparatively straightforward to formulate
- Formulations are usually easy to scale up using standard liquid processing equipment

Disadvantages

- Tolerability and toxicity (local and systemic) may be limiting. After oral administration, many surfactants cause stomach irritation followed by vomiting. Upon parenteral administration anaphylaxis may occur. Intravenously, high surfactant concentrations can give rise to hemolysis and consequently have to be administered at quite a dilute concentration
- If the poorly soluble compound does not fit well with the surfactant there is a risk for precipitation upon administration/dilution with aqueous media. This is why dilution regimes (of intravenous formulations) can be rather complicated and formulations have to be used soon after dilution

7) Scale-up of micelles

In most cases, standard liquid processing equipment can be employed. However, explosion proof precautions may be required if flammable solvents are used as co-solvents. For oral administration, the compatibility after filling into soft gelatin capsules needs attention if a variety of dosage strengths are required.

8) Phares micelle expertise

We rapidly identify the suitability of micelle structures to solubilize poorly soluble compounds and characterize the properties and maximum load of the poorly soluble compound that is feasible. The physical stability and precipitation tendency of poorly soluble drugs from micelles is also studied, specifically upon dilution with media relevant for *in vivo* performance.

9) Micelle products

Docetaxel Injection Concentrate (Taxotere®, Aventis) and amprenavir oral solution and capsules (Agenerase®, GSK) are micelle formulations used to solubilize the poorly soluble compounds. Amprenavir was withdrawn due to a reduction of demand and has been superseded by the prodrug Fosamprenavir.

KEY SERVICES:

