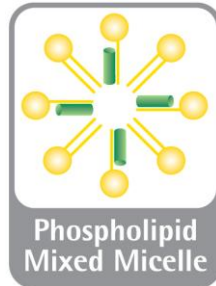


PHYSICAL FORM:**TECHNOLOGY TYPE:****1. What are phospholipid mixed micelles?**

The key components in phospholipid mixed micelles are found in the intestinal tract of mammals. Mixed micelles, as the name implies, are particles of phospholipids with a mixture of one (mono acyl) and two (di acyl) long chain fatty acids. This phospholipid mixture is formed after the phospholipid present in the intestinal fluids is enzymatically cleaved in response to food entering the intestines. Phospholipids are natural surfactants and co-emulsifiers of digested fatty food components. The extraordinary solubilizing properties of phospholipid mixed micelle components can be exploited in formulations designed for solubilization of poorly water soluble drugs. Although lipid based, this type of formulation is not usually put into the lipid classification. However, they fit into Type IV according to Pouton's classification if used without oils and Type IIIA or Type IIIB if oils are included.

2. Which administration route is our Phospholipid Mixed Micelle technology suitable for?

Phospholipid mixed micelles are only suitable for oral administration.

3. Which types of compound are suited to phospholipid mixed micelles?

Poorly water soluble drugs with high affinity for phospholipid mixed micelles, where the degree of oral absorption is limited by solubility. The compounds are typically lipophilic.

4. How do phospholipid mixed micelles increase bioavailability?

Good formulations of phospholipid mixed micelles do not require dissolution for absorption after oral administration because the drug is already molecularly dissolved. Solubilization in the extremely small (mono- and diacyl-) phospholipid mixed micelles may also increase the solubility of drugs significantly more than conventional surfactants or diacyl phospholipids on their own. Solubility is enhanced by the extra space created by removal of one of the two fatty acid chains attached to the phospholipid head group in the mixed micelles allowing poorly soluble compounds fit more snugly.

5. Which Phares services use the Phospholipid Mixed Micelle technology?

During Survey, the phospholipid mixed micelles can be used to produce aqueous solutions of poorly soluble compounds for oral testing and comparison against other solubilization principles.

During Speed tox service, the aqueous solutions may be administered in the form of a gavage. In contrast to synthetic surfactants, comparatively high doses of the phospholipid mixed micelles can be administered because of the low oral toxicity. However, the dosing level may be restricted if organic solvents are also co-administered to liquefy the vehicles.

During Icebreaker formulations, the phospholipid mixed micelle and drug complex can be converted to solid dosage forms such as powders for filling into HGCS or tableted. Liquid fills can also be produced with organic solvents.

6. The advantages and disadvantages of phospholipid mixed micelles

Advantages

- High solubilization potential yielding high drug loads
- Low oral toxicity. As excipients, enzyme-modified lecithin is assigned GRAS status by the FDA

Disadvantages

- For conversion into solid dosage forms, complexation of the drug with phospholipid may require organic solvents. This is guided by the solubility properties of the poorly soluble drug
- As with all solubilized systems containing lipids, the long term chemical stability of the drug may be inferior compared to the drug in a solid form

7. Scale-up of phospholipid mixed micelles

Production of solids by means of complexation of poorly water soluble drugs may require volatile organic solvents and corresponding facilities for handling organic solvents at a contract manufacturer. Liquid forms can be produced in a similar way to microemulsion pre-concentrates and will require encapsulation if a unit dosage form is desired.

8. Phares phospholipid mixed micelle expertise

A proprietary phospholipid mixed micelle technology consisting of mono- and di- acyl components has been developed by the Phares team. As with all of our technologies, we are able to share our inventions with clients by making access to them easy. Suitability of phospholipid mixed micelle formulations for tests with a poorly soluble drug can be identified rapidly. Optimization is supported by *in vitro* characterization and behaviour in biorelevant intestinal media along with precipitation studies in simulated intestinal fluid.

It is our goal to find the best approach for poorly soluble compounds. We will impartially compare the suitability of this exclusive yet accessible technology against the conventional approaches.

9. Phospholipid mixed micelles products

Phospholipid mixed micelle formulations are presently in pre-clinical and clinical testing with a variety of lipophilic poorly soluble compounds.

An example of a product that contains phospholipids with a small fraction (up to 5 % of total phospholipid) of mono-acyl phospholipids is Rapamune[®] (rapamycin / sirolimus oral solution (Wyeth)).

KEY SERVICES:

