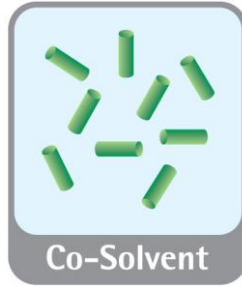


PHYSICAL FORM:**TECHNOLOGY TYPE:****1) What are co-solvents?**

Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Historically, this is one of the most widely used techniques because it is simple to produce and evaluate. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol.

2) Which administration route is our Co-Solvent technology suitable for?

Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally. Parenteral formulations may require the addition of water or a dilution step with an aqueous media to lower the solvent concentration prior to administration. The pharmaceutical form is always liquid.

3) Which types of compound are suited to co-solvents?

Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach.

4) How do co-solvents work to increase bioavailability?

Co-Solvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Very high drug concentrations of poorly soluble compounds can be dissolved compared to other solubilization approaches. However, the bioavailability may not be dramatically increased because the poorly soluble drug will typically uncontrollably crash out upon dilution into a crystalline or amorphous precipitate. In this case, dissolution of this precipitate is required for oral absorption.

Co-solvents may be combined with other solubilization techniques and pH adjustment to further increase solubility of poorly soluble compounds.

5) Which Phares services use the Co-Solvent technology?

Our Co-Solvent technology may potentially be used across all of our services. However, co-solvents often serve as formulation controls, particularly during our Survey service and early pre-clinical evaluations. Occasionally, the approach may be applied during our Speed tox service if the co-solvent level and dosing is not too high.

Co-solvents are not frequently used in Icebreaker because there are only a limited number of solvents that can be used clinically due to tolerability and regulatory acceptability in man. Although in the past this administration form has been used in many products, these formulations are unsuitable for many of today's indications due to patient compliance and acceptability.

6) Advantages and disadvantages of co-solvents

Advantages

- Simple and rapid to formulate and produce

Disadvantages

- As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered
- Uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be amorphous or crystalline and can vary in size. Many of the insoluble compounds Phares works with are unsuited to co-solvents alone, particularly for intravenous administration. This is because the drugs are extremely insoluble in water and do not readily redissolve after precipitation from the co-solvent mixture. In these situations, there is a potential risk for embolism and local adverse effects at the injection site
- As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state

7) Scale-up of co-solvents

Scale up is typically straightforward and can easily be carried out on a large scale without too much effort. The flammability of volatile solvents (such as ethanol) or viscous organic solvents (for parenterals) may slightly complicate larger scale production.

8) Phares co-solvent expertise

Phares has extensive experience and knowledge with the solvents that can be used in co-solvents for different applications by regulatory authorities. Phares will investigate the precipitation behaviour of orally administered poorly soluble drugs dissolved in co-solvents after *in vivo* administration, by dilution with biorelevant media (simulated intestinal fluid). The type and physical form of precipitate that results is also characterized. This gives an indication of how the compound is likely to behave physically *in vivo* and if variability is to be expected.

9) Co-solvent products

Nimodipine Intravenous Injection (Nimotop®, Bayer) and Digoxin Elixir Pediatric (Lanoxin®, GSK) are examples of co-solvent formulations.

KEY SERVICES:

