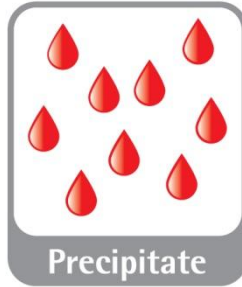


**PHYSICAL FORM:****TECHNOLOGY TYPE:****1. What is Precipitate?**

'Precipitate' is a technique for producing sub-micron particles of a poorly soluble drug. Typically, the particles are amorphous and stabilized. The amorphous particles are produced by precipitating the drug from a water miscible organic solvent solution of the drug into an aqueous phase (anti-solvent).

Using recommended dilution conditions, the dispersed colloidal precipitates usually have a particle size < 1 µm. Due to the amorphous form and small particle size they dissolve rapidly when administered. The term 'hydrosol' is often used to describe this type of amorphous particle.

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

Precipitate is suitable for oral and intravenous administration. As the approach comprises a dilution step, the resulting suspension of amorphous particles usually has to be concentrated to allow parenteral and oral dosing at an adequate drug concentration. Solvent may need to be removed to avoid toxic concentrations and physical instability.

If administered parenterally, the suspended drug particles should dissolve rapidly in the bloodstream. The technology may be considered an alternative to nano-milled drugs for intravenous use.

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

Poorly water soluble compounds with adequate solubility in water miscible and pharmaceutically acceptable organic solvents which form amorphous particles or submicron crystallites precipitates by dilution of the solvent. It is important that the resultant particles have satisfactory physical stability and the physical form does not change.

**4. How does Precipitate increase bioavailability?**

Orally, the amorphous particles undergo rapid dissolution and form super saturated solutions enabling a higher drug concentration gradient to be established in the GI fluids which provides faster diffusion at the absorption sites.

With the proviso that the drug dissolves in the bloodstream, intravenous injection of the colloidal hydrosol particles can allow much higher aqueous concentrations of the drug to be established compared to the amounts usually dissolved in an aqueous solution.

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

Precipitate is not recommended as a first line approach in Survey; more simple options should be explored first.

During our Speed service, Precipitate may be more suitable because at this stage slightly larger amounts of drug are available and controlled dilution can be tested and optimized more thoroughly. However, the suitability of the hydrosol particles for injection has to be cautiously and meticulously assessed.

Precipitate may be suitable in Icebreaker for the development of a clinical form. However, the production process is complex and can be challenging, particularly for intravenous administration of an NCE. Amorphous solids inherently present higher stability risks compared to well formulated, solubilized formulations.

#### **6. Advantages and disadvantages of Precipitate**

##### **Advantages**

- The solid amorphous state and small size of the drug particles allow intravenous injection of higher amounts of poorly soluble drugs compared to solubilized forms
- Typically, amorphous particles dissolve faster than finely milled crystalline particles

##### **Disadvantages**

- Manufacturing is relatively complex and multistep. For most poorly water soluble compounds, the probability of successfully generating small stable amorphous hydrosols which do not recrystallize is low
- The amorphous form of the drug requires real time stability testing to assess the risk of crystallization from moisture pick-up amongst other factors during storage. Furthermore, amorphous particles can quite happily revert to crystal forms, particularly when hydrated

#### **7. Scale-up of Precipitate technology**

The process is multi-step and many critical parameters need to be controlled and validated. It requires increasing the concentration of drug by removal of solvent and most likely a drying step. The process is particularly complicated for intravenous clinical forms where sterile preparation is essential. Freedom to operate generally with specific types of excipients and conditions may be excluded by third party patents. However, the restrictions need not prohibit assessing the suitability of the drug for the Precipitate method in view of the fact that earlier patents in this area are nearing expiration.

## 8. Phares Precipitate expertise

Critical surveillance of the formation and stability of an amorphous or a metastable form is a core competence of Phares. Phares combines expert knowledge in polymorphism and formulation of amorphous forms with successful background experience in dilution techniques for making liposomes - a similar process to the production of Precipitate. Phares pioneered the development and early commercial introduction of liposomes based on aqueous dilution of lipid solutions.

## 9. Products

ABRAXANE® (Abraxis, Inc.) for Injectable Suspension (lyophilized paclitaxel protein-bound particles for reconstitution) is an example of a hydrosol type formulation; it comprises albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. The paclitaxel particles exist in a non-crystalline, amorphous form.

### KEY SERVICES:

