



1. What is Spray?

'Spray' is Phares' description of spray drying. It involves dissolving a poorly water soluble drug along with stabilizers in a volatile organic solvent, spraying and rapidly drying this solution to form a powder. Due to rapid removal of the solvent, the drug is not given time to form crystals and instead favours the amorphous form conveniently stabilized in a solid polymer matrix.

Amorphous formulations of poorly soluble compounds are also referred to as 'solid dispersions' or 'solid solutions' or 'high energy solutions'.

2. Which administration route is our Spray technology suitable for?

Spray dried solid dispersions of poorly soluble drugs are most suited to oral administration. Though potentially used for parenteral applications (mainly biologics), producing sterile powders of NCEs in this way is technologically very difficult and expensive.

3. Which types of compound are suited to Spray?

Spray drying is particularly suitable for poorly water soluble lipophilic or crystalline drugs that are amenable to amorphous formation and have high solubility in volatile organic solvents. Infrequently, spray drying can also be used to prepare highly dispersed crystalline particles. However, the amorphous solid state is typically more effective in enhancing bioavailability.

4. How does Spray increase bioavailability?

On hydration, the higher energy of the amorphous particles of the poorly soluble compound result in faster dissolution and higher solubility due to oversaturation compared to crystal forms. Providing the compound is permeable, transient solubility enhancement facilitates drug diffusion across cell membranes and provides increased oral absorption.

5. Which Phares services use the Spray technology?

We can investigate the benefits of spray drying using very small quantities of drug in Survey but we typically recommend looking at more straightforward approaches first.

Spray dried solid dispersions of poorly soluble drugs are particularly suitable for use in our pre-clinical Speed toxicological service to achieve maximum systemic exposure allowing side effects of the NCE to be observed. The relatively short time frame of these studies reduces the need for long term stability, making it suitable for this stage of research.

Although potentially useful in our Icebreaker formulation development service, the decision to select an amorphous form even for early development has to be taken carefully given that most companies require low technical risk and moderate cost with complete predictability.

6. Advantages and disadvantages of Spray

Advantages

- Rapid solvent removal increases possibility of generating amorphous solid state
- Frequently, higher drug loads can be achieved compared to solubilization
- Suitable for thermolabile compounds

Disadvantages

- Handling of solvents complicates the process. Additional drying and careful particle size selection may also be necessary
- Although formulation development is supported by physically measurable analytical techniques, formulation development of amorphous forms is still largely empirical based on long experience
- Extensive real time stability testing under standard and stress conditions of multiple batches has to be conducted to assure that the amorphous drug is stable and does not change physically

7. Scale-up of spray dried formulations

A relatively small number of contract manufacturers are able to handle solvent evaporation processes, particularly for potent NCEs and NCEs. Lack of sufficient tox data for an NCE during early pre-clinical development may impede agreements with contract manufacturers.

The use of solvents per se is NEITHER a technological NOR a regulatory hurdle for oral dosage forms. The limits for residual solvents are very well regulated in pharmacopeias and ICH guidelines.

The excipients used in solid dispersions are not expensive. However, processing costs may be high depending upon details in the process and drug potency. Furthermore, upscaling from lab scale through pilot to pivotal must be carried out carefully. Potential differences in API quality from different batches and minor changes in processing parameters may significantly influence the particles produced. Freedom to operate with select excipients may be further limited by third party patents. Phares can advise on this.

8. Phares spray drying expertise

The design and development of amorphous solid dispersions requires a truly holistic assessment of the physico-chemical properties of the drug in terms of polymer matrix, drug load and the process parameters. Smart stability testing using the appropriate analytical methods is an absolute must. Phares has long term experience in screening and developing solid dispersions can evaluate production options in-house to assess the technology even when only minute amounts of the compound are available.

9. Spray dried products

Although there is significant freedom to operate within the field, due to the comparative industrial novelty of this approach there are not many commercialized products. Many products are in later stage clinical testing. An example of a commercialized spray dried dispersion is etravirine (Intelence® Tibotec) 100mg tablet (J&J).

KEY SERVICES:

