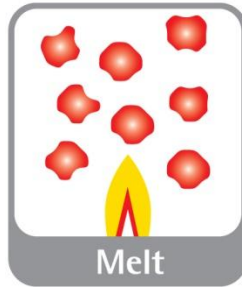


PHYSICAL FORM:**TECHNOLOGY TYPE:****1. What is Melt?**

'Melt' is a process Phares uses to embed the amorphous form of a poorly soluble drug stabilized in a hydrophilic polymer matrix. This is achieved by co-melting and rapidly cooling the drug and polymers.

The melting procedure can be carried out in a granulator applying 'hot melt technology' or by continuously extruding the polymer and insoluble drug mix through a heating device via 'hot melt extrusion'. If the amorphous solid dispersion is prepared by 'hot melt extrusion' then the resultant solids are called extrudates. Amorphous formulations of poorly soluble compounds are generally referred to as 'solid dispersions', 'solid solutions' or 'high energy solutions'.

The amorphous dispersions are solids which can be further developed into capsules or tablets. The end product is similar to spray dried material in terms of the physical state of the amorphous compound.

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

Melt is suitable for oral administration.

3. Which types of compound are suited to Melt?

Melt is particularly suitable for poorly water soluble drugs which have low melting points, are thermostable up to ca. 180 °C and have a tendency towards amorphous forms.

The technology may be considered for compounds which show inadequate oral absorption when administered as crystalline forms.

4. How does Melt increase bioavailability?

Upon hydration of the solid dispersion formulations, the amorphous particles of the poorly soluble compound dissolve and a supersaturated solution is typically formed. Supersaturation of the drug solution is encouraged because of the lower energy required for dissolution of the amorphous form compared to the crystalline drug. Supersaturation allows much higher concentrations of poorly soluble drugs to be reached stabilized by polymers. When membrane permeability is not a rate limiting step,

solubility enhancement often results in more drug being transported across the epithelial membrane thereby increasing oral absorption.

5. Which Phares services use the Melt technology?

Although Phares can assess the feasibility of solid dispersions using very small quantities of material, in Survey, we typically recommend focusing on more straightforward approaches as first line delivery strategies to minimize complexity.

Melt solid dispersions are particularly suited to our pre-clinical Speed toxicological service where drugs are in need of an extremely enhanced degree of oral absorption to obtain adequate systemic exposure for observing side effects. The relatively short time frame of these studies reduces the need for long term stability and makes it more 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 with complete predictability.

6. Advantages and disadvantages of Melt

Advantages

- No solvents required
- A post drying step is typically not required
- Reduced formation of dust with potential to mould into final dosage form

Disadvantages

- Unsuitable for thermolabile compounds
- As with all amorphous forms, extensive real time stability testing under standard and stress conditions of multiple batches has to be performed to assure that the poorly soluble drug is stable and has not undergone physical change
- Additional quality control steps for monitoring the physical state of the amorphous drug are required

7. Scale-up of Melt technology

For very early stage compounds where supply is limited, the process can consume relatively large amounts of API. However, the polymer excipients used in solid dispersions are not particularly expensive and the process costs are competitive. When larger amounts of API are available, melt extrusion is a continuous process that makes volume production efficient.

8. Phares Melt 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. Phares has long term experience and the requisite facilities to screen and develop solid dispersions. We start with very small amounts of API, using our in-house production options to assess the viability of melt extrusion. Phares will compare the strengths and weaknesses with other delivery methods such as spray drying for producing amorphous forms of your poorly soluble compound objectively and impartially. Freedom to operate with certain melt processes and excipients may be limited by third party patents. Phares can provide guidance on this.

9. Products

Due to the comparative novelty of this approach, there are as yet not many commercialized products. Quite a few formulations are in late stage clinical testing. An example of a commercialized extrudate is the antiretroviral combination of lopinavir and ritonavir (Kaeltra® Abbott 200 mg/50 mg).

KEY SERVICES:

