

# MELTDOSE® AN ONE STEP INDUSTRIAL PROCESS FOR THE MANUFACTURING OF SOLID DISPERSION

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## Introduction

The oral bioavailability enhancement of poorly soluble drugs remains one of the most challenging aspects of drug development. Poor absorption of drugs might lead to large variability in bioavailability. Further, the bioavailability is often being dependent on whether the drug is taken with or without food all resulting in unpredictable clinical effect. Incorporating the poorly soluble drug substance into a solid dispersion containing an appropriate vehicle is known to be effective in enhancing the oral bioavailability. In a solid dispersion the drug might be present as an amorphous phase or precipitated as crystalline drug particles or both (1). When the solid dispersion is exposed to gastrointestinal tract fluid, the vehicle dissolves and the drug is released as fine particles or precipitates as colloidal particles. The enlarged surface area of the drug in combination with hydrophilic and amphiphilic vehicles produces higher dissolution rates and enhanced bioavailability of poorly soluble drugs belonging to class II (BCS). In spite of these advantages, only a few products have been marketed since the development of this technology almost five decades ago. The limitations in commercializing this technology have been:

- Laborious and expensive methods of preparation
- Irreproducibility of physicochemical properties
- Difficulties in incorporating a solid dispersion into solid dosage form
- Scale-up problems of manufacturing process
- Chemical instability of drug and or vehicle
- Use of hazardous organic solvents

The older formulation strategy was based on dissolving the drug substance and the vehicle (i.e.HPMC) in organic solvents (i.e.dichloromethane-ethanol mixtures) and using the solution for coating non-parail pellets in a fluid bed. A product example is Sporanox® as an oral capsule formulation containing

using the solution for coating non-parail pellets in a fluid bed. A product example is Sporanox® as an oral capsule formulation containing amorphous itraconazole in solid solution (2).

Solvent free techniques include hot melt extrusion (3) using i.e. PVP as vehicle for the drug substance and extruding the mixture at elevated temperature i.e. 180 °C creating a solid solution at high shear forces. Despite the fact that melt extrusion has been explored for decades, no products based on this technology has reached the market probably due to up-scaling problems, chemical instability and the use of non-conventional pharmaceutical equipment.

Further, the filling of a drug dissolved in a low melting vehicle < 70°C e.g. PEG 1500 into hard gelatin capsules is possible. The main disadvantages are uncontrolled recrystallisation of the drug-vehicle and incompatibility of the formulation with the gelatin capsule shell.

## MeltDose®

### • Process description

The new proprietary technology is a process incorporating the drug substance in a meltable vehicle and subsequently spraying the mixture on a particulate carrier (e.g. lactose) using a fluid bed equipment. Most importantly this is a one step process in contrast to other approaches. A controlled increase in granular particle size is obtained by controlling the product temperature and optimization of feed rate and product temperature. The result of this process is a granular product with a loading at least 80% of a solid dispersion. The granular property makes it applicable for direct tableting without additional processing steps besides blending with a lubricant. Since the process is based on a fluid-bed technology, it is easily scaled-up to manufacturing scale.

The drug substance may be dissolved or dispersed in an appropriate meltable water-miscible vehicle or in a combination of vehicles. For drug substances dissolved in the vehicle, the drug may precipitate in either crystalline or amorphous form when congealed in the spraying process.

#### • Product example

Fenofibrate (aqueous solubility  $<0.3 \mu\text{g/ml}$ ) was dissolved in a concentration of 35% in a mixture of melted PEG 6000 and Poloxamer 188 (70:30 w/w). Fenofibrate was dissolved in a heated pressure tank at  $78^\circ\text{C}$  and sprayed on lactose 200 mesh in a fluid bed using a specialised heated binary nozzle. The granular product has a weight geometric mean diameter of approx.  $350 \mu\text{m}$  and contains 45% of lactose. Fenofibrate recrystallizes in a solid dispersion as crystalline particles with a median volume particle size of approx.  $1 \mu\text{m}$  as shown in Figures 1 and 2.

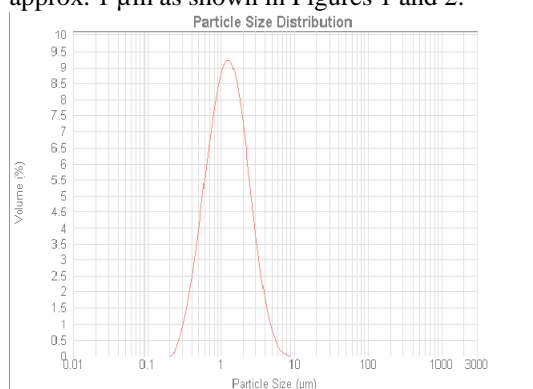


Figure 1. Particle size of fenofibrate determined by laser diffraction in a wet dispersion of the granular product.

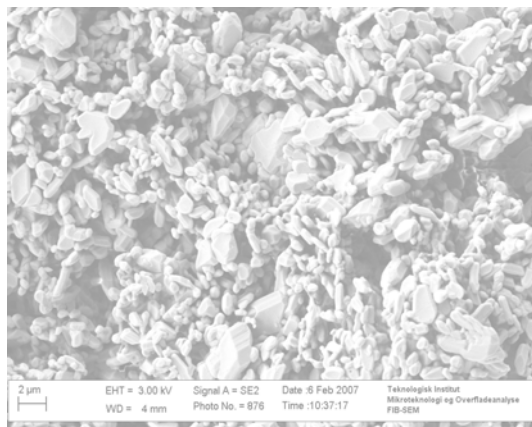


Figure 2. SEM micrograph of the crystalline fenofibrate particles as pre-washed granulate retained on a  $0.2 \mu\text{m}$  filter.

The granular product was tableted by direct compression. The dissolution profile of the tablets and the particle size of fenofibrate was stable during storage.

PK studies revealed increased bioavailability and elimination of the food effect as compared to 35% increased bioavailability with food observed for plain tablet formulations. The FDA approved product has been successfully up-scaled obtaining reproducible physicochemical form and crystal size of fenofibrate.

#### Conclusions

MeltDose® has shown to be an effective technology for producing solid dispersions of a number of poorly soluble drug substances. This technology eliminates the drawbacks being limiting for the use of the solid dispersion formulation principle in drug development. The process may be carried out under controlled atmosphere (nitrogen) in order to avoid degradation processes of drugs or polymers which might undergo oxidation.

In addition, the technology may be combined with a series of standard formulation techniques used for controlled-release formulations such as enteric coating, extended-release or slow-release. The MeltDose® technology has the following main process advantages:

- Gentle process: No water or organic solvents, controlled atmosphere, etc.;
- Flexibility in choice of excipients and processing;
- Flexibility in choice of vehicle;
- Direct tablet compression;
- High drug load;
- Easy scalability; and
- One step process
- Conventional equipment and low production cost.

#### References

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