

Factors Influencing the Fenofibrate Crystal Size in a PEG-Poloxamer Based Solid Dispersion

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ABSTRACT SUMMARY

Solid dispersion is a well established technology for oral bioavailability enhancement of poorly soluble drugs. The manufacturing of solid dispersions might be based on dissolving the drug substance in a melted polymer followed by subsequent solidification in an appropriate cooling process. This study examines the particle size of fenofibrate as recrystallised in a matrix of PEG-Poloxamer. The effect of PEG type, ratio between PEG-Poloxamer, Poloxamer type, fenofibrate concentration, melt temperature and cooling condition is examined in a factorial-designed beaker experiment. The particle size of fenofibrate is only affected by the Poloxamer content which is interrelated to the PEG content and by the amount of fenofibrate dissolved in the polymers. Surprisingly the cooling rate or the viscosity of the polymer did not affect the final particle size of fenofibrate in the solid dispersion.

INTRODUCTION

Since the 1960's the principle of solid dispersions has been known to provide oral bioavailability enhancement of poorly soluble drugs. The term solid dispersion describes a variety of dosage forms whereby the drug substance is dispersed in an inert vehicle or matrix at solid state (1). Although creation of solid dispersions had been a theoretically tempting approach for the formulation of poorly soluble drugs, primarily the lack of efficient manufacturing processes and physico-chemical instability prevented the industrial application of this approach. This was the background for the invention of a one-step process where the drug is incorporated in a meltable polymer and subsequently sprayed on a particulate inert carrier using conventional fluid bed equipment (2). A fenofibrate tablet product based on this process gained approval by the FDA in 2007 being based on a PEG-Poloxamer 188 solid dispersion (2).

The aim of this study was to investigate which factors related to polymer composition, polymer types and cooling conditions for the solidification process affect the particle size of fenofibrate recrystallising in the solid dispersion in beaker experiments.

EXPERIMENTAL METHODS

A quarter fraction factorial screening designed experiment was applied using 7 factors with one replicate. Fenofibrate was dissolved in a mixture of melted PEG and Poloxamer. The factors were viscosity (PEG4000/PEG20000), poloxamer type (188/407), Poloxamer content of polymers (5%/40%), Fenofibrate concentration (15%/35%), cooling temperature (-÷18°C/+20°C) and melt temperature (80°C/110°C)

when exposed to cooling conditions (cooling block or room temperature). The response was the median fenofibrate crystal size.

The constituents were heated and mixed at 120°C. Approx. 500-100 mg of the melt was transferred to a beaker and solidified at the predetermined cooling temperature. The solidification was followed visually for up to 4 hours.

The particle size of fenofibrate as recrystallised in the solid dispersion was determined the following way. A suspension in water corresponding to 2 mg/ml fenofibrate was prepared from the solidified melts (solid dispersions). Approx. 1.5 ml of the suspension was added to the dispersant (water) in the Mastersizer 2000 (Malvern Instruments Ltd, UK) to achieve an obscuration of 6-11%. The dispersion was deagglomerated using ultrasound before particle size measurement.

RESULTS AND DISCUSSION

The melts solidified in two different ways. Either the melt formed a crystalline polymer matrix at the initial solidification stage or the melt first formed a glass and later recrystallised. The latter route of solidification is shown in Figure 1. The white areas are crystalline polymers distributed in the transparent glass phase. The fenofibrate crystal size was not affected by the solidification pathway. This was surprising because larger crystals were expected when the melt first solidified to a glass and later recrystallised because of the lower mobility in the glass phase compared to the liquid melt. According to crystallisation theory (3) the lower mobility should result in fewer fenofibrate crystal nuclei formed and hence a larger crystal size is to be expected.



Figure 1. Melts in the process of crystallising from a glass form. The white areas are the crystalline polymer matrix. The samples are a triplicate.

The median fenofibrate crystal size was in the range of 0.8-2.5 µm. Two examples of crystal size distributions are shown in Figure 2.

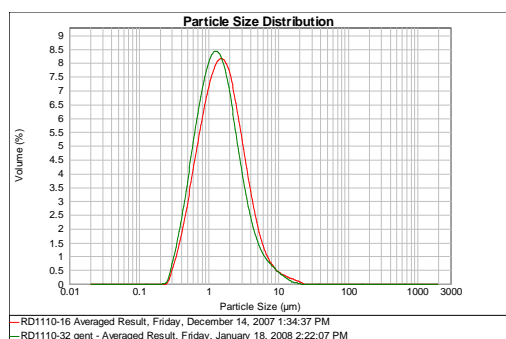


Figure 2. Examples of a fenofibrate crystal size distributions.

The ANOVA of the screening data showed the Poloxamer content to be the only significant ($p < 0.05$) factor. A higher Poloxamer content, which is inevitably interrelated to a lower PEG content, resulted in larger fenofibrate crystals. The resolution of the screening design did not allow statistical analysis of the complete two-way interactions. Instead the interactions were ranked according to their mean squares and the value was compared to the first order error mean square to give an estimate of the significance of the interaction. From this ranking it was observed that several two-way interactions had a significant influence on the crystal size. One of the significant interactions is shown in Figure 3.

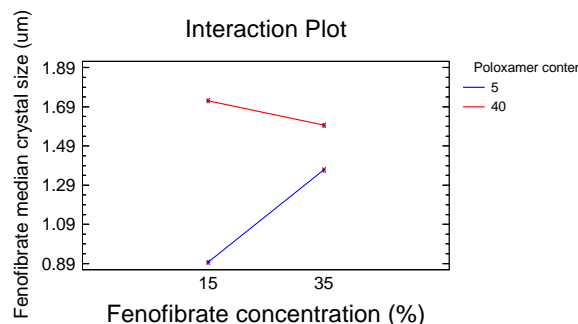


Figure 3. Interaction plot between fenofibrate concentration and Poloxamer content (5 or 40%).

It is seen that the lowest size crystals were obtained with a low fenofibrate concentration and low Poloxamer content.

The results showed that the composition ratio of the polymers (PEG-Poloxamer) and the ratio of polymers to fenofibrate had a larger influence on the crystal size than the cooling conditions. This indicates that the solubility of fenofibrate in the polymer along with intermolecular interactions between the constituents play a larger role in the crystallisation process than the cooling temperature.

CONCLUSION

It was found that the only significant factor involved in affecting the fenofibrate median crystal size in the solid dispersion was the Poloxamer content, which is interrelated to the PEG content. It was further observed that several two-way interactions between the factors are also involved in determining the crystal size. It is

therefore a complex matter to predict the fenofibrate crystal size recrystallised in the polymer matrix of the solid dispersion.

It was further seen that the ratio between the PEG-Poloxamer polymers and ratio of polymer:fenofibrate played a more prominent role than the cooling conditions for the resulting fenofibrate crystal size.

Lastly it was observed that the system either went into a crystalline phase or through a glass phase before the crystalline phase was formed. Surprisingly it was not possible to relate these solidification pathways to the resulting fenofibrate crystal size.

REFERENCES

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