In vitro and *in vivo* evaluation of an optimized fenofibrate lipid based solid dispersion produced by a PGSS process

A. Pestieau [1], S. Lebrun [2], B. Cahay [2], B. Evrard [1]
[1] University of Liege, [2] Galephar Research Center M/F

Purpose

The aim of this work is to study the interest of the PGSS (Particles from Gas Saturated Solutions) process for the production of fenofibrate lipid based Solid Dispersion (SD). By means of a design of experiments, a Gelucire® 50/13 formulation of fenofibrate and the PGSS process were optimized. Then, to evaluate the interest of this PGSS process, several Gelucire® based formulations of fenofibrate were assessed both *in vitro* and *in vivo*.

Methods

The PGSS formulation (fenofibrate + Gelucire® 50/13) and the PGSS process were optimized by means of a design of experiments. This optimal PGSS formulation was compared to a classical SD at the same concentration (220 mg of fenofibrate per gram of Gelucire®). This classical SD was obtained by melting both products together and micronizing this mixture to obtain a particle size comparable to the PGSS product. Initially, these two products were tested *in vitro* using a biphasic dissolution system. This system consisted of a USP II apparatus combined with the USP IV apparatus. Afterwards, both products were tested *in vivo*. This study was performed on Pietrain crossed Landrace pigs (n = 6) after an overnight fasting period of 12 h. The pharmacokinetic parameters C_{max}, T_{max} and AUC_{0-t} of fenofibric acid were calculated.

Results

Regarding the *in vitro* results (n = 6), the PGSS and the SD formulations had a very similar dissolution profile in the organic phase (f_2 = 61). However, the results were different in the aqueous phase. For the SD formulation, the maximal concentration (C_{max}) was reached after 10 h and decreased shortly afterwards. The average C_{max} was about 155 µg/mL and the calculated Maximum Supersaturation Ration (SR^M) was 1.89 ± 0.09. In comparison, for the PGSS formulation, C_{max} was reached earlier (7 h) and was maintained over a longer period (approximately 3 h). This average C_{max} was about 190 µg/mL and thus, the calculated SR^M was also higher (SR^M = 2.28 ± 0.14). Given these results, the improvement of the oral bioavailability of fenofibrate should be more pronounced with the PGSS formulation as a result both of supersaturation being maintained for a longer period and the higher SR^M value attained. Regarding the *in vivo* results (n = 6), the PGSS formulation showed a higher value of C_{max} and AUC_{0-t} compared to the SD formulation. The T_{max} value was also shorter for the PGSS formulation. Therefore, we can conclude that a good correlation of *in vitro* fenofibrate dissolution profiles and *in vivo* bioavailability can be established.

Conclusion

The optimized PGSS formulation and the classical SD were tested *in vitro* using a biphasic dissolution test and the observations in the aqueous phase seem to be well correlated with the results obtained *in vivo*. Therefore, the PGSS process is interesting compared to a classical method such as melt mixing for the production of fenofibrate lipid based SD. This could be probably explained by the high porosity of the produced powder and the reduced size of fenofibrate crystals generated by the process.