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

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1. INTRODUCTION

Solid dispersion (SD) is one of the most common strategies for improving the dissolution behavior of Biopharmaceutics Classification System (BCS) Class II compounds. In this study, we use a supercritical CO_2 (sc-CO_2) process for preparing SD, namely Particles from Gas Saturated Solutions (PGSS). The interest of this process was evaluated by testing several Gelucire® based formulations of fenofibrate *in vitro* and *in vivo*.

2. MATERIALS AND METHODS

Formation and optimization of fenofibrate solid dispersions

Particles were produced using a PGSS apparatus (Fig. 1) from Separex® (Champigneulles, France). It consisted of a saturation vessel (50 mL) equipped with a mechanic stirrer and an expansion chamber (18 L) connected to the saturation vessel through a manual valve and an expansion nozzle. The API was melted in the saturation compartment with Gelucire® 50/13 (Gattefossé, Saint-Priest, France). The melted mixture was put into contact with supercritical carbon dioxide and mixed during a predetermined period and speed at the established pre-expansion pressure and temperature conditions. The expansion valve was then opened and the gas saturated solution was expanded through a nozzle of a predetermined diameter.

The PGSS formulation (fenofibrate + Gelucire ® 50/13) and the PGSS process were optimized by means of a design of experiments [1]. This optimal PGSS formulation was compared to a SD produced by melt mixing at the same concentration (220 mg of fenofibrate per gram of Gelucire®). This SD was obtained by melting both products together and micronizing this mixture to obtain a particle size comparable to the PGSS product.

Fig. 1 : Photo of the PGSS equipment

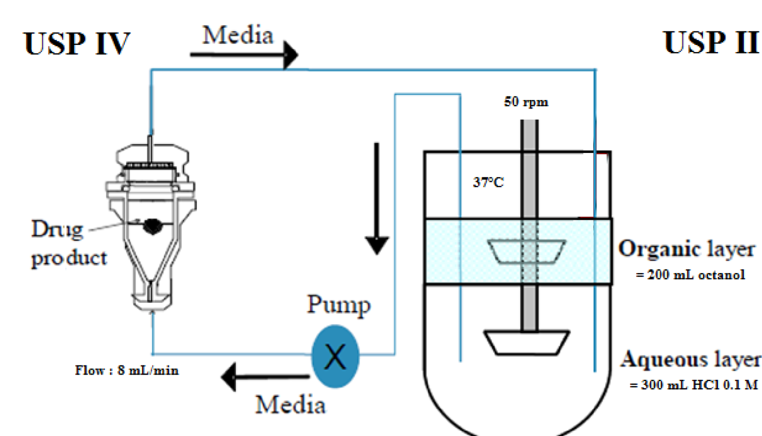


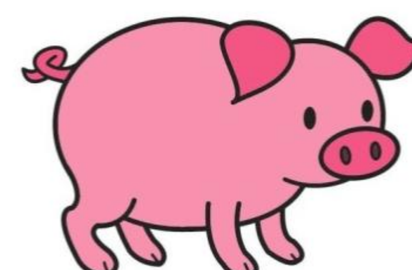
Fig. 2 : Schematic representation of the biphasic dissolution system

In vitro dissolution experiments

The *in vitro* dissolution test used was a biphasic dissolution test (Fig. 2). This biphasic system consisted of a aqueous phase (300 mL HCl 0.1 M) and an organic phase (200 mL octanol) in a USP II apparatus combined with an USP IV apparatus. Two dissolution profiles were determined (aqueous phase and organic phase) after quantification analysis of dissolution media samples by HPLC (n = 6).

In vivo experiments

The *in vivo* study was performed on Pietrain crossed Landrace pigs (n = 4) after an overnight fasting period of 12 h. Due to financial restrictions, this study was carried out according to a balance incomplete block design. The administered dose of fenofibrate was 2 mg/kg of body weight. After administration, blood samples (8 mL) were collected at time zero (pre-dosing), 1 h, 2 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 6.5 h, 8 h, 9 h, 10 h, 11 h, 12 h, 24 h and 36 h post-dosing. Fenofibric acid plasma concentrations were determined by liquid chromatography coupled to a tandem mass spectrometry detection system (LC-MS/MS, API 4000, AB Sciex, Toronto,Canada). The pharmacokinetic parameters C_{max}, T_{max} and AUC_{0-t} of fenofibric acid were calculated.



3. RESULTS AND DISCUSSION

In vitro study

Regarding the *in vitro* results, 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 10h 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 (7h) and was maintained over a longer period (approximately 3h). This average C_{max} was about 190 µg/mL and thus, the calculated SRM 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 SRM value attained.

$$SR^M = \frac{C_{max}}{C_s}$$

Fig. 3 : Dissolution profiles (n = 6) obtained in the aqueous phase of the biphasic dissolution test for the PGSS product (in orange) and the micronized solid dispersion (in green) at the same drug loading level (220 mg/g).

In vivo study

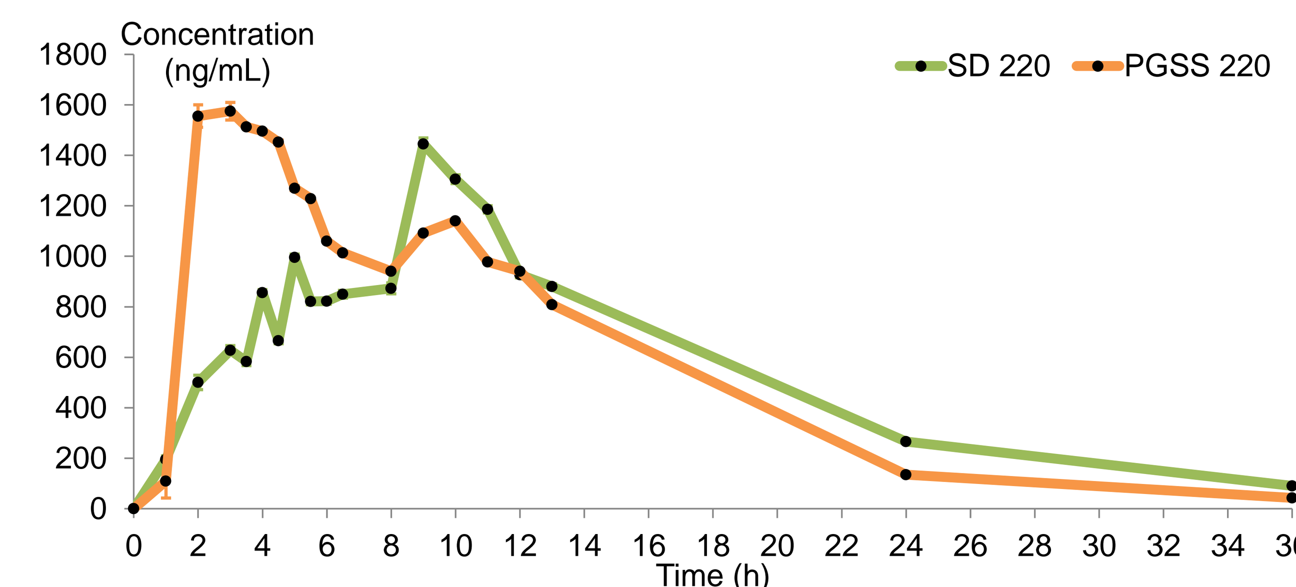


Fig. 4 : The mean measured (n = 4) plasmatic profiles of fenofibric acid after administration of the PGSS product (in orange) and the micronized solid dispersion (in green) at the same drug loading level (220 mg/g).

The mean measured plasmatic profiles of fenofibric acid after administration of the PGSS product and the micronized SD are shown in Fig.4. From these profiles, the pharmacokinetic parameters C_{max}, T_{max} and AUC_{0-t} were calculated (Table 1). 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. Regarding these results, the bioavailability of fenofibrate seems to be better after the administration of the PGSS formulation than after the administration of the micronized SD.

	C_{max} (ng/mL)	AUC	T_{max} (min)
SD 220	1536 ± 15	19216 ± 27	450
PGSS 220	2016 ± 12	19858 ± 27	190

Table. 1 : The calculated pharmacokinetic parameters of fenofibric acid after administration of the PGSS product (PGSS 220) and the micronized solid dispersion (SD 220) at the same drug loading level (220 mg/g). The variability was expressed by the Standard Error of Mean (SEM).

4. CONCLUSIONS

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.

5. REFERENCES

[1] *Pestieau, A., Krier, F., Lebrun, P., Brouwers, A., Streel, B., Evrard, B., 2015. Optimization of a PGSS (particles from gas saturated solutions) process for a fenofibrate lipid-based solid dispersion formulation. International Journal of Pharmaceutics 485, 295-305.*

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