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 CO₂ (sc-CO₂) process for preparing a PGSS formulation. 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

Particulates were produced using a PGSS apparatus (Fig. 1) from Saporé® (Champignelles, France). It consisted of a saturation vessel (50 mL) equipped with a mechanic stirs and an expansion chamber (19 L) connected to the saturation vessel through a manual valve and an expansion nozzle. The API was mixed with Polyethylene saturation component with Gelucire® 50/13 (Gattefosse, Saint-Priest, France). The melted mixture was put into contact with supercritical carbon dioxide and mixed during a predetermined period and speed, thus established pre-expansion pressure and temperature conditions. The expansion valve was then opened and the gasated 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]. The 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.

In vitro dissolution experiments

In vitro dissolution test used was a biphasic dissolution test (Fig. 2). This biphasic system consisted of an aqueous phase (300 mL, HCl 0.1 M) and an organic phase (200 mL, octanol). The 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).

The in vivo study was performed on Pietrain cross breed Landrace pigs (n = 4) after an overnight fasting period of 12 h. Due to financial restrictions, this study was carried out carrying to a balance incomplete with respect to the administration dose because fenofibrate was 2 mg/kg of weight. After administration, blood samples (8 mL) were collected at time zero (pre-dosing), 1, h, 2, h, 3, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, 12 h, 24 h and 36 h post-dosing. Fenofibric 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 Cmax, t1/2, and AUC0–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 with biphasic phase (Figs. 1 & 2). However, the results were different in the aqueous phase. For the SD formulation, the maximal concentration (Cmax) was reached after 10h and decreased shortly afterwards. The average Cmax was about 155 μg/mL and the calculated AUCmax was 155 ± 15 μg h/mL. For the PGSS formulation, Cmax was reached earlier (7h) and was maintained over a longer period (approximately 24h). This average Cmax was about 190 μg/mL, and thus, the calculated SRM was also higher (SRM = 2.28 ± 0.14). Given these results, the improvement of the oral bioavailability of fenofibrate should be more pronounced with a PGSS formulation as a result both of supersaturation being maintained for a longer period and the higher SRM value attained.

In vivo study

The mean measured plasmaic 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 Cmax, tmax, and AUC0–t were calculated (Table 1). The PGSS formulation showed a higher value of Cmax and AUC0–t compared to the SD formulation. The Tmax value was also shorter for the PGSS formulation. Regarding these results, the bioavailability of fenofibrate seems to be better achievable after the administration of the PGSS formulation than after the administration of the micronized SD.

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 administration of fenofibrate in SD should probably be explained by the high porosity and the produced powder and the reduced size of fenofibrate crystals generated by the process.

5. REFERENCES