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Research paper

Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: Comparison with commercial preparations

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Abstract

Several techniques were compared for improving the dissolution of fenofibrate, a poorly soluble drug. Particle size reduction was realized by jet milling (micronization; cogrinding with lactose, polyvinylpyrrolidone or sodium lauryl sulphate) and by media milling using a bead mill (nanosizing) with subsequent spray-drying. Solid state characterization by X-ray diffraction and Differential Scanning Calorimetry verified the maintenance of the crystalline state of the drug after dry milling and its conversion to the amorphous state during spray-drying. Micronization of fenofibrate enhanced its dissolution rate in biorelevant media (8.2% in 30 min) compared to crude material (1.3% in 30 min). Coground mixtures of the drug increased the dissolution rate further (up to 20% in 30 min). Supersaturated solutions were generated by nanosizing combined with spray-drying, this process converted fenofibrate to the amorphous state. Fenofibrate drug products commercially available on the German and French markets dissolved similarly to crude or micronized fenofibrate, but significantly slower than the coground or spray-dried fenofibrate mixtures. The results suggest that cogrinding and spray-drying are powerful techniques for the preparation of rapidly dissolving formulations of fenofibrate, and could potentially lead to improvements in the bioavailability of oral fenofibrate products.

Keywords: Biorelevant media; Cogrinding; Dissolution rate enhancement; Fenofibrate; Jet milling; Micronization; Particle size reduction; Spray-drying

1. Introduction

Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy.

Nowadays, pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs. Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states [1,2]. The increase in bioavailability after micronization of drugs, e.g., by jet or ball milling has been well documented (e.g., danazol [3], progesterone [4], digoxin [5]). Cogrinding processes are comparatively seldom described in the literature and have often employed large quantities of water-soluble polymers as dispersion carriers [6,7]. Reduction of particle size to the nanometer scale can be achieved by precipitation or by milling. The latter requires special techniques such as bead milling [8,9] or high pressure homogenization [10]. In order to obtain a dry form, further pharmaceutical operations are required (e.g., lyophilisation or spray-drying). Spray-drying is known to produce amorphous material due to rapid solvent evaporation [11].

Fenofibrate has been used for many years to lower cholesterol levels and its pharmacokinetic profile is well understood [12,13]. Originally launched in 1975, it is currently on

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the market in more than 85 countries [14]. The compound is practically insoluble in water [15,16] and has high lipophilicity (log $P = 5.24$) [12]. Thus the dissolution rate of fenofibrate is expected to limit its absorption from the gastrointestinal tract. Attempts to increase the oral bioavailability of the drug have therefore chiefly centered on particle size reduction. Increasing the rate and extent of dissolution of fenofibrate by micronization has been shown to lead directly to an increased oral bioavailability, which in turn enables dosage reduction [12]. Recently, ''suprabioavailable'' tablets have been developed combining the classic micronization process with a specific microcoating technology, through which micronized drug particles are coated onto hydrophilic polyvinylpyrrolidone (PVP) cores [14].

The current paper compares the production of fenofibrate preparations by several physical techniques including micronization; cogrinding with lactose, polyvinylpyrrolidone (PVP) and sodium lauryl sulphate (SLS); and nanosizing in a bead mill combined with spray-drying. These preparations were evaluated with respect to their X-ray diffraction (XRD), Differential Scanning Calorimetry (DSC) and dissolution behaviour. In vitro dissolution studies of the formulations were performed in biorelevant media and included comparison with two commercial fenofibrate products from the German market (Lipanthyl®, Lipidil®) and one product from the French market (Secalip®).

2. Materials and methods

2.1. Chemicals

Fenofibrate was purchased from Sigma (Steinheim, Germany). Its chemical structure is given in Fig. 1. SLS, lactose monohydrate and Polyvidone 25 (PVP) were from Merck KGaA (Darmstadt, Germany). Sodium taurocholate was obtained from Prodotti Chimici E Alimentari S.P.A. (Basaluzzo, Italy). Egg-phosphatidylcholine, Lipoid E PC, was purchased from Lipoid GmbH (Ludwigshafen, Germany). All other chemicals used were of HPLC grade or analytical grade. Commercial products of fenofibrate were Lipanthyl® (lot 77744/NK, expiry 01/2009), Lipidil® (lot 74493, expiry 01/2006) and Secalip® (lot 74185, expiry 02/2008).

2.2. Solubility determination

The solubility of fenofibrate was determined in water and the biorelevant media FaSSIF (Fasted State Simulated Intestinal Fluid) and FeSSIF (Fed State Simulated Intestinal Fluid) [17] using a standardized shake flask method at 37 °C with shake times of 48 h. The sample was then filtered through a 0.22 μm membrane filter and the filtrate was assayed per HPLC.

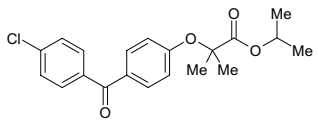

Fig. 1. Chemical structure of fenofibrate (MW = 360.8).

2.3. Preparation of physical mixtures and commercial products

Physical mixtures were prepared by physically blending fenofibrate (10%) with excipient(s), and then manually filling the blend into Coni-Snap Supro A hard gelatine capsules (Conisnap, Belgium). The commercial products of fenofibrate were all hard gelatine capsules. They were quantitatively emptied, then appropriate amounts of the powder accurately weighed and manually filled into Coni-Snap Supro A hard gelatine capsules.

2.4. Preparation of micronized drugs and coground mixtures

Micronized fenofibrate and coground mixtures were prepared by milling the drug by itself or as a physical mixture with various excipients in an Alpine 50 AS jet mill (Hosokawa Alpine AG, Germany) operating at 5 bar air pressure and a feed rate of 0.5–1.0 g/min. The milled powder was then manually filled into Coni-Snap Supro A hard gelatine capsules, after blending with lactose (if necessary) to obtain a concentration of the active substance of 10%. Homogeneity of the mixtures was confirmed by quantitative HPLC determination of the drug content after accurate weighing of an aliquot of powder ($n = 3$), dissolving and diluting with mobile phase.

2.5. Preparation of spray-dried powder

A nanoparticulate dispersion of fenofibrate was prepared by a media milling process using a Dyno Mill (Willy A. Bachofen AG Maschinenfabrik, Switzerland) operating in the circulation mode. A 300 ml cylindrical steel vessel with inside coating was filled with 0.1 mm grinding spheres to fill approximately 85% of the volume. A 600 ml suspension containing 30 g fenofibrate, 30 g lactose and 3 g SLS in water was pre-treated in an Ultra-Turrax at 20,500 min^{-1} before processing in the mill for 90 min – it had been previously demonstrated that nanoparticles are produced quantitatively after that period of milling. A Büchi Mini Spray Dryer B-191 (Büchi Labortechnik AG, Switzerland) was connected directly to the mill, enabling continuous transfer of the suspension from the milling chamber outlet to the spray nozzle. The mill was kept operating during the spray-drying process in order to maintain homogeneity of the suspension. Just before starting the spray dryer, the nanoparticulate suspension was diluted with 300 ml water. The spray dryer was fitted with a 0.7 mm pneumatic nozzle and operated at 6 bar air pressure, 11 ml/min pump speed, 600 l/h air flow rate, 80% aspirator level and 150 °C inlet temperature.

2.6. Particle size measurement

Particle size was determined by laser light diffraction. The equipment consisted of a Malvern Mastersizer 2000 (Malvern Instruments, Germany) including a Scirocco 2000 module for dry measurement purposes operating at 3.0 bar air pressure for dispersion – it had been established that a sufficient dispersion of particles but no milling occurs at this level of air pressure – with evaluation of data by Malvern software version 4.0 using the Fraunhofer approximation as the evaluation algorithm [18].

2.7. HPLC analysis

The system consisted of a Merck Hitachi pump L-6200 A, a Merck Column Thermostat T-6300 operating at 36 °C, a Merck Hitachi Interface D-6000 A, a Merck Hitachi UV–Vis Detector L-4250 and a Merck Hitachi Autosampler AS-4000 A. Data acquisition and evaluation was performed with Merck Hitachi D-7000 Chromatography Data Station Software version 4.0. Using a LiChrospher 60 RP select B 125-3 (5 μm) column and a mobile phase consisting of 40% of pure water and 60% of acetonitrile at a flow rate of 1.35 ml/min, fenofibrate was eluted at approximately 3 min. The detection wavelength was set at 288 nm.

2.8. X-ray diffraction studies

Powder X-ray diffraction was used to assess the degree of crystallinity of micronized, coground and spray-dried fenofibrate at ambient temperature using a Bruker AXS diffractometer (Bruker AXS GmbH, Germany) with a PSD-50 M detector and EVA Application Software version 6. Measurements were performed with a Cu Kα radiation source at 40 kV voltage, 30 mA current and a scanning speed of 2°/min.

2.9. Differential scanning calorimetry

DSC curves were obtained by a Differential Scanning Calorimeter (DSC 821^e, Mettler-Toledo, Switzerland) at a heating rate of 5 K/min from 25 to 250 °C under nitrogen.

2.10. Dissolution testing

Release from the capsules was determined in a calibrated USP XXVIII apparatus 2 (paddle method) in 900 ml medium using a PharmaTest dissolution tester (Type PTWS, PharmaTest, Germany) operating at 75 rpm and 37 °C. Helix sinkers (11/31, 8/23, Sotex GmbH, Germany) were used to prevent floating of the capsules. Samples were taken according to USP guidelines by withdrawal of 3 ml at each sampling time. Each sample was immediately filtered through a 0.2 μm PTFE filter and appropriately diluted with HPLC mobile phase prior to analysis.

2.11. Statistical evaluation and presentation

Results from solubility determinations ($n = 3$) and dissolution studies ($n = 3$) are presented as mean values with standard deviations. Particle size distribution data, $d(0.10)$, $d(0.50)$ and $d(0.90)$, are reported based on volume.

3. Results and discussion

3.1. Solubility studies

Table 1 summarizes the experimentally determined solubility of fenofibrate in pure water, FaSSIF and FeSSIF as well as in the corresponding buffers free of bile components (blank media). With an aqueous solubility of 0.3 μg/ml (at 37 °C), fenofibrate is clearly poorly soluble. FaSSIF and FeSSIF sharply increase the solubility of fenofibrate. With a reported log P of 5.24 [12], it is to be expected that fenofibrate would be solubilised well by micellar structures [19,20]. Even so, at a dose of 60 mg, fenofibrate still exhibits high dose:solubility ratios: 4.4 L in FaSSIF and 1.7 L in FeSSIF. The solubility of fenofibrate is therefore expected to limit its absorption from the gastrointestinal tract.

3.2. Dissolution studies after dry milling processes

In Fig. 2 the dissolution of three coground mixtures of fenofibrate is compared with a physical mixture of lactose and micronized fenofibrate and also with unprocessed fenofibrate. Dissolution from unprocessed fenofibrate approximated zero order kinetics with a very slow dissolution rate (<10% in 3 h). The enhancement of the dissolution rate from crude to micronized fenofibrate is in accordance with its pronounced particle size reduction (Table 2).

Physically mixing lactose with micronized fenofibrate resulted in a further improvement in the dissolution rate, but fenofibrate still took over 3 h to approach the saturation limit. By contrast, the mixture coground with lactose reached the saturation limit within 30 min. The superiority of the coground mixture over the physical mixture cannot be explained simply by particle size changes: the particle size distribution was slightly coarser after cogrinding. It is likely that the presence of the hydrophilic lactose on the fenofibrate surface enabled more effective wetting of the coground powder mixture. The mixture coground with lactose and SLS optimized the dissolution rate of fenofibrate further, reaching the saturation limit within 15 min. It is hypothesized that the wettability of the small lipophilic

Table 1
Solubility study of fenofibrate in various media at 37 °C in μg/ml (mean ± SD)

Water	Blank FaSSIF	FaSSIF	Blank FeSSIF	FeSSIF
0.3 ± 0.0	0.2 ± 0.0	13.7 ± 0.5	0.2 ± 0.0	35.6 ± 1.0

fenofibrate particles was further improved by the presence of the surfactant.

Cogrinding of fenofibrate with PVP was slightly less successful in increasing the dissolution rate than the coground mixture with lactose. Polymers, including PVP, are known to be able to surround fine drug crystals, hindering their recrystallization from solution [21,22] by reducing the surface area for crystallization on the drug particles – but this can also hinder dissolution by forming a barrier to penetrating water molecules [23–25].

Dissolution rate enhancement of drugs by cogrinding with surfactants is often caused by generation of amorphous drug [26,27]. Indeed, the mechanical stress associated with milling may cause partial amorphous states, since the particle surface may be destabilized by the energy input, generating an amorphous layer on the crystalline core [28]. In the jet milling experiments, however, fenofibrate was found to maintain its crystallinity. Identical X-ray patterns and a very sharp melting endotherm in the DSC thermogram (onset approximately 80 °C) for unprocessed and jet milled fenofibrate verified the crystalline structure of the drug (Fig. 3). Thus, cogrinding provides a technology for enhancing dissolution without changing the crystalline form of the drug. This may be advantageous in terms of the physical stability of the drug, maintaining the release properties of the drug product with time.

For highly lipophilic compounds like fenofibrate, it has been hypothesized that the uptake across the gut membrane is very efficient, resulting in sink conditions in the gut lumen, where the drug is dissolving. In such cases, an enhancement in dissolution rate would be expected to be reflected in a higher absorption rate and hence bioavailability, even when no supersaturation occurs.

Table 2
Particle size distribution of fenofibrate in various formulations and commercial products

	$d(0.10)$ (μm)	$d(0.50)$ (μm)	$d(0.90)$ (μm)
Fenofibrate, crude	1.7	7.7	40.9
Fenofibrate, micronized	0.9	2.2	4.2
Fenofibrate/lactose	0.9	3.8	8.0
Fenofibrate/PVP	0.6	2.6	5.2
Fenofibrate/SLS/lactose	0.8	1.9	3.7
Fenofibrate, co-spray-dried	0.8	1.6	3.5
Lipanthyl® powder	2.9	42.7	231.3
Lipidil® powder	1.9	19.9	242.9
Secalip® powder	2.9	38.8	206.2

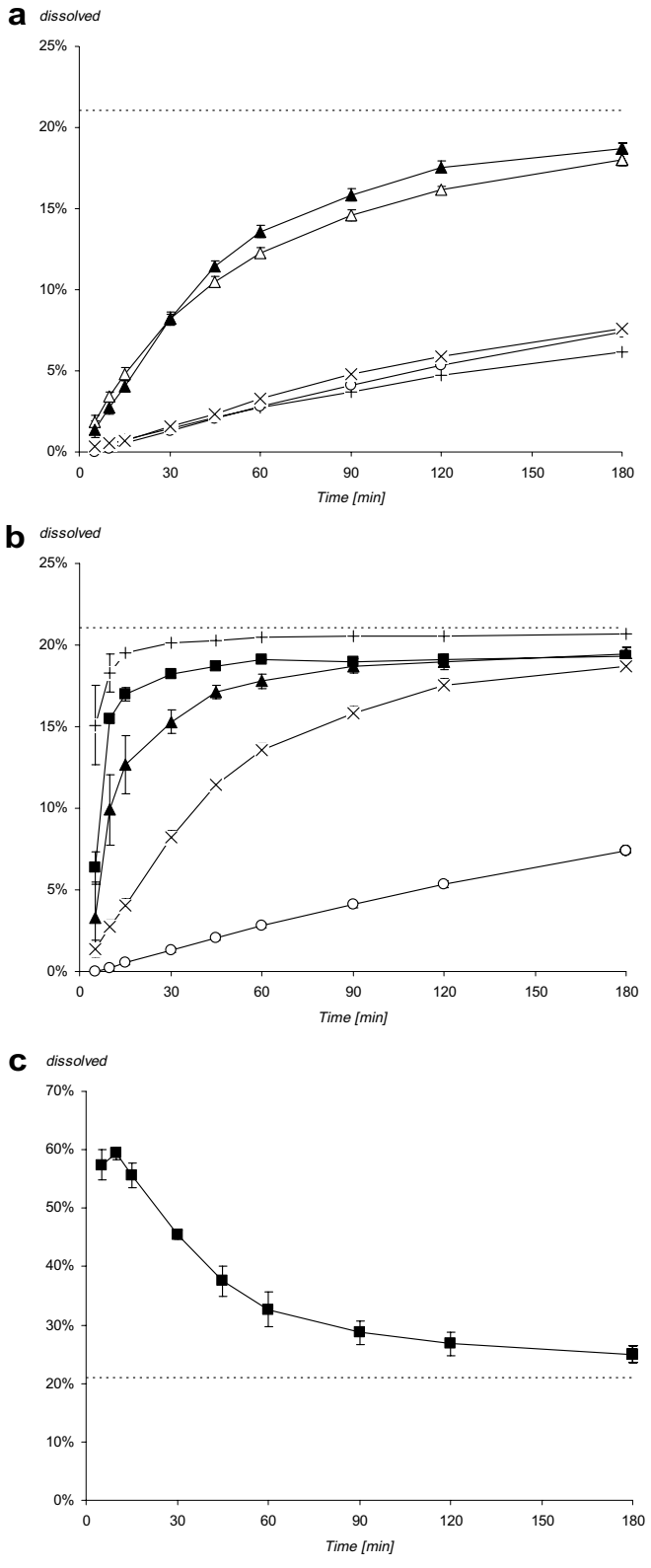

Fig. 2. Dissolution profiles of 60 mg fenofibrate in FaSSIF ($n = 3$, ±SD). (a) Comparison of commercial preparations: (▲) indicates micronized active in physical mixture with lactose. (○) indicates unprocessed drug substance in physical mixture with lactose. (△) indicates Lipidil® powder; (+) indicates Lipanthyl® powder; (×) indicates Secalip® powder. (b) Coground mixtures: (○) indicates unprocessed drug substance in physical mixture with lactose; (×) indicates micronized active in physical mixture with lactose; (■) indicates a binary coground mixture with lactose; (▲) indicates a binary coground mixture with PVP (1:1), physically blended with lactose; (+) indicates a tertiary coground mixture with SLS/lactose (1:44). (c) Spray-dried formulation with lactose and SLS. Dotted lines indicate the fenofibrate solubility limit in the medium.

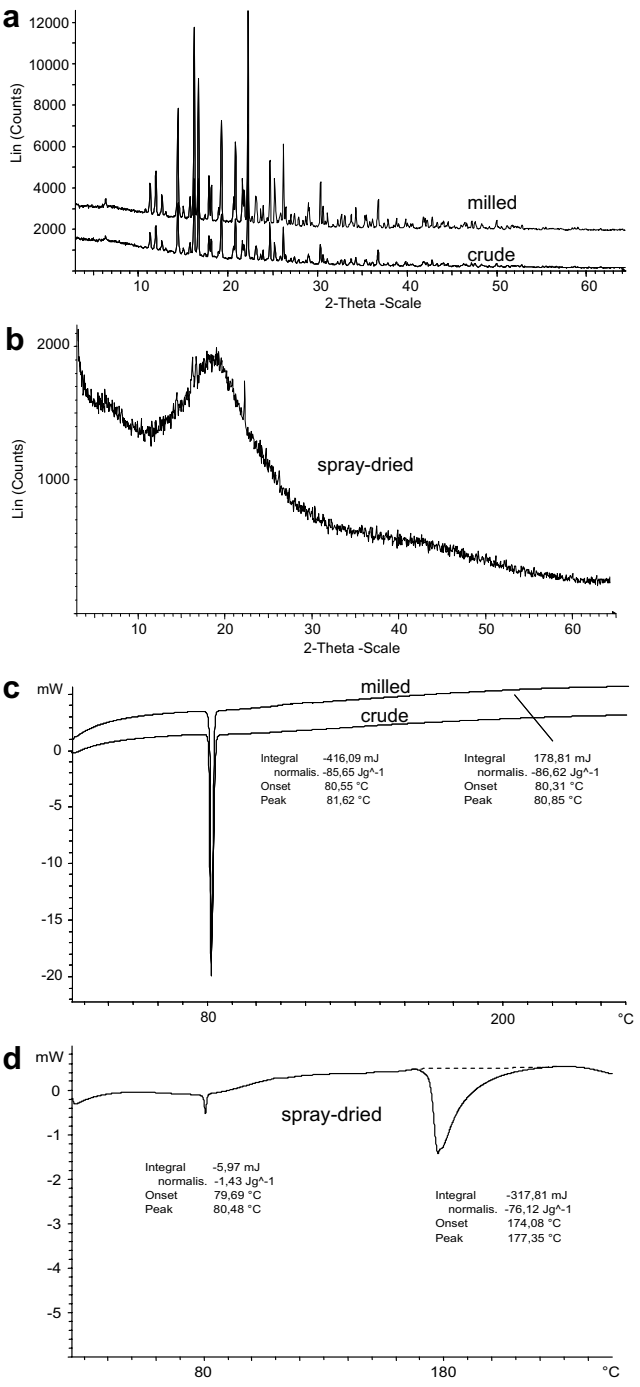

Fig. 3. X-ray analysis (a and b) and DSC (c and d) of untreated and milled fenofibrate as well as the spray-dried drug.

3.3. Dissolution studies after nanosizing/spray-drying

Fig. 2 also shows the dissolution profile in FeSSIF of fenofibrate prepared by nanosizing and spray-drying. The formulation, which contained lactose and SLS, reached a supersaturation, with peak concentrations at 10 min. This initial supersaturation proved to be unstable: recrystallization and precipitation occurred rapidly and the concentration returned to the saturation limit within about 3 h. The

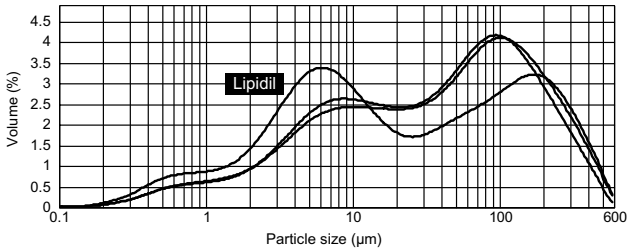

Fig. 4. Particle size distribution (frequency curves) of the commercial fenofibrate powders Lipidil®, Lipanthyl® and Secalip®.

generation of the supersaturated solution could be attributed to the almost complete conversion of crystalline to amorphous fenofibrate. Fig. 3 demonstrates that only very small crystalline spikes, which correspond to the crystalline form of the unprocessed drug substance, occurred on the amorphous halo in the X-ray diffraction pattern. The excipients were also converted to the amorphous state, whereby the content of SLS may have been too small to reliably detect reduced amounts of the crystalline form. Correspondingly, DSC investigation confirmed a very minor melting endotherm for fenofibrate (onset approximately 80 °C) in the nanosized/spray-dried formulation.

3.4. Dissolution studies of commercial fenofibrate formulations

Particle size and dissolution from the commercial fenofibrate products Lipanthyl® and Lipidil® (German market) and Secalip® (French market) were compared to the fenofibrate formulations prepared by micronization, cogrinding and nanosizing/spray-drying. Fig. 4 illustrates the particle size distribution of the commercial fenofibrate powders. Lipanthyl® and Secalip® exhibited identical frequency curves. Lipidil® showed higher quantities of smaller particles, but, generally, the overall particle size distributions of the powders do not allow a firm conclusion to be drawn about the relative particle size of the active drug. Fig. 2 reveals that the dissolution profiles of Lipidil® powder and micronized fenofibrate on the one hand, and those of Lipanthyl® powder, Secalip® powder and unprocessed fenofibrate on the other hand, are identical, implying that Lipidil® contains the drug in a micronized form while Secalip® and Lipanthyl® appear to contain coarse fenofibrate. The coground and spray-dried products prepared in our laboratories showed a much higher dissolution rate.

4. Summary and conclusion

Commercial products of fenofibrate (Lipanthyl® and Secalip®) show poor dissolution rates, similar to that of unprocessed fenofibrate powder. Lipidil® powder showed enhanced dissolution, similar to that of micronized fenofibrate. Nonetheless, the dissolution performance of all three commercial products was significantly lower compared to coground mixtures. Fenofibrate was maintained

in crystalline state after cogrinding, which may be advantageous in the context of maintaining the release characteristics of the product over time. Spray-drying of a nanoparticulate fenofibrate suspension prepared by media milling generated amorphous fenofibrate, which showed an unstable supersaturation in biorelevant media.

In conclusion, cogrinding and nanosizing/spray-drying are powerful techniques for the preparation of rapidly dissolving formulations of fenofibrate. Both processes could potentially lead to better bioavailability of fenofibrate drug products.

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