Comparative In Vitro and In Vivo Evaluation of Fenofibric Acid as Anti-Hyperlipidemic Drug

Yulias Ninik Windriyati, Yeyet Cahyati Sumirtapura, Jessie Sofia Pamudji
School of Pharmacy, Bandung Institute of Technology, Bandung, Indonesia

ABSTRACT:

Introduction: Fenofibric acid (FA) is antihyperlipidemic agent and commercially available as a tablet formulation weighs 840 mg for 105 mg active substance. A new formulation with less inactive substance was developed as an alternative to conventional formulation. The purpose of this study was to evaluate the dissolution study and the relative bioavailability of the surface solid dispersion (SSD) and conventional formulations of FA by comparing them to the reference formulation in its commercial tablets. The in vitro-in vivo correlation (IVIVC) among these tablet formulations was also evaluated.

Materials and Methods: The dissolution study was performed in phosphate buffer pH 6.8 and biorelevant Fasted State Simulated Intestinal Fluid (FaSSIF). Dissolution efficiency (DE) and mean dissolution time (MDT) was used to compare the dissolution profiles. The bioavailability study using nine healthy volunteers was conducted based on a single-dose, fasted, randomized, crossover design. The in vivo performance was compared using pharmacokinetic parameters $C_{\text{max}}$, $T_{\text{max}}$, $AUC_{0-72}$, and $AUC_{0-\infty}$. Linear correlation model was tested using MDT and mean residence time (MRT).

Results: The results indicated that there were significant differences found in the dissolution performances and no significant differences observed among the mean $C_{\text{max}}$, $T_{\text{max}}$, $AUC_{0-72}$, and $AUC_{0-\infty}$, estimated from the SSD, conventional, and reference formulations. Poor correlation was found between MRT and MDT of three formulations.
**Discussion and Conclusion:** The SSD formulation led to an instantaneous dissolution of the drug due to the presence of the polymer and physical structure of the SSD. The conventional formulation could not achieve rapid dissolution despite it satisfied the requirement for immediate drug release dosage form. The both formulations could be considered bioequivalent with reference. The *in vitro* dissolution behavior of FA using single medium did not reflect their *in vivo* properties at the fasted condition. There was no correlation between the *in vitro* dissolution and the *in vivo* bioavailability of fenofibric acid at this condition.

**Keywords:** fenofibric acid; surface solid dispersion; dissolution; bioavailability; correlation
INTRODUCTION

Fenofibric acid (FA), the active moiety of fenofibrate, is an antihyperlipidemic agent because it is the synthetic ligand that binds to nuclear peroxisome proliferator-activated receptors alpha (PPARα)\(^1\)-\(^3\). FA is a carboxylic acid moiety, while fenofibrate is an ester moiety\(^4\). Figure 1 shows the chemical structures of both FA and fenofibrate. In its marketed form, fenofibrate is insoluble and recommended to take with food, and it typically includes non-micronized tablets, micronized capsules, micro-coated micronized tablets, and hard gelatin capsules. The nanocrystal formulation of fenofibrate and the conventional formulation of FA currently available in the market can be taken with or without food\(^3\). A single 105-mg dose of FA is bioequivalent to a single 145-mg dose of fenofibrate in both fed and fasted states\(^5\). Not only is the production of the nanocrystal formulation of fenofibrate inflexible, but the expensive cost is also necessary to take into account. As a result, FA has been chosen and developed as an alternative to fenofibrate for oral administration.

Like fenofibrate, FA mainly absorbed from the gastrointestinal (GI) tract. However, it does better than the first, causing its bioavailability to be higher than that of fenofibrate in all GI regions\(^6\). The absolute oral bioavailability of FA in rats stands at 40%\(^7\). Physicochemically, FA is characterized as a poorly soluble weak acid drug. The pKa of FA is determined\(^4\), and the log P is calculated 3.85\(^8\). FA has relatively poor solubility at gastric pH (the pH is lower than its pKa), but it has fairly good solubility at intestinal pH\(^9\). The solubility of FA is 162.5 µg/ml in water and 1156 µg/ml at pH 6.8\(^9\). Due to its adequate permeability, FA is classified as a class II drug in the Biopharmaceutical Classification System (BCS) subclass (a) for the weak acid\(^10\). The poor solubility of FA in water may cause its dissolution to be reasonably slow and its bioavailability to be unpredictable.

Recently, FA is commercially available as a tablet formulation, namely Fibricor\(^\circledR\) (the brand for 105-mg FA). The weight of this formulation is 840 mg and consists of so many ingredients for the active substance of 105 mg. The dosage form of FA with the increased dissolution is developed to examine other possible platforms. The dissolution rate of BCS class II drugs is the limiting step for their oral bioavailability. The surface solid dispersion formulation is accepted as a method to improve the dissolution rate and bioavailability of poorly soluble drugs. The distribution of drug particles on the carrier surface can enhance wettability, dissolution rate, and
consequently bioavailability of drugs\textsuperscript{11,12}. The FA surface solid dispersion has been investigated. In the simulated intestinal fluid, the data showed that the dissolution of FA increased more than that of the pure drug\textsuperscript{13}. In this study, a new FA formulation with enhanced dissolution and less inactive ingredients was developed and evaluated for the \textit{in vitro} and \textit{in vivo} performance, which has never appeared in any publication.

The drug dissolution rate and bioavailability are influenced by the manufacturing process and the changes happening during the formulation. Therefore, bioavailability issues are frequently used to assess the safety and efficacy of drug products. Only two studies have been reported so far to enhance the dissolution and bioavailability of FA. The FA-loaded pellet is prepared with magnesium carbonate and k-carrageenan employing the extrusion/spheronizing technique followed by coating with ethyl cellulose. The pellet is bioequivalent to the commercial product in beagle dogs\textsuperscript{14}. Additionally, the mixture of FA and magnesium carbonate at a weight ratio of 2/1 can improve the solubility, dissolution, and oral bioavailability of FA\textsuperscript{9}. No information about the \textit{in vitro-in vivo} correlation (IVIVC) of this drug is available. One of the challenges of biopharmaceutics research is to figure out the correlation of the \textit{in vitro} drug release information of various drug formulations with the \textit{in vivo} drug profiles. In relation to FA, the correlation between the dissolution rate and the \textit{in vivo} performance is likely to predict.

This study tries to describe the results of both the bioavailability and the dissolution of the two tested formulations and the immediate-release reference formulation. The formulations tested in this study are the surface solid dispersion (SSD) and conventional methods. The \textit{in vitro} dissolution characteristics of these tablets exhibited different release pattern, meaning the correlation between the \textit{in vitro} dissolution and the \textit{in vivo} bioavailability of these tablet formulations have also been under investigation.

**MATERIAL AND METHODS**

**Materials**

The FA and the standard FA used in this study were purchased from BOC Science and Sigma, both of which are based in USA. While other materials such as croscarmellose sodium (CS), Avicel PH 101, lactose monohydrate, Manihot starch,
magnesium stearate, and talc were obtained from the local supplier in Indonesia. The 105-mg Fenofibric acid® (FA®) tablets, the generic version of Fibricor® reference tablets (Mutual Pharmaceutical), were bought from International Pharmacy, USA. The biorelevant medium FaSSIF was purchased from Biorelevant.com Ltd, Croydon, UK. Then, a number of materials were acquired from the Merck Group of Germany, including sodium hydroxide, potassium dihydrogen phosphate, sodium dihydrogen phosphate monohydrate, and sodium chloride. In addition, the distilled water used for all dissolution experiments and all other reagents were of analytical grade. The internal standard of 4’-chloro-5-fluoro-2-hydroxy benzophenone (CFHB) was obtained from Apollo Sci (UK), the blank plasma from Indonesia Red Cross, Bandung (Indonesia), and the rest (methanol, ethyl acetate, hydrochloric acid, and acetonitrile) from JT Baker (USA). All reagents used herein were of analytical grade, with the exception of acetonitrile of HPLC grade.

Methods

Preparation of surface solid dispersion and conventional formulations

The SSD formulation of FA with CS (1:1 w/w) was prepared by the solvent evaporation method. At first, the drug was dissolved in ethanol to obtain a clear solution. The carrier CS was then dispersed in the drug solution, and the solvent was removed using a rotary evaporator. The viscous residues produced were made dry in an oven with a temperature of 40°C to allow complete evaporation of ethanol in order to obtain the constant weight of powder. Subsequently, the mass was passed through a 40-mesh sieve to get dry free-flowing powder ready for compression into tablets by the direct compression method. Avicel PH 101 and magnesium stearate (1% w/w) were later added as a diluent and lubricant. The characteristic of this mixture was checked out for flowability and compressibility before the compression of this mass into tablets was conducted. The blend was compressed by a single punch tablet press with punch size 10 mm into 300-mg tablets with the FA concentration of 105 mg.

The conventional formulation was prepared by the wet granulation method. The drug was mixed thoroughly with lactose monohydrate as a diluent and then granulated with starch paste 10% w/w. The dried granules were incorporated with dried starch (10% w/w), magnesium stearate (1% w/w), and talc (2% w/w). The same procedures
of flowability, compressibility, and compression also applies to this mixture with the same tablet press, punch size, and FA concentration. Besides the above formulations, the reference formulation of FA was also used in this study. FA\textsuperscript{®} itself is actually a generic version of Fibricor\textsuperscript{®}, whose formulation contains fenofibric acid, copovidone, crospovidone, magnesium stearate, and microcrystalline cellulose in its 840-mg tablet weight.

**Drug content uniformity in tablet formulations**

In each formulation, the tablet samples were weighed accurately and transferred into a 100-mL volumetric flask. The solvent mixture of 2 M urea and 1 M sodium citrate (5 mL each) was added, and the mixture was heated for 15 minutes. This procedure was performed for the solubilization of FA, and the solvent mixture was used as a hydrotropic agent\textsuperscript{15}. The solution was eventually filtered through a Whatman filter paper, while the remaining filtrate was diluted with distilled water and analyzed by using a UV/Vis Spectrophotometer (Shimadzu 1800A) at 299 nm. The FA concentration was determined based on the calibration curve previously built. The experiment with the drug content was repeated three times, and the results were expressed as the mean ± standard deviation (SD).

**Dissolution studies**

The release characteristics of the tested formulations and the reference formulation were evaluated for the dissolution rate in Type 2 (paddle) dissolution apparatus (Electrolab TDT-08L, USP), using 500 mL of phosphate buffer pH 6.8, and the biorelevant medium FaSSIF was maintained at 37 ± 0.5 °C. The paddle rotation speed was set at 50, 75 and 100 rpm. The samples were taken at specified time intervals and replaced with equal volumes of fresh dissolution media to keep the constant volumes in the flasks. The samples were filtered through membrane 0.45 µm. The filtered samples were diluted with the dissolution medium, the FA concentration was determined by a UV/Vis spectrophotometer at the wavelengths of 298.7 nm for phosphate buffer and 299 nm for FaSSIF. The FA concentration was determined based on the calibration curve previously built. The dissolution experiment was conducted three times, and the results were expressed as the mean values of the dissolution efficiency parameter DE\textsubscript{60} (%).
Bioavailability studies

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine Universitas Padjadjaran Bandung (897/UN6.C.10/PN/2017) in accordance with Declaration of Helsinki and International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines. There were nine eligible subjects used in this study. The subjects taken were all healthy and male. The age of participants varies from 22 to 48 years, weight from 47 to 68 kg, and height from 155 to 175 cm. These criteria follow the standard body mass index 18-25 kg/m^2. Besides, they were required not to have any significant medical history and evidence of hepatic, renal, gastrointestinal, or hematological disorders; acute or chronic diseases; clinically significant abnormalities; or drug abuse or allergy. Also, they were instructed to abstain from taking any concomitant medication, food supplement, or herbal medicine for at least 14 days prior to and during the study. The exclusion was made to those who participated in any clinical study or used investigational drugs within the past 30 days prior to starting this study. In addition to it, caffeine-containing beverages were not allowed during the study being conducted. All chosen participants were given written informed consent forms after the nature and purpose of the study was explained.

The protocol applied the randomized, three-way crossover design with nine subjects in each period. In the first period, after an overnight fasting and a pre-dose blood sampling, every subject was given a single dose of any formulation in a random way along with 250 ml of water. Food and drinks (other than water 2 hours after dosing) were not allowed until 4 hours after dosing. Standard meals for both lunch and dinner were served at the 4th and 10th hour respectively, while snack at the 8th hour after drug administration. Blood pressure, heart rate, respiration rate, and adverse events were monitored during blood sampling. Approximately 5 ml of the serial venous blood samples were drawn using drawing needles 22G into vacuette tubes containing 100 µL of sodium citrate 0.485 M as the anticoagulant at pre-dose (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 h post-dose^5. The blood samples were centrifuged with Germany's EBA 20 Hettich at 5000xg for 15 minutes, and the plasma samples were separated and kept frozen at -20°C in three Eppendorf tubes with distinct codes until the analysis was done. The participants returned on a non-confined basis for continued pharmacokinetic blood sampling at
36, 48, and 72 h after drug administration in each period. After one-week washout, they were requested to return to the laboratory for the same blood sample analysis as to complete the crossover design.

**HPLC Assay**

The concentration of FA in plasma was determined using the HPLC method, developed and validated by Shah et al., 2014\textsuperscript{16}. CFHB was used as the internal standard (IS). The method has been verified before being used in the study. Stock solutions of 1 mg/mL were prepared for FA and CFHB respectively and were diluted in methanol to obtain seven FA-containing standard solutions of 0.05-20 µg/mL and one IS-containing solution of 250 µg/mL. All of these solutions were then stored at the temperature of -20°C. The calibration curve was established by spiking the working standard solutions (50 µL) and the IS solution (50 µL) into drug-free human plasmas (450 µL). In relation to the concentration, matrix-matched FA solutions were prepared in plasmas at various concentrations of 0.05, 0.1, 0.5, 1, 5, 10, 20 µg/mL, whereas IS solution was at concentration 250 µg/mL. The similar method was employed to prepare for QC samples in human plasmas. In this study, four additional QC samples were of 0.05, 0.5, 10 and 15 µg/mL.

The analytical separation was performed on an Inertsil® C18 (4.6 x 150 mm, Waters) column, and the mobile phase was the gradient of acetonitrile and 0.01 M phosphate buffer pH 2.8 (75:25), with the flow rate of 1 mL/min which runs for 7 minutes. The samples were detected at 287 nm (Waters 2487 dual λ absorbance detector). The retention times for both FA and CFHB as the IS were 3.5 and 5.5 min respectively. No interfering peaks were observed at both retention times. A typical chromatogram is shown in Figure 2. The limit of quantification for FA was 0.05 µg/mL. Plasma concentrations of FA were obtained from standard curves linear over a range of 0.05-20 µg/mL.

**Plasma sample and preparation**

Samples were prepared using the liquid-liquid extraction technique. Into 500 µL plasma sample, 50 µL of IS solution (250 µg/mL) and 1 mL of 1 N HCl were added and mixed for 30 seconds in a vortex mixer. Three mL of ethyl acetate was put on, and the mixture was mixed in a roller mixer for 30 minutes, followed by centrifugation for 15 minutes at 5000xg. The top organic layer was separated and evaporated for
drying at 40°C using a stream of nitrogen. The residue was reconstituted in 100 µL of the mobile phase, and 60 µL was injected into the HPLC system (Waters 1525 binary pump).

**Dissolution data analysis**

Dissolution efficiency (DE) was used for comparison of dissolution rates, calculated from the area under the dissolution curves at 60 minutes, and expressed as a percentage of the rectangle area described by 100% dissolution within the same time. ANOVA was used to compare the DE of test and reference tablets profiles at 60 min (α = 0.05).

**Pharmacokinetic analysis**

The pharmacokinetic parameters were calculated by a non-compartmental method. The elimination rate constant (\(K_{el}\)) was obtained from the least-square regression log-linear portion (the last 3-5 points) of the plasma concentration-time profile. The area under the curve to the last measurable concentration (\(\text{AUC}_{0-t}\)) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity (\(\text{AUC}_{0-\infty}\)) was estimated with an equation of \(\text{AUC}_{0-t} + C_t / K_{el}\), where \(C_t\) is the last measured concentration. The peak plasma concentration (\(C_{\text{max}}\)) and the corresponding time to peak (\(T_{\text{max}}\)) were estimated by inspecting the individual drug plasma concentration-time profiles.

**Statistical analysis**

For the parameters of \(\text{AUC}_{0-t}\), \(\text{AUC}_{0-\infty}\), \(C_{\text{max}}\), \(T_{\text{max}}\), and \(t_{1/2}\), an analysis of variance (ANOVA) was applied for untransformed data. The level of significance was \(\alpha = 0.05\) and a p-value of < 0.05 was considered to be statistically significant.

**Correlation development**

The principle of statistical moment analysis was utilized to assess the correlation of mean FA plasma concentration versus time in connection with the ingestion of three formulations. Mean dissolution time (MDT) was used to determine the correlation with \textit{in vivo} mean residence time (MRT).
RESULTS

In vitro studies

All products fulfilled the general pharmaceutical requirements for weight variation, content assay, and content uniformity assay. The prepared tablets complied with the official specifications for disintegration time, hardness, and friability. The in vitro dissolutions were conducted in two different medium (phosphate buffer pH 6.8 and biorelevant FaSSIF) and each at three different rotation speed to determine dissolution profile under various conditions.

The in vitro dissolution profiles of the SSD (F1) and conventional formulations (F2) are presented in Figure 3, and the summary of the mean DE60 of all FA tablets is given in Table 1. Significant differences existed between F1: F2 and F2: FA® at all conditions, whereas no significant difference arose from F1: FA® for 5 conditions.

In vivo studies

The concentration-time profiles of oral administration of both the SSD and conventional formulations and the reference formulation are depicted in Figure 4. All formulations resulted in an identical curve of plasma drug concentration versus time. The mean pharmacokinetic parameters of all FA tablets are summarized in Table 2. No significant difference was seen for all pharmacokinetic parameters from those formulations.

In vitro-in vivo relationship

Statistical moment analysis has been suggested as a better parameter to examine the IVIVC. A poor correlation between in vivo MRT and in vitro MDT for the three formulations was found in this study (Figure 5).

DISCUSSION

The new formulation of FA, a BCS Class II drug, was developed in this study and selected as an alternative to fenofibrate for oral administration. The SSD formulation was prepared by the solvent evaporation method to increase the dissolution of FA and compared to conventional and reference formulation. A conventional formulation of FA was prepared using wet granulation method. All of these formulations met the general pharmaceutical requirements for physicochemical properties. However,
significant differences were observed between both. The SSD formulation (F1) led to an instantaneous dissolution of the drug, releasing approximately 90% within the first five minutes at 75 and 100 rpm conditions. In contrast, the conventional formulation (F2) released nearly 80% of the drug within 45 minutes. Meanwhile, the reference formulation (FA®) yielded the same dissolution as the F1. The FA dissolution from F1 increased due to the presence of the polymer and physical structure of the SSD. In this case, FA was dispersed well on the CS surface, and the fine particles were able to increase its surface area for solubilization. When the CS contacted the dissolution medium, it became swelling and made it possible for FA to be wet to dissolve in the media. The swelling of the CS caused the cluster deaggregation of the drug particles and facilitated the dissolution process. Meanwhile, F2 could not achieve rapid dissolution despite the fact that around 80% of the drug dissolved within 45 min, and it satisfied the requirement for immediate drug release dosage form. Based on the data of the in vitro dissolution, there were significant differences found in the dissolution performances and therefore included in the development of the IVIVC.

The mean of all pharmacokinetic parameters from each product was not statistically different (p > 0.05), suggesting that the plasma profiles generated by FA® were comparable to those produced by F1 and F2. The intra-subject CV was relatively small. Based on this analysis, F1 and F2 could be considered bioequivalent with FA®.

An appropriate condition of the dissolution study based on the in vivo performance was adapted for a routine and in-process control for the FA formulation. The condition of dissolution in this study was similar to what is proposed by FDA (in pH 6.8 & 75 RPM) and correlated with the plasma profiles already obtained by performing bioavailability studies. Four correlation levels were defined in the IVIVC. It has been suggested to employ statistical moment analysis as a better parameter for examining the IVIVC. A level B correlation used all in vitro and in vivo data, and it was therefore employed between MRT and MDT. There was no correlation (R² = 0.028) between MRT and MDT of three formulations found in this study. Since the dissolution of the drug from F2 was slower than that of FA®, the IVIVC could not be achieved.

The in vitro dissolution behavior of FA did not reflect their in vivo properties at the fasted condition. The used of single medium dissolution for FA in the present study failed to become in vivo correlation. Also, a relatively significant difference was
observed between the dissolution properties of both F1: F2 and F2: FA\textsuperscript{®}. These formulations as \textit{in vivo} bioequivalences are shown in Figure 4 and Table 2. Apparently, the dissolution media in this study did not completely simulate the conditions of the GI tract. It is reported that biorelevant dissolution medium have ability to predict well the \textit{in vivo} performances of insoluble drugs. However, that purpose is not achieved in this study. Further studies are suggested to use biorelevant pH-gradient methods to obtain a strong IVIVC.

In most cases, statistically significant differences of \textit{in vivo} MRT among various formulations were not significant enough to produce a strong correlation between MRT and MDT. For a 105-mg dose of FA and aqueous solubility of 0.162 mg/mL, 650 mL of fluid was required to dissolve a single dose. Therefore, the volume of water taken initially not only dissolved the drug to a great extent but also decreased the dependency of drug absorption to the drug dissolution\textsuperscript{17}. This phenomenon led to a nil correlation in this study. The fact that the \textit{in vitro} differences in the early dissolution were not realized into the \textit{in vivo} differences attributed to the continuous excretion of bile that happened in the GI tract\textsuperscript{18}. There was still a possibility that FA absorbed with the help of a transporter (facilitated transport) and or energy (active transport). However, the amount was likely to be limited, even if much was dissolved.

**STUDY LIMITATION**

The present study limited on using a single medium method for dissolution testing. Further studies are suggested to use biorelevant pH-gradient methods to obtain a strong IVIVC.

**CONCLUSION**

The \textit{in vitro} dissolution behavior of fenofibric acid using single medium did not reflect their \textit{in vivo} properties at the fasted condition. There was no correlation between the \textit{in vitro} dissolution and the \textit{in vivo} bioavailability of fenofibric acid at this condition.

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CONFLICTS OF INTEREST:

The authors declare no conflict of interest. The founding sponsors have no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; and in the decision to publish the results.

REFERENCES


**Table 1.** Dissolution parameters (DE$_{60}$) of fenofibric acid from three formulations at six conditions.

<table>
<thead>
<tr>
<th>Code</th>
<th>50 RPM</th>
<th>75 RPM</th>
<th>100 RPM</th>
</tr>
</thead>
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<tr>
<td></td>
<td>pH 6.8</td>
<td>FaSSIF</td>
<td>pH 6.8</td>
</tr>
<tr>
<td>F1</td>
<td>92.55±3.50</td>
<td>85.05±1.53</td>
<td>87.88±4.96</td>
</tr>
<tr>
<td>F2</td>
<td>41.55±1.64</td>
<td>40.29±4.31</td>
<td>53.44±3.89</td>
</tr>
<tr>
<td>FA®</td>
<td>63.79±3.71</td>
<td>75.35±1.34</td>
<td>75.81±5.91</td>
</tr>
</tbody>
</table>

**Table 2.** Pharmacokinetic parameters of fenofibric acid after single-dose oral administration of three different formulations in nine healthy male subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1 (Mean±SD)</th>
<th>F2 (Mean±SD)</th>
<th>FA® (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-72}$ (µg.h/mL)</td>
<td>136.94 ± 30.85</td>
<td>157.57 ± 55.81</td>
<td>150.57 ± 40.49</td>
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<tr>
<td>AUC$_{0-\infty}$ (µg.h/mL)</td>
<td>148.45 ± 34.62</td>
<td>171.09 ± 62.95</td>
<td>158.22 ± 42.14</td>
</tr>
<tr>
<td>C$_{max}$ (µg/mL)</td>
<td>11.79 ± 3.72</td>
<td>12.94 ± 3.95</td>
<td>14.12 ± 2.68</td>
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<tr>
<td>T$_{max}$ (hrs)</td>
<td>2.99 ± 0.39</td>
<td>2.67 ± 0.41</td>
<td>2.63 ± 0.35</td>
</tr>
<tr>
<td>T$_{1/2}$ (hrs)</td>
<td>20.97 ± 3.36</td>
<td>19.72 ± 6.65</td>
<td>17.25 ± 4.12</td>
</tr>
</tbody>
</table>

SD: standard deviation.
Figure 1. Chemical structures of fenofibric acid and fenofibrate

Figure 2. Chromatographic profiles of FA and CFHB as the internal standard in extracted human plasma
Figure 3. Dissolution profiles of SSD formulation (F1), conventional formulation (F2), and reference formulation (FA®) in phosphate buffer pH 6.8 (a) and FaSSIF biorelevant medium (b) at 50, 75, and 100 rpm.
Figure 4. Average plasma concentration vs. time profiles of FA after oral administration (105-mg doses) of SSD formulation (F1), conventional formulation (F2), and reference formulation (FA®) in nine healthy male subjects. Data are shown as mean ± SD.
Figure 5. Correlation between mean dissolution time (MDT) of *in vitro* dissolution (in pH 6.8; 75 RPM) and mean residence time (MRT) of plasma drug concentration from three formulations F1 (●), F2 (■) and FA® (▲).

\[ y = 0.0315x + 22.86 \]

\[ R^2 = 0.0281 \]