



## A Comprehensive Review on the Drug: Fenofibrate

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### ABSTRACT

Fenofibrate is currently used as antihyperlipidemic drug, which has a direct effect on lowering cholesterol, triglycerides and LDL (Low-Density Lipids), VLDL (Very Low-Density Lipids) levels along with raising the level of HDL (High-density Lipids) in the blood. It also plays a significant role in insulin resistance metabolic disorder. This drug is mainly used for controlling diseases related to lipids like hypercholesterolemia, severe hypertriglyceridemia and dyslipidaemia. Along with statins, it significantly controls the level of hypercholesterolemia and hypertriglyceridemia. It belongs to the group of drugs called 'Fibrate'. Fenofibrate was patented in 1969. In 1974, it was synthesized as a derivative of clofibrate and launched at the French market. It was marketed in 1975. In 2017, it was available as a generic medicine. Presently this API is being marketed in around 85 countries all over the world. Fenofibrate is a BCS Class-II drug having poor water solubility. The poor aqueous solubility of this drug causes low bioavailability and limited permeability through the GIT membrane. This API degrades at higher temperatures and in a humid environment, with one of the resultant degradation products being fenofibric acid. In the present review, we have discussed the historical development, pharmacology, analytical profile with its physicochemical properties and ongoing research scenario on this API.

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### INTRODUCTION

Fenofibrate is used for controlling the lipid profile within the circulatory system. It belongs to the fibrates class of drug, structurally similar to the other fibrates like clofibrate (Grundy *et al.*, 2004). This drug is mainly used for controlling diseases

related to lipids like hypercholesterolemia, severe hypertriglyceridemia and dyslipidaemia (Toth *et al.*, 2003). Historically it was being employed as an antihyperlipidemic agent. It was marketed for the first time in 1975. At present, this API is being marketed in around 85 Countries all over the world (Fischer *et al.*, 2006). Its chemical name is 2-[4-[4-chlorobenzoyl]phenoxy](2-methyl propanoic acid 1-methyl ethyl ester). It's a BCS class-II drug having poor aqueous solubility but a higher permeability profile (Lalloyer and Staels, 2010). Fenofibrate works by regulating the blood cholesterol or lipid levels in healthy subjects and hyperlipoproteinemia patients. It has a bioavailability profile of 60-81% (Vlase *et al.*, 2011). This drug is a prodrug of fenofibric acid, hydrolysed by plasma esterase's enzymes to the active metabolites (Adkins and Faulds, 1997). This prodrug controls the levels of cholesterol by modifying the levels of high-density lipoprotein

(HDL), low-density lipoprotein (LDL) and very-low-density lipoprotein levels, which play a key role in patients with cardiovascular disorders (Saurav *et al.*, 2012). It also plays a significant role in insulin resistance metabolic disorders (Filippatos and Elisaf, 2011). Along with statins, it significantly controls the levels of hypercholesterolemia and hypertriglyceridemia (Keating and Croom, 2007). Fenofibrate is an agonist of PPAR- $\alpha$  receptor, it activates the lipoprotein lipase and reduces the concentration of apo C-III, which is an inhibitor of lipoprotein lipase activity. By activating the PPAR- $\alpha$  receptor, it increases the synthesis of apo A-I, apo A-II and cholesterol (Koda-Kimble *et al.*, 2005). Both apo A-I and apo A-II have a specific role in lipid metabolism (Staels *et al.*, 1998). Some suggestions from Israel and U.S researchers in July 2020 state that the prodrug of fenofibric acid significantly reduces the replication of the SARS-CoV-2 in lung cells (British Pharmacopoeia, 2010). Currently, this hypothesis requires approval from clinical trials. It increases the level of sulfatide, which seems to be beneficial against COVID -19 (<https://www.jpost.com/health-science/hebrew-u-scientist-drug-could-eradicate-covid-19-from-lungs-in-days-635028>).

### History

This drug belongs to the fibrate class. It was synthesized for the first time in the mid 1950's. Clinical development of fibrates came under observation in 1953. From de-hydrochloric acid, around 80 structures were synthesized and some of them showed the hypercholesterolemic properties in human volunteers and rats. After that, a lot of pharmaceutical industries started work to improve the pharmacokinetic and pharmacodynamic profiles of clofibrate. Clofibrate is a lipid-lowering agent, which was used to control triglycerides and high cholesterol levels (Lalloyer and Staels, 2010). It has no effects on hyperchylomicronaemia and high-density lipoproteins. To improvise its effects and efficacy, a lot of modifications were tested. Phenoxy 2-methyl-2-propionic acid chain of clofibrate was maintained and by different hydrophobic groups, chlorine atoms of chain substituted and phenyl ketone molecules were obtained. From obtained molecules, no one was showing interested hypolipidemic drug activity except procetofen (which was a benzoyl derivative having chlorine atom at position 4). Initially, this benzoyl derivative was named as procetofen, later by WHO, it was renamed as Fenofibrate. Currently, it is known as fenofibrate. It was patented in 1969. In 1974, it was synthesized as a derivative of clofibrate and launched at the French market. It was marketed in 1975. In 2017, it was available as a generic medicine. Presently this API

is being marketed in around 85 countries all over the world. Fenofibrate was developed by Groupe F.S.A, then it was acquired by a business unit run by Belgian corporation Solvay S.A. Solvay sold its business unit to Abbott labs, which is currently known by name AbbVie in the United States, Australia and Japan (Fischer *et al.*, 2006).

### Physicochemical Properties

It is a white or yellowish crystalline powder that is stable under ordinary conditions. Its chemical formula is  $C_{20}H_{21}ClO_4$ . It's a chlorobenzophenone that is (4-chlorophenyl)(phenyl)methanone substituted by a [2-methyl-1-oxo-1-(propan-2-yloxy)propan-2-yl]oxy group at position 1 on the phenyl ring. It is practically insoluble in water. It is sparingly water soluble compound, the volume of water to dissolve 1gm fenofibrate at 37°C being larger than 410 dm<sup>3</sup>. Table 1 succinctly summaries some properties (Staels *et al.*, 1998). It is soluble in organic solvents, i.e. Ethanol, DMSO, DMF (Meng *et al.*, 2010). Log P value of a fenofibric indicates the permeability of drugs to reach the target tissue in the body. It is highly lipophilic. Serum protein binding was approximately 99% bound to plasma protein in normal and hyperlipidaemic subjects. By suppressing expression in adipose tissue, it reduces serum retinol binding protein-4. The melting point of fenofibrate is 80-81°C, during thermogravimetric measurements from 20-200°C, no thermal effects besides melting were observed, nor any mass loss was noticed on DTA curves. Figure 1 shows the structure of fenofibrate (Hussain *et al.*, 2016).

### Method of analysis

The starting material for the synthesis of fenofibrate is fenofibric acid. This drug is a prodrug of fenofibric acid. Different Pharmacopoeia's like Indian pharmacopoeia, British pharmacopoeia, United States pharmacopoeia (United States Pharmacopoeia, 2009) and European pharmacopoeia specify limits of impurities in the API, i.e. it should not be less than 0.1 % and in the marketed formulation, it should not be less than 0.5 % as per USP (Jain *et al.*, 2008).

These pharmacopoeia's have already included the test for related substances in dosage forms. Fenofibrate is assayed by a liquid chromatography method in British Pharmacopoeia (BP) (Lacroix *et al.*, 1998). Including HPLC, LC-MS, stability indicating HPLC (Kadav and Vora, 2008) and capillary electrophoresis and many more other methods to identify fenofibrate in formulations (Salamaa *et al.*, 2011). In addition, voltammetry, polarography and derivative spectrophotometry were also reported for the determination of fenofibrate.

### By RP-HPLC method

Dedhiya *et al.*, performed a study to identify fenofibric acid using the compendial RP-HPLC method. To identify fenofibric acid related substances, a column of 250 × 4.6 mm, 5 μm length, C18, was used with acetonitrile 70 % and 30% water as the mobile phase (Lassner *et al.*, 2001). The pH was regulated at 2.5 with orthophosphoric acid. The flow rate was kept at 1ml/min. Ultraviolet processing was used at 286 nm. For specificity, precision and accuracy RP-HPLC method was used (Elsherif *et al.*, 2013). The recovery rate of fenofibric acid and fenofibrate was found to be 99.76-100.38% to 99.58-100.19%, respectively (Gabhe and Satish, 2014).

### By UV-spectrophotometric Method

Kutty *et al.*, performed a study for estimation of fenofibrate by using the UV-visible spectrophotometric method. This method was developed for the estimation of fenofibrate in pharmaceutical dosage forms and bulk drugs. This method of estimation is based on the absorbance of drugs. Kutty *et al.* performed this method using methanol (0.5% of MBTH in 0.5% HCl and 1% of ferric chloride in 0.5% HCL) at 596nm. Lambert Beer law was obeyed over the linear range. The method was validated in accordance with the current ICH guidelines. The recovery rate of fenofibric acid by the UV-spectrophotometric method was found to be 99.36% (Scott *et al.*, 2009).

### Pharmacological action

Fenofibrate is the commonly prescribed drug for the treatment of hyperlipidaemia. It is being prescribed alone or in combination with other medication. It is used to decrease the amount of fatty substances, i.e. triglycerides and cholesterol, in the circulatory system to heighten the amount of high-density lipoproteins. For better results, patients are advised to have a less fat intake in their diet and include ample physical exercise in their routine (Toth *et al.*, 2003). If the level of cholesterol and fats increases in our body system within artery walls, it leads to decreases the oxygen supply to body parts and reduces the flow of blood towards major body parts like the heart, brain etc. If the blood circulation decreases in the body, this may lead to serious disorders like heart diseases. Fenofibrate helps to reduce the bad cholesterol from the circulatory system to avoid these serious diseases. It works by boosting the natural process to decrease cholesterol levels (Third Report of the National Cholesterol Education Program, 2002).

### Mechanism of action

It is mainly used to control diseases related to lipids, i.e. hypertriglyceridemia, bad cholesterol in the serum (Heller and Harvengt, 1983). Figure 2 shows

that the peroxisome proliferator-activated receptor-α (PPARα) is the member of the nuclear receptor family that regulates lipid metabolism (Malmendier *et al.*, 1989). Fenofibrate increases the expression of apo C-I and apo C-II, which results in increased HDL levels (Staels *et al.*, 1998).

### Pharmacodynamic properties

In hyperlipoproteinemia patients, considerable reduction of atheromatous plaques in arteries occurs and patients having elevated baseline, in this case, level of LDL regularly decreases and on the other side level of HDL increases when baseline level is low. Changes that occur in apolipoprotein level leads to change in lipoprotein fraction. It decreases the level of apolipoprotein CII, CIII, E and increases the level of AI and AII. In the case of patients having lignocellulosic pre-treatment LDL cholesterol levels, the level of apolipoprotein B may be increases and the level of apolipoprotein decreases when the level of baseline LDL cholesterol is elevated. Fenofibrate shows an effect on TGA and cholesterol metabolism, but it cannot define anywhere which type of effect is primary and which is secondary (Balfour *et al.*, 1990). The main effect of the drug is increasing lipase activity to increase triglyceride-rich lipoprotein metabolism and it also helps to reduce biosynthesis of cholesterol, which results in an enhanced LDL clearance by increasing hepatic LDL receptor activity. Mobilisation of cholesterol deposited in peripheral tissues (including arterial walls) may occur-regression of xanthomas and xanthelasmas has been observed. In clinical studies and preliminary studies, administration of fenofibrate and nicotinic acid reported evidence of regression of atherosclerosis. Reduction in the formation of fatty deposits in arteries achieved by decreasing the activity of platelets derived growth factor and platelets hyperaggregability. It can be achieved by increasing the esterification of cholesterol in plasma. In combination therapy, decreasing bile acid concentration and increasing cholesterol level results in increases in the lithogenic index of bile. In healthy volunteers and hyperlipoproteinemia patients, the drug shows a decrease in serum uric acid level (Zhu *et al.*, 2010).

### Pharmacokinetic properties

When the drug is orally administered, it is hydrolysed by plasma esterase to its active metabolites. In the case of healthy volunteers, an unchanged drug is detected. After conjugation with glucuronic acid, a few amounts of drug is reduced from carbonyl moiety to benzhydrol metabolites and excreted out through urine. Some research study shows that *in*

**Table 1: Physicochemical and pharmacological properties of fenofibrate**

Properties of Fenofibrate	
Drug	Fenofibrate
Chemical name	2-[4-(4-chlorobenzoyl) phenoxy]2-methylpropanoic acid
Alternate name	Antara
Empirical formula	C <sub>20</sub> H <sub>21</sub> ClO <sub>4</sub>
Molecular weight	360.83g/mol
Melting point	80-81°C
Density	1.177g/cm <sup>3</sup>
Solubility profile	Soluble in organic solvents, Insoluble in water.
Physical appearance	A White, yellowish crystalline powder
Category	Antilipemic
Protein binding	99%
Log P	4.68
T <sub>1/2</sub> value	19-27hr (Healthy Patients)
Volume of distribution	0.89L/kg
Clearance Value	1.1L/h (In young adults)
Storage	Fenofibrate should be stored at room temp between 15-30°C

**Table 2: Drug interaction of fenofibrate and their adverse drug reactions**

Sl.No	Object drug	Interacting drug	Side effects / adverse effects
1	Fenofibrate	Warfarin	Increase risk of bleeding
2	Fenofibrate	Rosuvastatin	Increase risk of rhabdomyolysis
3	Fenofibrate	Simvastatin	Increase risk of myopathy and rhabdomyolysis
4	Fenofibrate	Citalopram	Increase risk of irregular heart rhythms
5	Fenofibrate	Teriflunomide	Increase risk of liver toxicity
6	Fenofibrate	Dicumarol	Increase risk of bleeding
7	Fenofibrate	Colestipol	Decrease fenofibrate absorption

*vivo* metabolism of fenofibrate and fenofibric acid cannot undergo oxidative metabolism. After administration of a single 300 mg dose in healthy fasting volunteers in 4-6 hours the peak of plasma concentration achieved 6-9.5mg/l. After 120 hours in healthy volunteers following a dose of 300mg daily divided into two doses, steady state concentration of approx. 10mg/l was reached. Bioavailability of drugs having poor solubility are not being determined. After administration, peak plasma levels of fenofibric acid were found to be an average of 3 hours. When the triglide 160 mg tablet administered under low fat conditions, a similar extent of absorption was found, but in comparison of the 200 mg micronized fenofibrate capsule, it exhibited a 32 percent higher rate of absorption. In healthy volunteers, the protein binding of the drug was found to be 99.99%.

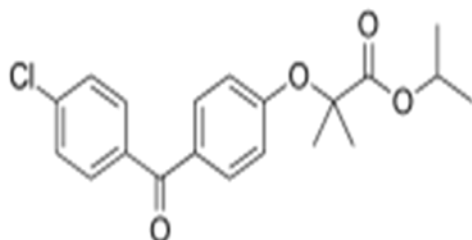
The volume of distribution of fenofibrate was found

to be 0.89l/kg. Fenofibric acid is mainly excreted throughout our renal pathway in the form of metabolites. When radiolabelled fenofibrate administered, approx. 60 % of the dose excreted through urine and 25 % in the form of feces (Balfour *et al.*, 1990). In clinical settings, the half-life of a drug was reported to be 16 hours during once a day administration. In healthy subjects, the mean elimination half-life of the drug was reported 19.6-26.6 hours. In the case of patients having renal failure, the plasma half-life of the drug substantially prolonged, no correlation between creatinine clearance and elimination half-life found. Patients having chronic renal failure, the use of fenofibrate without physician consultation is prohibited (Zhu *et al.*, 2010).

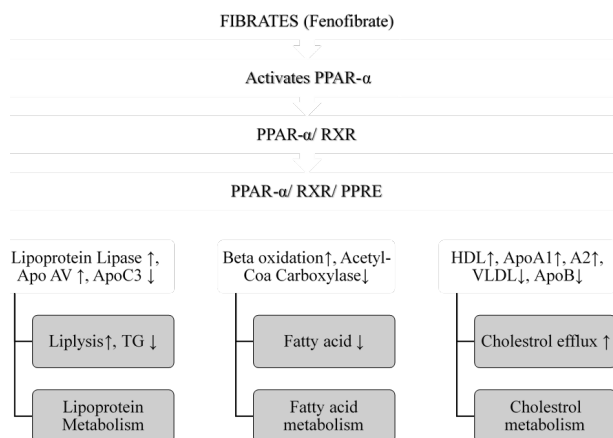
#### Therapeutic use

It is used in the treatment of hypertriglyceridemia and type III hyperlipidaemia. In comparative and non-comparative studies, while performing a long





**Figure 1: Chemical structure of fenofibrate**



**Figure 2: Mechanism of action of fenofibrate**

term trial, fenofibrate exhibited a lipid regulating effect. During trial studies, different types of patients included having hyperlipoproteinemia type IIa, IIb, type III, IV and type V (Fazio, 2009). Some paediatrics are also included in the study. Administration of a dose of 200-400 mg/day following 100mg (1-1-1) results in a reduction in the levels of triglycerides and total plasma concentration in volunteers. In type IIb, a total of around 30-60% of TGA level reduced and constitutive reduction achieved in type III, IV, V patients. In type IIb and IIa volunteers cholesterol level reduces up to 13-32%, 20-30 % respectively (Steiner, 2009). In type III, some reduction in levels of cholesterol was also reported. Fenofibrate generally increases the level of HDL cholesterol in patients with low pre-treatment levels and some volunteers reported a reduction effect. In some studies, fenofibrate was compared with some other fibrate drugs like clofibrate and bezafibrate and found that the effect on lipoprotein varies with other drugs. In the case of hypercholesterolaemia patients, fenofibrate results to be more effective than clofibrate to reduce total cholesterol level in plasma (Khanna and Fitzgerald, 2012). When we compared it with simvastatin, fenofibrate founds to be less effective to reduces the TGA level. In dyslipidaemia patients, when fenofibrate administered with other medications like nicotinic acid and colestipol, then an additive effect on lipid regulation is observed. When this type of single ther-

apy does not work properly, then combination therapy should be used to reduce the cholesterol levels (Wong et al., 2012).

### Adverse effects

In short term, 6% and in the long term trials, 11 % incidence reported adverse reactions towards fenofibrate. The common side effect is GI upset. Another reported adverse effect is a predisposition to form gallstones due to increased biliary cholesterol excretion. Myositis (inflammation of muscles), muscle weakness or tenderness occur. Myopathy and rhabdomyolysis have also been reported in patients that took gemfibrozil and statins together, so gemfibrozil is contraindicated with simvastatin. These agents may increase the effect of warfarin, these should not be used in patients with severe hepatic dysfunction or patients with pre-existing gallbladder disease. In a number of studies, analysts and patients reported that in aspartate aminotransferase, non-symptomatic sporadic level increases (US food and Drug).

### Effect of fenofibrate on major body system

#### Central nervous system

Many drugs are unable to produce their therapeutic effects due to the Blood Brain Barrier because they are unable to cross the blood brain barrier and cannot reach their destination sites within CNS. To overcome this problem, different types of drug delivery systems help us to reach a drug at their target sites to produce their effect. Controlled drug delivery systems are a type of delivery system that helps overcome this problem, but it's a challenging task. Active metabolites of fenofibrate are encapsulated in PLGA microparticles. These fenofibrate loaded microparticles reduce the effect of Ischemic stroke on wistar rats. It is an agonist of PPAR- $\alpha$ , by activation of PPAR- $\alpha$ , it enhances the cerebral artery relaxation in the brain. Additionally, PPAR-alpha activation shows anti-inflammatory action, which may prevent WBC and platelets aggregation towards microvessels. Fenofibrate may also improve CBF in the Ischemic brain (Klose et al., 2009).

#### Respiratory system

Peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ) is the member of the nuclear receptors family (Qiu et al., 2007). It regulates genes up and down, which is involved in many functional changes in the process, such as oxidative stress and leukocyte interactions (Tasaka et al., 2012). Some studies show that in kidney I/R (Ischemia-reperfusion), injury reduces by the anti-inflammatory and anti-ischemic role of fenofibrate. It is a ligand of PPAR- $\alpha$ . Binding with the PPAR- $\alpha$

receptor results in lipoprotein lipase, apo A-I and apo A-II (Greally *et al.*, 1993). On the other side binding of fenofibrate to the PPAR- $\alpha$  receptor causes a decrease in the apolipoprotein C-II level. Overall, it decreases the level of TGA and increases HDL levels (Koehler *et al.*, 2004). In endothelial cells, monocytes and some smooth muscle cells, fenofibrate shows anti-inflammatory properties. There is not sufficient data that shows the effect of drugs on the production of neutrophil chemokines in airways (Jensen *et al.*, 2006). Some research studies show that drugs reduce the production of chemokines in airway epithelial cells from healthy volunteers having cardiac failure history (Liu *et al.*, 2009).

### Cardiovascular system

Cardiovascular function could be modified to a larger extent by modifying lipid profiles via changing the levels of low density lipoprotein, increasing HDL cholesterol, reducing triglycerides levels. By using fenofibrate, the risk of myocardial infarction, coronary events, unstable angina and the need of coronary revascularization procedures were significantly reduced. Fenofibric acid is used to reduce the LDL cholesterol to less than 3mmol/l (115mg/dl) and total cholesterol to less than 5mmol/l (190mg/dl) (Manninen *et al.*, 1992). Scott Russell *et al.* 2009 performed a research study on the effect of fenofibrate in the treatment of cardiovascular disease risks. Study shows that in case of metabolic syndrome subjects, fenofibrate reduces the cardiovascular diseases risk from 14.5 to 13.1%. On another side in a smaller group of patients having no metabolic syndrome, it reduces cardiovascular disease risk from 11.3 to 9.7% (Scott *et al.*, 2009).

### Drug interaction of fenofibrate and their adverse drug reactions

Simultaneous intake of fenofibric acid along with different medicines may deliver adverse effects. Since fenofibrate is the most frequently prescribed second line drug, patients should be aware to read and understand the labels, so they can understand the dose, its dosing frequency etc to avoid overdosing. Fenofibric acid binds to protein up to 99 percent protein bound. Table 2 succinctly summaries some drug interactions.

If the bile acid sequestrants like colestipol and fenofibrate are administered together, then the resin of bile acid shows an effect on the downfall in the absorption of fenofibrate. Fenofibrate additionally interacts if vitamin k antagonist warfarin administered together, then the warfarin anticoagulant effect enhances the chances of bleeding and sometimes, with statins, it enhances the chances

of myopathy. Immunosuppressant (cyclosporin) increases the risk of renal dysfunction (Package Insert, 2010).

### Pharmaceutical research work performed on fenofibrate and future prospective

Fenofibrate is poorly soluble in water. There were various attempts made by researchers to beat the issue by planning orally dispersible tablets, film coated tablets and capsules and so on. Different strategies incorporate solid dispersions, complex development, co-crystallization and so on. Sanku-laraokameswara *et al.*, prepared solid dispersions to enhance the dissolution profile of fenofibrate by using a different method of preparation, i.e. melting method, melt extrusion method, physical mixture utilising fenofibrate and beta cyclodextrin and hydroxypropyl-beta-cyclodextrin in respectively ratio 1:0.5, 1:1, 1:2 (Drug : Carrier). In solid dispersion approach using feasible kneading method. Dissolution rate of fenofibrate could be enhanced to a great extent. While in another investigation, Dixit *et al.* (2015) performed research work on enhancing solubility and dissolution profile of fenofibrate using spray drying technique by making microspheres (containing a ratio of pluronic F-127 ) using chloroform as solvent. The study showed that the dried microspheres exhibit low crystallinity. Solubility profile of microspheres containing pluronic F-127(1:3 w/w). Fenofibrate exhibited thirty times increased dissolution profile then the commercial formulation. The dissolution profile of the same proportion of microspheres showed 99% drug release in 40 min, while on the other side same proportion of physical mixture shows 37% release in 20 min. Tejas *et al.* (2011) performed research work on improvement of dissolution behaviour by solid dispersion technique using lyophilization technique. Shelakes *et al.* arranged fenofibrate loaded nanoparticles by precipitation method. Dissolution profile of nanoparticles was found to be higher than the pure drug.

### CONCLUSIONS

Fenofibrate is currently used as antihyperlipidemic drug, which has a direct effect on lowering cholesterol, triglycerides and LDL (Low-Density Lipids), VLDL (Very Low-Density Lipids) levels along with raising the level of HDL (High-density Lipids) in blood. It belongs to the group of drugs called 'Fibrate'. Fenofibrate is a BCS Class-II drug having poor water solubility. The poor aqueous solubility of drugs causes low bioavailability and limited permeability through the epithelial membrane. Fenofibrate is having poor aqueous solubility and high

permeability along with stability issues at higher temperatures and moisture, leading to its conversion into fenofibric acid. There are some newer techniques, including nanotechnology, solid dispersion approach, complex formation, nanoparticles etc., having a bright future in the pharmaceutical scenario for improving the dissolution rate, the bioavailability of poorly water soluble drugs. Generally speaking, these investigations require further developed research concerning different strategies to improve fenofibrate solubility.

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### Conflict of Interest

The authors declare that they have no conflict of interest.

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