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Bioavailability Enhancement of Pemafibrate by Various Formulation Approaches: A Review

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ABSTRACT

Pemafibrate is a new generation of anti-hyperlipidemia drugs. However, its poor solubility in water (0.410 mg/mL at 25 °C) has limited its oral bioavailability. In this study, we discuss the methods, or certain formulation approaches available to improve solubility and consequently the oral bioavailability of pemafibrate. Innovative formulation approaches aim to optimize absorption, stability, and therapeutic efficacy, thereby improving clinical outcomes in lipid management (Yamashita *et al*., 2020). However, their low bioavailability due to poor solubility, high first-pass metabolism, and efflux by transporters, limits their therapeutic efficacy and requires high doses to achieve desired effects. Pemafibrate, one of SPPARMsα, was synthesized by Kowa Company, Ltd. for better efficiency and safety. Clinical trials in Japan have established the superiority of pemafibrate on effects on serum triglycerides (TG) reduction and HDL-C elevation as well safety. Although available fibrates showed worsening of liver and kidney function test values, pemafibrate indicated improved liver function test values and was less likely to increase serum creatinine or decrease estimated glomerular filtration rate (eGFR). Very few drug-drug interactions were observed even when used concomitantly with Statins. Furthermore, pemafibrate is metabolized in the liver and excreted into the bile, while many of available fibrates are mainly excreted from the kidney. Therefore, pemafibrate can be used safely even in patients with impaired renal function since there is no significant increase in its blood concentration. A large-scale trial of pemafibrate, Prominent, for dyslipidemic patients with type 2 diabetes is ongoing.

KEY WORDS: Pemafibrate, anti-hyperlipidemia drugs, type 2 diabetes, Statins.

INTRODUCTION:

Fibrates were developed in the 1950s based upon the discovery of phenylethyl acetate from agricultural chemical ingredients which were found to reduce serum lipids. Clofibrate was the first fibrate which was classified as a lipid-lowering agent. Later, several fibrates were developed and shown to enhance the proliferation of peroxisome in mice, but the mechanism of action of fibrates remained unknown for many years. Currently available fibrates were developed without definitive knowledge of their specific mechanism of action. However, fibrates were later demonstrated to act on PPARα and elicit their biological effects such as reduction of serum triglycerides (TG) levels and increase in serum HDL-C levels. Although the activation of PPARα by fibrates markedly improved serum lipid levels, a variety of off-target effects such as abnormal test values suggesting liver and kidney dysfunctions was observed, which were difficult to be overcome.[1]

Large-scale clinical trials of fibrates for prevention of cardiovascular (CV) events were subsequently conducted. In the Helsinki Heart Study (HHS) and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), administration of gemfibrozil significantly reduced CV event rate, the primary endpoints of the trials. However, significant drug-drug interactions between gemfibrozil and cerivastatin resulted in a very high incidence of rhabdomyolysis in patients. Furthermore, in subsequent trials, including Benzafibrate Infarction Prevention (BIP) study (using bezafibrate alone), Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (using fenofibrate alone), and the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-lipid study (using fenofibrate on top of simvastatin), primary endpoints were statistically negative and the clinical efficacy of fibrates on CV events was questioned.[2]

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Need for the Study:

Cardiovascular diseases (CVDs) remain a leading cause of morbidity and mortality worldwide. Lipid-lowering agents, including fibrates, play a pivotal role in the management of dyslipidemia, a major risk factor for CVDs. Pemafibrate, a selective peroxisome proliferator-activated receptor alpha modulator, has shown promising therapeutic potential in reducing lipid levels (Yamashita *et al*., 2020) [1]. However, its clinical efficacy is often hampered by poor bioavailability. This research aims to develop innovative formulation strategies to enhance the bioavailability of pemafibrate, thereby improving its therapeutic efficacy.

Innovative formulation strategies have emerged as a key approach to improving the bioavailability of poorly soluble drugs. These strategies include the use of nanoparticle encapsulation, lipid-based formulations, and solid dispersions, among others. By enhancing the solubility and stability of the drug, these formulation approaches can significantly improve the bioavailability and therapeutic efficacy of the drug (Jones *et al*., 2011) [2]. However, there is still a need for further research to fully explore the potential of novel formulation approaches for enhancing the bioavailability of fibrates.

This research aims to develop and evaluate novel formulation strategies to enhance the bioavailability of pemafibrate, thereby improving its therapeutic efficacy in the management of dyslipidemia. The study will systematically review existing literature, identify key challenges, and design optimized formulations of pemafibrate. The effectiveness of these formulations will be assessed through preclinical and clinical studies to determine their pharmacokinetic and pharmacodynamic performance.[3]

APPROACHES TO OVERCOME THESE PROBLEMS

A. Pharmacokinetic Approach

The pharmacokinetics of a drug can be altered by modifying its chemical structure. However, this approach is often expensive and time-consuming, requiring repeated clinical studies and longer regulatory approval periods.

B. Biological Approach

Changing the route of drug administration, such as switching from oral to parenteral routes, can also alter bioavailability. Given the limitations of pharmacokinetic approaches, optimizing the formulation, manufacturing process, or the physicochemical properties of the drug without altering its chemical structure is mainly aimed at enhancing the dissolution rate, which is a major rate-limiting step in the absorption of most drugs (Brahmankar DM and Jaiswal SB, 2006).[4]

C. Pharmaceutical Approach (Formulation Approach)

This involves modifying the formulation, manufacturing process, or the physicochemical properties of the drug without changing its chemical structure. The pharmaceutical or formulation approach to enhance bioavailability can be applied through the following techniques:

1. Enhancement of drug solubility and dissolution rate.
2. Enhancement of drug permeability.
3. Enhancement of drug stability.
4. Enhancement of gastrointestinal retention (GR).

Solid Dispersions:

Solid Solution

In this system, when the two components crystallize together, they form a single homogeneous phase system. The drug particle size is decreased to its molecular size in the solid solution. As a result, a faster rate of dissolution will be achieved in the solid solution than in the corresponding eutectic mixture. The solution can be categorized (as continuous or discontinuous) depending on the level of miscibility of the two compounds or how the solvate molecules are circulated (substitutional, interstitial, or amorphous)

In the crystalline carrier, the drug may also precipitate in an amorphous form instead of simultaneous crystallization of the drug and the carrier (eutectic system). High dissolution rates are usually produced in this form because of the high energy of the drug in the amorphous state

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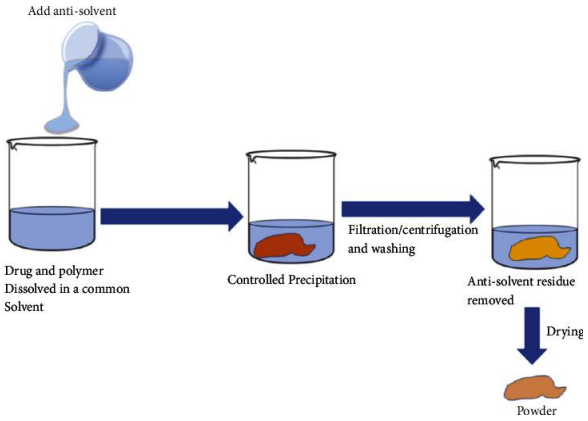
Sekiguchi and Obi proposed the fusion method in 1961, also known as the melt method. A physical mixture of drug and polymer is heated to generate a molten mixture, which is then cooled and hardened while vigorous stirring is performed. To reach the desired particle size, the solid mass is crushed, pulverized, and sieved. Despite its popularity, several drawbacks to employing this process in making solid dispersions are present. [5]

Hot-Melt Extrusion Method:

The hot-melt extrusion method is the modern version of the fusion method in which the extruder induces intense mixing of the components. Compared with the traditional fusion method, melt extrusion offers the potential to shape the molten drug-polymer mixture into implants, pellets, or oral dosage forms. However, this method requires the complete miscibility of the drug and the polymer in the molten state.

Coprecipitation Method (Coevaporate)

The carrier is accurately weighed and dissolved in water, while the medication is dissolved in an organic solvent. The aqueous carrier solution is then added to the organic drug solution after complete dissolution. After that, the solvents are ejected. The dispersion is crushed, sieved, and dried using a pestle and mortar



The solvent approach entails dissolving both the medication and the polymer in a single solvent and then removing the solvent to create a solid dispersion. This method allows for molecule-level mixing, which is favored for improving product solubility and stability.[6]

Spray Drying:

Spray drying has become a prominent processing method for creating solid drug dispersions. It is used to turn a liquid or a suspension into a dry powder in one step. This method allows for more precise control of process factors, resulting in powders with the required size, shape, density, flow characteristics, and crystalline forms. In spray drying, the solvent evaporates at a rapid rate, resulting in a dramatic increase in viscosity and trapping of drug molecules in the polymer matrix.

Supercritical fluids have both liquid and gas characteristics. Materials exhibit liquid-like solvent characteristics and gas-like viscosity, diffusivity, and thermal conductivity under supercritical conditions. While the solvent properties are advantageous for drug/polymer solubilization, the gas-like properties considerably improve the fluids' mass transport characteristics. This approach is most commonly used with supercritical carbon dioxide (CO_2) as a drug and polymer solvent or as an antisolvent. The polymer and medicine are dissolved in supercritical CO_2 and blasted into a low-pressure zone through a nozzle, generating adiabatic CO_2 expansion and fast cooling. As a result, this approach enables the creation of drug particles with much smaller particle sizes.[7]

Kneading Method

In a glass, a mixture of precisely weighed medication and carriers is wet with a solvent and is thoroughly kneaded for some time. In the kneading method, the liquid (which may be water or a hydroalcoholic mixture) is added dropwise while the drug and polymers are triturated in a pestle and mortar. This results in the formation of slurry and the reduction of particle size, which increases bioavailability because of the kneading action. Then, the mixture is dried and placed through the mesh to bring the contents into homogeneity [8]

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Electrospinning Method

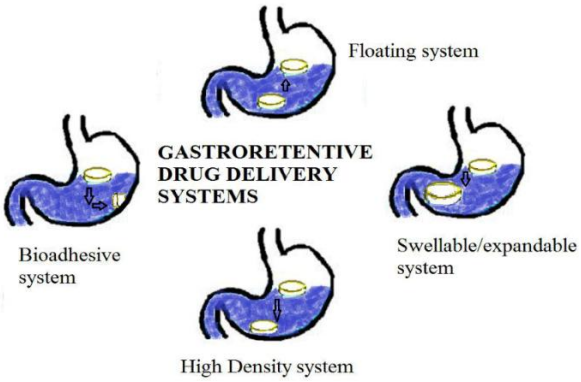
This technology combines solid dispersion technology with nanotechnology to be used in the polymer industry. This technique exposes a liquid stream of a drug/polymer solution to a voltage between 5 and 30 kV. Fibres of submicron diameter arise when electrical forces exceed the surface tension of the drug/polymer solution at an air contact. The generated fibres can be collected on a screen to make a woven fabric, or they can be gathered on a spinning mandrel as the solvent evaporates. Surface tension, dielectric constant, feeding rate, and electric field strength all influence the fibre diameter. Because it is the simplest and cheapest technology for preparing nanofibers and controlling the release of medicines, it has enormous potential.[9]

Gastroretentive Drug Delivery Systems (GRDDS)

The oral route is the most preferred method of drug delivery due to its ease of administration, low therapy cost, patient compliance, and flexibility in formulation. Effective oral drug delivery depends on factors such as the gastric emptying process, gastrointestinal transit time, drug release from the dosage form, and the drug's absorption site. However, most oral dosage forms face physiological limitations, such as variable gastrointestinal transit and gastric emptying, leading to non-uniform absorption profiles, incomplete drug release, and shorter residence time in the stomach. This results in incomplete absorption for drugs with absorption windows in the upper gastrointestinal tract, as any drug passing beyond the absorption site remains unabsorbed.**[10].**

Gastric emptying in humans is influenced by several factors, causing significant inter- and intra-subject variations. Since many drugs are best absorbed in the upper gastrointestinal tract, such variability can lead to unpredictable bioavailability. Therefore, an effective delivery system should control and prolong gastric emptying time (GET) and deliver drugs in higher concentrations to the absorption site (i.e., the upper part of the small intestine).

Dosage forms that can be retained in the stomach are known as Gastroretentive Drug Delivery Systems (GRDDS). GRDDS can enhance the controlled delivery of drugs with an absorption window by continuously releasing the drug for a prolonged period before it reaches the absorption site, ensuring optimal bioavailability.



Various approaches for Gastroretentive Drug Delivery Systems.

One of the most feasible approaches for achieving prolonged and predictable drug delivery profiles in gastrointestinal tract is to control the Gastric Residence Time (GRT) using Gastro Retentive Dosage Forms (GRDFs) that offer a new and better option for drug therapy.**[11]**

CRITERIA FOR SELECTION OF DRUG CANDIDATE FOR GRDDS:

Gastro retentive drug delivery systems are suitable for the following types of drug therapy:

- Absorption from upper GIT: Drugs have a particular site for maximum absorption.
- Eg: Ciprofloxacin
- Drug having low pKa, which remains unionized in stomach for better absorption.
- Drugs having a reduced solubility at higher pH. Example: Captopril
- Local action as it is seen in the treatment of H. pylori by Amoxicillin trihydrate as in case of ulcers. The bioavailability of drugs that get degraded in alkaline pH can be increased by formulating gastro retentive dosage forms. Example: Doxifluridine; which degrades in the small intestine.

- To minimize gastric irritation this may be caused by the sudden increase of drug concentration in the stomach. Example: NSAIDs
- Drugs that act locally in the stomach. Example: Antacids, Antibiotics for bacterially based ulcers
- Drugs that are absorbed primarily in the stomach. Example: Albuterol
- Drugs that are poorly soluble in alkaline pH.
- Drugs that have a narrow window for absorption, i.e., Drugs that are absorbed mainly from the proximal part of small intestine. Example: Riboflavin, Levodopa.
- Drugs that are absorbed rapidly from the GI tract. Example: Amoxicillin.[12]

APPROACHES FOR GRDDS

The different approaches established for formulating dosage form to produce a satisfactory gastric retention and release within gastric region, are as follows:[12]

- High-density system
- Floating system
- Hydrodynamically balanced system
- Gas-generating system
- Raft-forming system
- Low-density system
- Expandable system
- Super porous hydrogels
- Mucoadhesive or bioadhesive system
- Magnetic system
- Self-unfolding systems

Nanoparticles:

Colloids Synthesis:

These are the phase-separated sub-micrometre particles in the form of spherical particles, rods, tubes and plates etc.These are the particles suspended in some hot matrix. Metal, alloy, semiconductor and insulator particles of different sizes and shapes can be synthesized in an aqueous or non-aqueous medium. The synthesis of colloids is a very old method. M. Faraday synthesized gold nanoparticles by wet chemical route. The particles are so stable. Colloidal particles are synthesized in a glass reactor. Glass reactors have a provision to introduce some precursors, and gases as well as measure temperature, pH etc; during the reaction.

It is possible to remove the products at suitable time intervals. The reaction is carried out under an inert atmosphere to avoid any uncontrolled oxidation of the prod Chemical methods provide an easy way to synthesize silver nanoparticles (Ag NPs) in solution. These metal nanoparticles have great potential for biomedical applications as antibacterial, antifungal, and antiviral agents or in wound healing. The adjustment of the parameters involved in these reactions permits precise control over the size, shape, monodispersed and surfaces of the nanoparticles. These nanoparticles are being used in the design of new hybrid organic-inorganic or inorganic nanomaterials for biomedical applications.[13]

Methods Based on Evaporation

Physical Vapour Deposition

This method usually involves the use of materials of interest as sources of evaporation. Inert gas or reactive gas for collisions with material vapour. A cold finger on which nanoparticles can condense, a scraper to scrape nanoparticles and a piston anvil. All the processes are carried out in a vacuum chamber so that the desired purity of the end product can be obtained. Generally, high vapour pressure metal oxides are evaporated from filaments of refractory metals like W, Ta, and Mo in which the materials to be evaporated are held. The density of the evaporated material close to the source is quite high and particle size is small[5nm] such particles would prefer to acquire a stable lower energy state. Due to small particle-particle interaction, bigger particles can be formed. Hence, they should be removed away from the source as fast as possible. This is done by forcing an inert gas near the source, which removes the particles from the vicinity of the source. In general, the rate of evaporation and the pressure of gases inside the chamber determine the particle size. Evaporated atoms and clusters tend to collide with gas molecules and make bigger particles, which condense on cold fingers.

The preparation of thin films by physical vapour deposition methods is described. At first, the different processes for the ejection of particles into the vacuum and the characteristic properties of the particles (ionization degree, kinetic energy etc.) are discussed. The influence of the growth parameters on the initial growth and the growth after coalescence is reported. The interrelations are illustrated by experimental findings and computer simulations.[14]

A. Synthesis of Metal Nanoparticles by Colloidal Method

This process is done by the reduction of some salt or acid. For example, copper particles can be obtained by reducing Chloroauric acid (HAuCl4) with trisodium citrate (Na3C6H5O7). The reaction will be, HAuCl4 + Na3C6H5O7 Au+ + C6H5O7 - + HCl +3 NaCl The reaction will be carried out in water. Obtained nanoparticles exhibit colour depending upon the particle size. i.e. (intense red colour for gold metal). In a similar way Silver, Gold, Palladium and a few other metal nanoparticles can be synthesized using appropriate precursors, temperature, pH, and duration of synthesis.

B. Sol-Gel Method

In this method two types of materials or compounds ‘sol’and ‘gel’ involves. This process is a low-temperature process, hence less energy consumption and less pollution. Sols are solid particles in a liquid. They are a sub-class of colloids. Gels are nothing but a continuous network of particles with pores filled with liquid. A sol-gel process involves the formation of sols in a liquid and then connecting the sol particles to form a network. By drying the liquid, it is possible to obtain the powders and thin films.

This method is useful to synthesize ceramics or metal oxides, sulphides, borides and nitrides. Sol-gel synthesis involves hydrolysis of precursors, condensation followed by polycondensation to form particles, gelation and drying process by various routes. Precursors are to be chosen so that they tend to form gels. Both alkoxides and metal salts can be used. It is also possible to synthesize nanoparticles like nanorods, nanotubes etc. by sol-gel technology. [15]

Biological Methods

A. Synthesis using Plant Extracts

The use of plants in the synthesis of nanoparticles is quite a less studied area as compared to the use of microorganisms to produce nanoparticles. There are a few examples which suggest that plant extracts can be used in the synthesis of nanoparticles. To obtain gold nanoparticles from geranium plant extract is discussed here. Finely crushed leaves are put in an Erlenmeyer flask and boiled in water just for a minute. Leaves get ruptured and cells release intracellular material.

The solution is cooled and decanted. This solution is added to the HAuCl4 aqueous solution, and nanoparticles of gold start forming within a minute.

B. Bio-Based Methods

Several reports prevailed in the literature indicate that the synthesis of nanoparticles by chemical approaches is eco-unfriendly and expensive. Thus, there is a growing need to develop environmentally and economically friendly processes, which do not use toxic chemicals in the synthesis protocols. This has conducted researchers to look at the organisms. The potential of organisms in nanoparticle synthesis ranges from simple prokaryotic bacterial cells to eukaryotic fungi and plants. Some examples of nanoparticle production include using bacteria for gold, silver, cadmium, zinc, magnetite, and iron NPS; yeasts for silver, lead and cadmium NPS; fungi for gold, silver and cadmium NPS; algae for silver and gold NPs; plants for silver, gold, palladium, zinc oxide, platinum, and magnetite NPs.

Bio-based protocols could be used for the synthesis of highly stable and well-characterized NPs when critical aspects, such as types of organisms, inheritable and genetical properties of organisms, optimal conditions for cell growth and enzyme activity, optimal reaction conditions, and selection of the biocatalyst state have been considered. Sizes and morphologies of the NPS can be controlled by altering some critical conditions, including substrate concentration, pH, light, temperature, buffer strength, electron donor (e.g., glucose or fructose), biomass and substrate concentration, mixing speed, and exposure time. In the following section, we discussed the synthesis of NPs.[16]

C. Tollens’s Method

A simple one-step process, Tollens’s method, has been used for the synthesis of silver NPs with controlled size. This green synthesis technique involves the reduction of Ag(NH3)2+ (as Tollens ‘s reagent) by an aldehyde. In the

modified Tollens procedure, silver ions are reduced by saccharides in the presence of ammonia, yielding silver nanoparticle films (50-200 nm), silver hydrosols (20-50 nm) and silver NPs of different shapes. In this method, ammonia concentration and the nature of the reducing agent play an important role in controlling the size and morphology of silver NPs. It was revealed that the smallest particles were formed at the lowest ammonia concentration. Glucose and the lowest ammonia concentration (5 mM) resulted in the smallest average particle size of 57 nm with an intensity maximum of surface plasmon absorbance at 420 nm. Moreover, an increase in NH3 from 0.005 M to 0.2 M resulted in a simultaneous increase in particle size and polydispersity. Silver NPs with controllable sizes were synthesized by reduction of [Ag(NH3)2] + with glucose, galactose, maltose, and lactose.

The nanoparticle synthesis was carried out at various ammonia concentrations (0.005-0.20 M) and pH conditions of 11.5-13.0 resulting in average particle sizes of 25-450 nm. The particle size was increased by increasing (NH3), and the difference in the structure of the reducing agent (monosaccharides and disaccharides) and pH (particles obtained at pH 11.5 were smaller than those at pH 12.5) influenced the particle size. Polydispersity also decreased by lowering the ph. Produced silver NPs were stabilized and protected by sodium dodecyl sulphate (SDS), polyoxymethylene sorbinatemonooleate (Tween 80), and polyvinylpyrrolidone (PVP 360). [16]

C. Irradiation Methods

Silver NPs can be synthesized by using a variety of irradiation methods. Laser irradiation of an aqueous solution of silver salt and surfactant can produce silver NPs with a well-defined shape and size distribution. Furthermore, the laser was used in a photo-sensitization synthetic method of making silver NPs using benzophenone. At short irradiation times, low laser powers produced silver NPs of about 20 nm, while an increased irradiation power produced NPs of about 5 nm. Laser and mercury lamps can be used as light sources for the production of silver NPs. In visible light irradiation studies, photo-sensitized growth of silver NPs using thiophene (sensitizing dye) and silver nanoparticle formation by illumination of Ag (NH3) + in ethanol have been done.[17]

D. Electrochemical Synthetic Method

The electrochemical synthetic method can be used to synthesize silver NPs. It is possible to control particle size by adjusting electrolysis parameters and to improve the homogeneity of silver NPs by changing the composition of electrolytic solutions. Polyphenolpyrrolecoated silver nanospheroids (3-20 nm) were synthesized by electrochemical reduction at the liquid/liquid interface. This nano-compound was prepared by transferring the silver metal ion from the aqueous phase to the organic phase, where it reacted with the pyrrole monomer. Inanother study, monodisperse silver nanospheroids (1-18 nm) were synthesized by electrochemical reduction inside or outside zeolite crystals according to the silver exchange degree of compact zeolite film-modified electrodes.

Furthermore, spherical silver NPs (10-20 nm) with narrow size distributions were conveniently synthesized in an aqueous solution by an electrochemical method. Poly N-vinylpyrrolidone was chosen as the stabilizer for the silver clusters in this study. Poly N-vinylpyrrolidone protects NPs from agglomeration, significantly reduces silver deposition rate, and promotes silver nucleation and silver particle formation rate. Application of rotating platinum cathode effectively solves the technological difficulty of rapidly transferring metallic NPs from cathode vicinity to bulk solution, avoiding the occurrence of flocculates in the vicinity of the cathode, and ensures monodisperses of particles. The addition of sodium dodecyl benzene sulfonate to the electrolyte improved particle size and particle size distribution of silver NPs.[17]

Conclusion:

Several innovative formulation approaches have been discussed in this article that can improve the solubility and bioavailability of pemafibrate. These strategies are crucial in optimizing therapeutic efficacy of pemafibrate. It reduces the need for high dose and ensures consistent and reliable clinical outcomes. The use of technologies like gastro retentive drug delivery systems, nano structures, solid dispersions, self-emulsifying systems, and cyclodextrin complexes represents a promising path forward in enhancing the clinical utility of pemafibrate in managing lipid disorders.

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