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Fenofibrate Nanosuspension: A Novel Strategy to Enhance its Bioavailability for the Management of Hyperlipidemia

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ABSTRACT

Hyperlipidemia, a metabolic condition marked by elevated plasma levels of cholesterol or triglyceride-carrying lipoproteins, is a major contributor to atherosclerosis and cardiovascular diseases. Antihyperlipidemic drugs are classified according to their primary mechanism of action. Fenofibrate's role in regulating cholesterol and managing insulin resistance-associated metabolic disorders makes it a preferred choice in combination therapies with statins for cardiovascular disease management. Nanoparticles have gained attention for enhancing the bioavailability of poorly water-soluble drugs by reducing particle size to the nanoscale (100-200 nm), which increases solubility, dissolution rate and adhesion to cell surfaces. Nanosuspensions improve drug solubility and bioavailability through methods like media milling, high-pressure homogenization and precipitation. Despite advancements, producing stable Fenofibrate nanoparticles below 100 nm at an industrial scale remains a challenge. Recent strategies include using sonication and freeze-drying to enhance bioavailability and solubility, achieving significant improvements in drug dissolution and therapeutic efficacy.

Introduction

Hyperlipidemia refers to a condition where the levels of cholesterol or triglyceride-carrying lipoproteins in the plasma surpass the normal range [1]. It plays a significant role in the development of atherosclerosis and is recognized as a key risk factor for cardiovascular diseases [2]. Contributing risk factors include stroke, myocardial infarction, cerebrovascular disease, coronary heart disease, heart attack and the advancement of diabetes [3]. Hyperlipidemia is a metabolic disorder characterized by an abnormal serum lipid and lipoprotein profile, with elevated levels of low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), total cholesterol (TC) and triglycerides (TAG) along with a decrease in high-density lipoprotein (HDL) concentrations in the bloodstream [4].

Antihyperlipidemic drugs

Drugs used to treat lipid disorders (LDs) are categorized based on their primary mechanism of action. These include HMG-CoA reductase inhibitors (statins), lipoprotein lipase activators (fibrates), cholesterol absorption inhibitors (ezetimibe) and bile acid sequestrants (resins). Fibrates, such as clofibrate, fenofibrate, gemfibrozil and bezafibrate are commonly prescribed for managing hyperlipidemia, particularly in patients with lipid disorders [5,6].

Table 1: Drug profile of Fenofibrate

Generic Name	Fenofibrate
Brand Names	Tricor, Lipofen, Fenoglide, Triglide, Antara
Drug Class	Fibrate (Fibric Acid Derivative)
Chemical structure	$C_{20}H_{21}ClO_4$
Molecular weight	360.83 g/mol
Half-Life:	19-27hr
Protein binding	99%
Category	Antilipemic
Log P	4.68
Volume of Distribution	0.89L/kg
Clearance Value	1.1L/h (In young adults)
Dosage Forms	Tablets and capsules (54 mg, 67 mg, 145 mg and 160 mg)
Adverse Effects	Nausea, diarrhea and abdominal pain.

Fenofibrate is a widely used anti-hyperlipidemic agent for managing hyper-cholesterolemia, hyper-triglyceridemia and mixed hyper-lipidemia. It is preferred in combination with statins due to its lower risk of interactions. Fenofibrate reduces cholesterol, triglycerides, LDL and VLDL while increasing HDL, improving lipid profiles. A key challenge is enhancing its bioavailability due to poor

solubility, leading to the development of new formulations. It is a prodrug converted into fenofibric acid, and plays a role in managing insulin resistance-related metabolic disorders. Fenofibrate also plays an important role in managing insulin resistance-related metabolic disorders. When combined with statins, it effectively regulates hypercholesterolemia and hypertriglyceridemia levels [7,8].

Mechanism of action

Fenofibrate acts by activating the peroxisome proliferator-activated receptor alpha (PPAR-α), a nuclear receptor that regulates lipid metabolism. This activation increases lipoprotein lipase activity, which leads to the breakdown of triglycerides present in lipoproteins. Consequently, fatty acid oxidation in the liver is enhanced, leading to a reduction in both fatty acid and triglyceride levels in the blood. Additionally, fenofibrate decreases the production of apolipoprotein C-III (ApoC-III), a protein that inhibits lipase, thus further contributing to the reduction in triglycerides. These metabolic effects also result in increased production of high-density lipoprotein (HDL) cholesterol, which is associated with improved cardiovascular outcomes. Overall, the drug helps improve the lipid profile by lowering triglyceride and low-density lipoprotein (LDL) cholesterol levels, while simultaneously increasing HDL cholesterol. This makes fenofibrate a valuable treatment option for managing hyperlipidemia and related cardiovascular conditions [9,10].

Challenges with current dosage forms

Many new drug compounds, especially lipophilic (fat-loving) ones, have low water solubility. This reduces their bioavailability when taken orally, leading to the need for higher doses, increased side effects and lower patient adherence. Fenofibrate, a lipid-lowering drug, is a prime example where improving its solubility is crucial for enhancing its absorption and bioavailability.

Approaches to Enhance Solubility

Reducing Particle Size: Smaller particles have a larger surface area, which increases the drug's dissolution rate.

Creating Amorphous Forms: The amorphous state of a drug has higher solubility compared to its crystalline form.

Techniques: Strategies like micronization, nanoparticle formation and solid dispersions (SDs) are widely used to alter physical properties, enhancing solubility and dissolution rates. Improving the solubility of poorly water-soluble drugs remains a major focus in pharmaceutical research to optimize drug delivery and patient outcomes.

Importance of nanoparticles

Nanoparticles for Poorly Soluble Drugs: Nanoparticles, or drug nanocrystals, typically range between 100–200 nm in size. They represent a promising approach to improve the bioavailability of drugs with poor water solubility.

Enhanced Bioavailability: The tiny size of nanoparticles enhances aqueous solubility, speeds up the dissolution rate and improves the drug's ability to adhere to cell surfaces or membranes.

Comparison to Micronized Particles: Nanoparticles, which are smaller than 1 micron, offer a much larger surface area compared to micronized particles. This results in a faster dissolution rate, as described by the Noyes-Whitney equation.

Increased Retention Time: Nanoparticles adhere better to target cells, increasing retention time at the absorption site and promoting better drug uptake.

Nanosuspension

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. Nanoparticles are pure drug particles dispersed in an aqueous medium, with sizes less than 1 µm. Their smaller size enhances the dissolution rate due to increased surface area and higher saturation solubility. The rise in saturation solubility and dissolution speed is due to the increased vapor pressure of the smaller particles. These provide a simple and effective solution for delivering poorly water-soluble and poorly water- and lipid-soluble drugs. They offer advantages over other drug delivery approaches. Over 40% of new drugs have poor water solubility, leading to low bioavailability and difficulties in formulating traditional dosage forms. Nanosuspensions can be administered through oral, parenteral, pulmonary, ocular and topical routes. Nanotechnology enhances drug solubility and bioavailability. Techniques like melt emulsification and precipitation are used to create nanoparticles of drugs like fenofibrate [11-14].

Preparation of nanosuspension

There are two primary methods for preparing nanosuspensions.

Bottom-Up Technology: This conventional method involves dissolving the drug in a solvent and then adding it to a nonsolvent to precipitate the crystals, forming hydrosols. During this precipitation process, it is crucial to control crystal growth by adding surfactants to prevent the formation of microparticles.

Top-Down Technology: This approach includes several techniques such as media milling (Nanocrystals), high-pressure homogenization in water (Dissocubes), high-pressure homogenization in non-aqueous media (Nanopure) and a combination of precipitation & high-pressure homogenization (Nanoedge) [15,16].

Table 3: Formulation of Fenofibrate with various method of preparation [17-19]

Formulation	Method of preparation	Drug release
Fenofibrate loaded nanoparticles	Precipitation method	Percent drug release for the optimized batch was 89.01 % at the end of 30 min.
Fenofibrate nanosuspension	Melt emulsification method combined with high-pressure homogenization	Drug release is 90.62% (2 hrs)for nanosuspension when 34.9% for coarse suspension and 70.7% for micronized suspension
Fenofibrate nanocrystal suspension	Bead milling method	Bioavailability of the spray-dried formulation was determined to be 89.6% than the micronized.
Fenofibrate nanosuspension	Probe sonicator	Dissolution of nanosuspension is 73.89% and pure drug is 8.53% for 1% sodium lauryl sulfate medium
Fenofibrate nanosuspension	High pressure homogenization	Marketed fenofibrate tablet shows 64.3% release within 60 min. While Freeze dried fenofibrate nanoparticles shows 96.2% release within 60 min.

Advances and Challenges in Nanotechnology-Based Formulation of Fenofibrate:

Nanotechnology in Fenofibrate: Advances in nanotechnology have improved fenofibrate by enhancing solubility, dissolution, bioavailability and controlled release.

Particle Size Reduction: Reducing the particle size increases surface area, improving water solubility. Techniques have succeeded in creating fenofibrate nanoparticles smaller than 500 nm.

Milling (Top-Down Method): Bead milling has been used to reduce fenofibrate particle size. Nanoparticles produced through bead milling dissolve similarly to Lipidil®. Almost 61% bioavailability was achieved in beagle dogs.

Bottom-Up Methods: Solvent precipitation, sonochemical techniques and supercritical fluids are effective in producing fenofibrate nanoparticles.

Scalable Methods: Combining antisolvent precipitation with spray drying is a scalable method for nanoparticle production.

Sonication: Boosted oral bioavailability of fenofibrate by five times in rabbits.

Freeze-Drying: Freeze-drying fenofibrate nanoparticles helped control fatty liver and lipid levels in high-cholesterol rabbits.

Applications to Other Drugs: These techniques can also be applied to improve the solubility of other drugs, including cancer treatments that struggle with solubility issues.

Alternative Strategies: Self-emulsifying drug delivery systems (SEDDS) and solid lipid nanoparticles (SLNs) have been tested to improve fenofibrate bioavailability.

Challenges in Nanoparticle Production: Producing stable fenofibrate nanoparticles under 100 nm is challenging, especially for large-scale production.

Preferred Industrial Methods: Media milling and supercritical fluid techniques are favored by the pharmaceutical industry for making nanoparticle-based products.

Key Factors for Industrial Scale Formulations: To produce fenofibrate formulations on an industrial scale, it's essential to balance solid content, particle size, reproducibility and scalability.

Cost and Efficiency Considerations: This summarizes the strategies, challenges and considerations for improving fenofibrate formulations at an industrial scale [20].

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