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An Overview of the Applications of Gemfibrozil Nano-Formulation in Hyperlipidemia †

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Abstract: Gemfibrozil is a benzene derivative of valeric acid that belongs to the class of medications known as fibrates. Its chemical name is 5-(2,5 dimethylphenoxy)-2,2-dimethylpentanoic acid. It is the treatment of choice in clinical settings for hyperlipidemia (type III) and hypertriglyceridemia (type IV), and it has been shown to reduce serum triglycerides and very low-density lipoprotein cholesterol while increasing high-density lipoprotein cholesterol by activating the peroxisome proliferator-activated receptors (PPARs), acting primarily on the PPARα isoform. Gemfibrozil's effective absorption and bioavailability after oral administration are constrained by its small molecule size, poor water solubility (0.01 mg/mL), and slow rate of digestion. These factors are caused by the drug's physicochemical characteristics. Gemfibrozil's solubility may be increased by creating nano-specific drug delivery methods, such as nanocrystals, nanosuspensions, or lipid-based formulations. In literature, the lipid-based drug delivery system has received substantial coverage for improving drug solubility, permeability, and bioavailability. Self-nano-emulsified delivery systems (SNEDDS), for example, are lipid-based formulations that are supposed to improve lipophilic drug absorption. When gently stirred, SNEDDS, which are isotropic solutions of oil, surfactant, co-surfactant, and medicine, produce an oil-in-water emulsion in an aqueous environment. This review will demonstrate the techniques used to increase the solubility and bioavailability of gemfibrozil.

Keywords: gemfibrozil; poor water solubility; nano-specific drug delivery system; SNEDDS; increase solubility

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1. Introduction

A significant area of current research is nanotechnology, which deals with the design, production, and manipulation of particle structures starting from about 1–100 nm in one dimension. The physical, chemical, and biological characteristics of the nanoparticles in this size range diverge significantly from those of individual atoms and molecules, as well as the comparable bulk materials [1]. Nanoparticles (NPs) are colloidal particles with a diameter of less than one nanometer. The NPs' matrix contains a medication that is either encapsulated, trapped, or attached, as shown in Figure 1. Depending on whether a polymerization reaction is necessary for the synthesis or if it may be performed directly from a pre-existing polymer or macromolecule, there are two main groups of nanoparticle production methods. The type of polymers used and the medicine that will be enclosed influence the production method chosen. Because these tiny particles can shield the drug from enzymatic and hydrolytic degradation in the gastrointestinal tract (GIT), extend the time the drug spends there by adhering to mucous membranes, and significantly

increase the bioavailability of drugs, NPs have been investigated extensively for oral drug delivery [2].

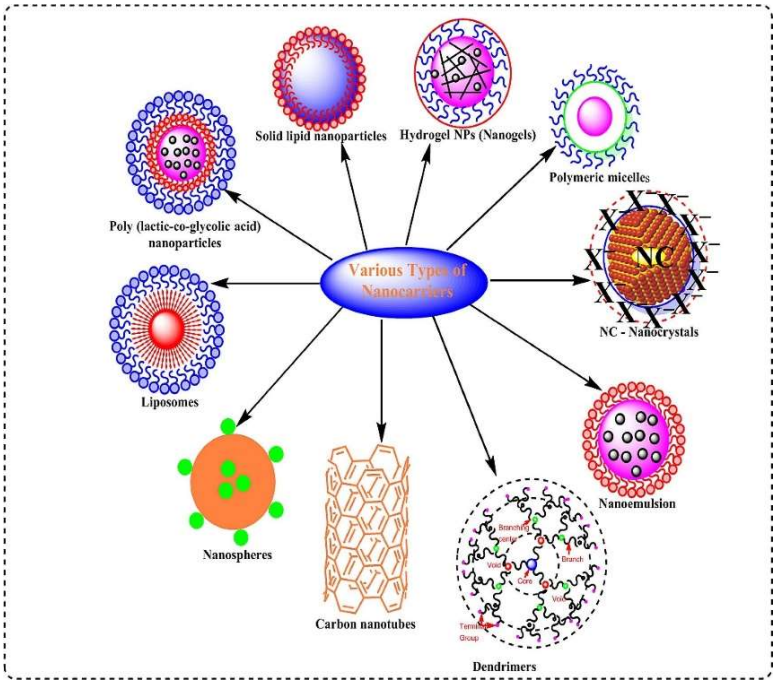

Figure 1. Schematic representation of various multifunctional nanocarriers.

Gemfibrozil, also referred to as "lopid" in the pharmacy, is a fibrate medication that has received FDA approval and is chemically an amphipathic carboxylic acid molecule. It was initially developed in 1968 at Parke Davis Research Laboratories in Detroit, Michigan to decrease serum lipid. Gemfibrozil, a new medicine with the ability to decrease cholesterol, was proposed and sent for a clinical study in 1971 after three years of intensive research [3]. Gemfibrozil, a medicine with a substantial potential to lower plasma triglyceride levels, was successfully launched to the market as a hypolipidemic medication in the year 1976 [4].

Gemfibrozil has a few advantages over other lipid-lowering medications in general. It has two advantages over other lipid-lowering medications: it can be delivered orally, which is less unpleasant, and it produces substantially less side effects. As a result, numerous studies on gemfibrozil's ability to decrease cholesterol have been undertaken since it was first introduced to the field [5].

2. Hyperlipidemia

A rise in one or more plasma lipids, such as triglycerides, cholesterol, cholesterol esters, phospholipids, and/or plasma lipoproteins, such as very low-density lipoprotein and low-density lipoprotein, along with a decrease in the levels of high-density lipoprotein, characterizes the medical condition known as hyperlipidemia. A greater flow of free fatty acids is frequently a defining feature (FFAs). One of the most important risk factors for cardiovascular illnesses is this increase in plasma lipids. Until then, statins and fibrates, which have serious side effects on the muscles and the liver, remain the principal anti-hyperlipidemic medications used to treat high plasma cholesterol and triglycerides, respectively [6].

- Although only a small percentage of individuals have genetic abnormalities that can be predicted, primary hyperlipidemia is likely hereditary in origin.
- Diabetes, liver illnesses, kidney disorders, thyroid problems, Cushing's syndrome, thyroid disease, obesity, estrogen treatment, alcohol intake, and other drug-related changes in lipid metabolism are only a few of the conditions that can cause secondary hyperlipidemia.

- There are some variables that can affect cholesterol or lipoprotein levels.
- Certain diuretics can increase the levels of triglycerides and total cholesterol.
- In women, menstruation can result in a drop in LDL levels and a rise in HDL levels.
- Total cholesterol levels during pregnancy may rise and stay high for as long as 20 weeks after delivery.
- The summer and the winter have the lowest and highest total cholesterol levels, respectively.
- Lower levels of LDL and total cholesterol are achieved with estrogen replacement therapy, whereas HDL levels increase.

Treatment of Hyperlipidemia

The role of the nanoparticles that are studied in hyperlipidemia is improving the safety and effectiveness of the medication by using a medication with reduced toxicity, breaking down harmful cholesterol (LDL), and boosting drug efficacy [7].

One of the most prevalent, potentially fatal metabolic illnesses worldwide is hyperlipidemia, which is defined as an abnormal increase in lipid and lipoprotein in the plasma. A popular class of lipid-lowering medications on the market is called fibrates. Gemfibrozil has a well-established hypolipidemic effect among other fibrate medications [8].

3. Drug Profile of Gemfibrozil

Gemfibrozil, a lipid regulator, is used to lower serum triglyceride levels in high-risk hyperlipidemic individuals. Gemfibrozil is a fibrate, or derivatives of fibric acid, substance. The chemical nomenclature of gemfibrozil is 5-(2,5-dimethylphenoxy)-2,2-dimethyl-pentanoic acid, with a molecular formula and a molecular weight of $C_{15}H_{22}O_3$ and 250.33 g/mol, respectively. The physical appearance of the drug is a white solid, and it is soluble in water (slightly) and acid. The melting point of gemfibrozil is 61–63 °C, along with 4.5 pka. Gemfibrozil is absorbed from the gastrointestinal tract [9]. The structure of gemfibrozil is shown in Figure 2.

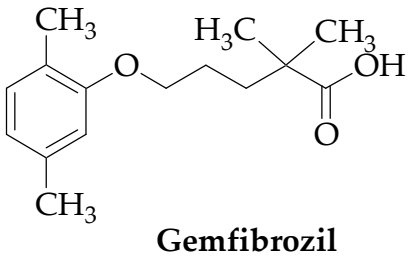

Figure 2. Structure of gemfibrozil.

3.1. Mechanism of Action

Gemfibrozil changes lipid metabolism by activating the PPAR (peroxisome proliferator-activated receptor). Increases in HDL, apo AI, apo AII, lipoprotein lipase (LPL); suppression of apo B synthesis and peripheral lipolysis; a decrease in the liver's ability to remove free fatty acids; and an increase in apoB clearance are all results of this activation.

Plasma triglyceride levels are decreased by upregulated LPL. The synthesis of triglycerides is decreased by the decreased hepatic clearance of fatty acids. The reduction in VLDL generation caused by the effects on apoB synthesis and clearance also lowers plasma triglyceride levels. The glucuronide metabolite of gemfibrozil inhibits CYP2C8 as well [9].

3.2. Pharmacology of Gemfibrozil

Gemfibrozil is a lipid-regulating medication that raises HDL cholesterol while decreasing serum triglycerides and very low-density lipoprotein (VLDL) cholesterol. While treatment with gemfibrozil tablets may result in small reductions in total and low-density lipoprotein (LDL) cholesterol, it frequently causes an increase in LDL cholesterol in individuals with increased triglycerides, as a result of type IV hyperlipoproteinemia. Gemfibrozil

medication generally has no effect on LDL cholesterol levels in Type IIb patients with elevated blood LDL cholesterol and triglyceride levels; however, gemfibrozil typically causes a considerable increase in HDL cholesterol in this population. Apolipoproteins AI and aII, as well as the HDL subfractions HDL2 and HDL3, are all upregulated by gemfibrozil. Low HDL cholesterol and high LDL cholesterol are separate risk factors, according to epidemiological studies.

The exact mechanism of gemfibrozil's effect is still unknown. Inhibiting peripheral lipolysis and lowering the hepatic extraction of free fatty acids in humans have both been demonstrated to lower hepatic triglyceride synthesis. Gemfibrozil reduces the development of VLDL by inhibiting the synthesis of apolipoprotein B, the VLDL carrier, and by enhancing its clearance [10].

4. Applications of Nanocarriers in Gemfibrozil

Poor drug solubility and low bioavailability frequently place restrictions on the oral distribution of therapeutic entities. Almost 40% of recently developed medications have poor water solubility. Poor drug solubility has prevented numerous medicines from becoming commercially successful, since it is so important in medication formulation. By using standard techniques, such as complexation, polymorphism, co-solvency, solubilizers, solid dispersions, self-micro-emulsifying drug delivery systems, micronization, and co-crystallization, much effort has been made to increase the solubility of pharmaceuticals. The creation of nanocrystals, or nanosuspension, is one of the most often used methods being researched right now (NS). When a medicine is reformulated for NS, the FDA considers it to be a novel drug that can be patented, and it is not regarded as generic. Given the drawbacks of alternate strategies, such as their inability to be applied to all medications, as is the case with inclusion complexes and micro-emulsion, nanoparticle engineering continues to be the preferred option for pharmaceutical application and could be a useful tool for "brick dust candidates".

Nowadays, nanotechnology is a crucial method for making poorly water-soluble pharmaceuticals more soluble. Due to their increased surface area and saturation solubility, these medicines' particle size reductions to the nanometer range may enhance their bioavailabilities and rates of dissolution [11].

Finding secure and efficient ways to dissolve medications that are not easily soluble is a growing, significant topic of pharmaceutical research [12]. To address this issue, a number of technical experiments have been used, such as the micronization of gemfibrozil [13]; delivery methods such as microspheres and macromolecular conjugates have also been tested [14].

4.1. Self-Emulsifying Drug Delivery System

Emulsion systems have their own set of issues, such as stability issues and manufacturing limitations related to their commercial production. The drawbacks of traditional emulsion systems can be avoided with the use of self-emulsifying drug delivery systems (SEDDS) [1]. Throughout the past two to three decades, research has focused on creating self-nano-emulsifying drug delivery systems and nano-emulsions to increase the oral bioavailability of BCS class II medicines [15]. The greater solubilization and protection of the medication against enzymatic and physicochemical degradation may be the cause of the increased oral bioavailability of pharmaceuticals from these systems. The GIT experiences uniform and widespread medication dispersion because the small droplet size increases the contact between the watery gut medium and the lipophilic droplets [16,17].

Poorly water-soluble actives can be delivered via lipid-based formulations; of these, self-nano-emulsifying drug delivery systems (SNEDDS) are thought to be a promising approach for increasing the pace and amount of absorption [15,18].

Drug delivery systems that self-nano-emulsify are isotropic mixtures of the drug, lipids, and surfactants, typically with one or more hydrophilic co-solvents or co-emulsifiers that, upon mild agitation in an aqueous medium, form fine oil-in-water nano-emulsions, with

droplet sizes ranging from 20 to 200 nm [19,20]. This mechanism spontaneously emulsifies in the fluid and the motility-rich environment of the gastrointestinal tract [21–23]. They can enhance intestinal membrane penetration through a wide dispersion in the GIT (owing to the small droplet size), improving medication solubilization (the water-insoluble medicine is often dissolved in the oil phase) and reducing the food effect [24,25]. Contrarily, SNEDDS formulations with bioenhancers and specific surfactants, such as Cremophor®, increase the bioavailability of ingested substances by promoting transcellular and paracellular absorption [26].

SNEDDS contributes significantly to improving a poorly aqueous-dissolvable drug's water solubility and boosting oral drug transport and effectiveness. Chemically, they are durable. It provides medication fortification against hydrolysis and corrosion in the O/W phase. It can be used as a substitute for vesicles and lipophilic transporters. In comparison to micellar solution, SNEDDS have a higher solubilization capability and a longer shelf life. Additionally, compared to micro-emulsion, it has nano-sized droplets. SNEDDS has a targeted drug delivery system with a particular site response. The potential of SNEDDS is to protect against enzymatic breakdown [27].

4.2. Wet Milling Method

The solubility of poorly water-soluble pharmaceuticals can now be improved with the help of nanotechnology. By increasing their surface area and saturation solubility, these medications' particle size reductions to the nanometer range may increase their bioavailabilities and dissolving rates [28,29]. A submicron colloidal dispersion of pharmaceutical active ingredient particles in a liquid phase, with a size below 1 m, without any matrix material, and stabilized by surfactants and polymers, is referred to as a nanosuspension [30]. Wet milling is a reliable method for shrinking medication particles to the nanoscale range and improving their aqueous solubility [31]. This method uses small, hard beads to crush the drug particles in an aqueous mixture to minimize their size. Attrition between the drug particles and the grinding media reduces the size of the drug particle [32]. The high surface area of nanoparticles makes them more likely to agglomerate [33]. Drug particles must be stabilized using stabilizers, such as polymers and surfactants, in order to reduce drug particle aggregation [34]. Drug particles are stabilized by the stabilizers once they adsorb on their surfaces and interact with one another ionically or sterically [35]. In order to make gemfibrozil more water soluble, this effort aims to prepare gemfibrozil nanosuspensions (GEM NS) using a modified wet milling process. For the preparation of GEM NS in this study, we combined the wet milling process with sonication. The processing time for wet milling was shortened by this combination.

In comparison to other techniques, wet milling usually produces batches with greater batch homogeneity and consistency from batch to batch. Since the materials are suspended in the proper solvent, it is also not necessary to use special containment for managing potent compounds. Heat-sensitive chemicals are safeguarded [36].

5. Conclusions

The present review recapitulates various nano-formulations of gemfibrozil used in drug delivery. The creation of efficient and secure nano-formulation is still difficult. For the biological environment, the developed formulation needs to be safe. A promising new medication formulation of gemfibrozil can be made using the nanosuspension. Gemfibrozil nanosuspension has a better solubility in water than pure gemfibrozil, according to a solubility study. In order to increase the bioavailability of gemfibrozil, the gemfibrozil nanosuspension and the proposed SNEDDS with gemfibrozil for oral admission may represent a feasible alternative drug delivery strategy.

Since "nanostructured lipid carriers" are currently used as carriers and have a number of advantages over the other carriers, including superior drug loading capacity, improved release characteristics, and multiple drug incorporation, it is clear that the nano-aided drug delivery system is an effective method. The drug's solubility and bioavailability are

increased by SNEDDS and the wet milling method, which also keeps it in a dissolved state and consistency. Therefore, these nanocarriers are the appropriate options for gemfibrozil. Therefore, it has been concluded that gemfibrozil nanocarriers are more significant than the drug's conventional prescription forms.

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