Available online on 15.04.2026 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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Review Article

An Antihyperlipidemic Agents Review for Atherosclerosis Treatment

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ABSTRACT

Elevated levels of one or more plasma lipids, including triglycerides, cholesterol, cholesterol esters, phospholipids, and/or plasma lipoproteins, including very low-density lipoprotein and decreased levels of high-density lipoprotein are indicative of a medical condition called hyperlipidemia. This elevation in plasma lipids is one of the primary risk factors for cardiovascular diseases.Statins and fibrates remain the main antihyperlipidemic drugs for the treatment of elevated plasma cholesterol and triglycerides, respectively, at the cost of major negative effects on the liver and muscles. Hyperlipidemia is the main risk factor for coronary heart disease.

Keywords: Antihyperlipidemic, Atherosclerosis, Fibrate

ARTICLE INFO: Received 2025 15 Nov. ; Review Complete 20 Jan.2026 ; Accepted 22 March 2026; Available online 15 April. 2026

Cite this article as:
Talekar R, Gorade N, Jadhav S, Chormage P, Gadekar S, Tarkase SH, Sanap G, An Antihyperlipidemic Agents Review for Atherosclerosis Treatment , Asian Journal of Pharmaceutical Research and Development. 2026; 14(2):174-181.
DOI: http://dx.doi.org/10.22270/ajprd.v14i2.1734

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INTRODUCTION

Elevated blood levels of fat particles, or lipids, characterize a disorder known as hyperlipidemia, increased lipid plasma levels that are stored as lipoproteins. For instance, triglycerides and cholesterol. These fats can accumulate in the walls of blood arteries and obstruct blood flow. This increases the risk of stroke and heart attack. .(1-3)

What is hyperlipidemia?

An excess of lipids (fats) in the blood is referred to as hyperlipidemia, dyslipidemia, or high cholesterol. Your liver produces cholesterol to aid in food digestion and the production of hormones. However, you also consume cholesterol-containing foods from the dairy and meat sections. Your liver can produce all the cholesterol you require, so the cholesterol in food is in excess. It is unhealthy to have too much cholesterol (200 mg/dL to 239 mg/dL is borderline high, and 240 mg/dL is high) because it can obstruct the artery highways that carry blood throughout your body. When your arteries don't supply enough blood to your organs, it causes damage. (4)

The most dangerous kind of cholesterol is bad cholesterol (LDL), which leads to the accumulation of plaque, or hardened cholesterol deposits, inside your blood vessels. This makes it more difficult for your blood to flow, increasing your risk of heart attack or stroke. If the plaque is irritated or inflamed, a clot may form around it. A heart attack or stroke may result from this, depending on the location of the obstruction. Consider cholesterol as a type of fat that moves through your blood in lipoprotein cars. Because it can clog your arteries like a big truck that broke down and is obstructing a traffic lane, low-density lipoprotein, or LDL, is referred to as bad cholesterol. 130 mg/dL to 159 mg/dL is considered borderline high. 160–189 mg/dL is considered high. Because very low-density lipoprotein (VLDL) contains triglycerides that contribute to artery plaque, it is also referred to as bad. This is an additional kind of traffic blocker. High-density lipoprotein (HDL) is referred to as good cholesterol because it transports cholesterol to the liver, where it is eliminated. This is comparable to the tow truck that pulls disabled cars out of traffic lanes so other cars can pass. It's making it easier for

your blood to pass through your blood vessels in this instance. You don't want your HDL to be less than 40 mg/dL. (4-5)

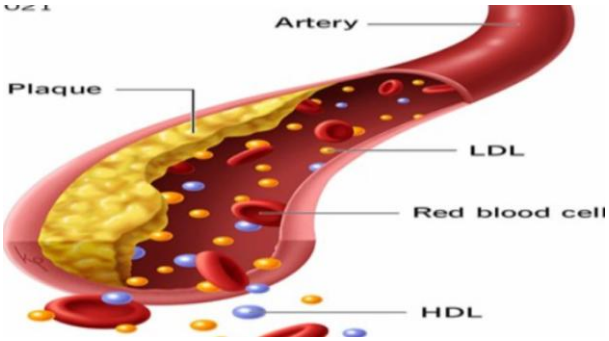


Figure 1: Process of Atherosclerosis

Cardiovascular diseases continue to be the leading cause of death worldwide, including in India and the United States. Hyperlipidemia also includes oxidative stress that produces free oxygen radicals, which may cause oxidative modification of low density lipoprotein and contribute to the progression of atherosclerosis and related cardiovascular disease..(5)

HYPERLIPIDEMIA CAUSING AGENT:

Beta blockers, diuretics, hormonal birth control, steroids, and antiretroviral medications for HIV are among the medications that can cause your cholesterol levels to fluctuate. Other causes of hyperlipidemia include smoking and heavy alcohol consumption. eating foods heavy in saturated and trans fats. excessive sitting and inactivity. Feeling tense, having unhealthy high cholesterol due to genetics. being overweight..(6)

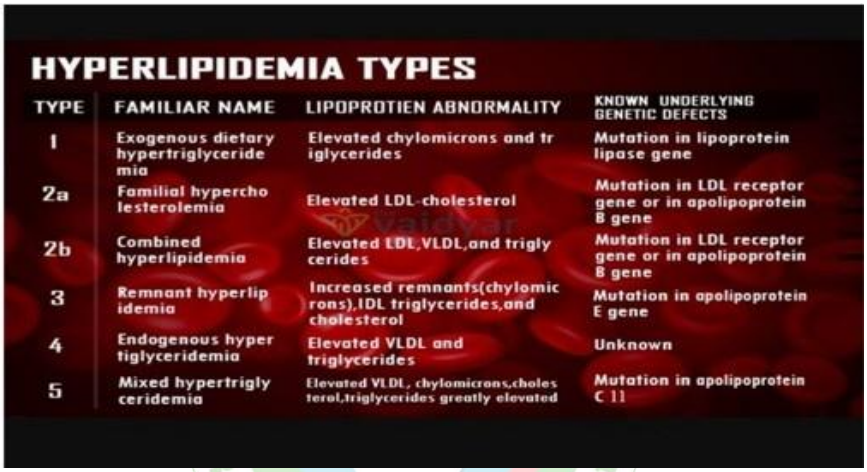


Figure 2: Types of hyperlipidemia

CAUSES OF HYPERLIPIDEMIA: (7-9)

- Familial hypercholesterolemia
- Chronic kidney disease
- Chronic liver disease
- Diabetes
- HIV / AIDS
- Hypothyroidism
- Lupus
- Overweight and Obesity
- Sleep apnea

SYMPTOMS :(10)

- Chest pain
- Confusion and trouble speaking
- Leg cramps mostly in calves
- Pain in feet or toes
- Trouble breathing
- Shortness of breath
- Weakness

KEY RISK FACTORS (11)

- Age
- Gender
- Underlying conditions
- Geographic location

PREVENTION STEPS AND STRATEGIES (12)

- Maintain a healthy weight
- Get a regular physical activity
- Quit smoking
- Limit alcohol
- Work with your health care team

COMPLICATION OF HYPERLIPIDEMIA:

Atherosclerosis (13)

The most significant risk factor for atherosclerosis, the primary cause of cardiovascular disease, is hyperlipidemia. The pathologic process known as atherosclerosis is typified by the buildup of fibrous plaques and lipids, cholesterol, and calcium in the walls of large and medium arteries..

Coronary Artery Disease (CAD)(13-15)

The primary cause of coronary artery disease, atherosclerosis, is characterized by the buildup of fat and the development of fibrous plaques in the artery walls. This narrowing of the arteries that supply blood to the myocardium limits blood flow and leaves the heart with insufficient oxygen. A higher lipid profile has been linked to coronary **atherosclerosis..**

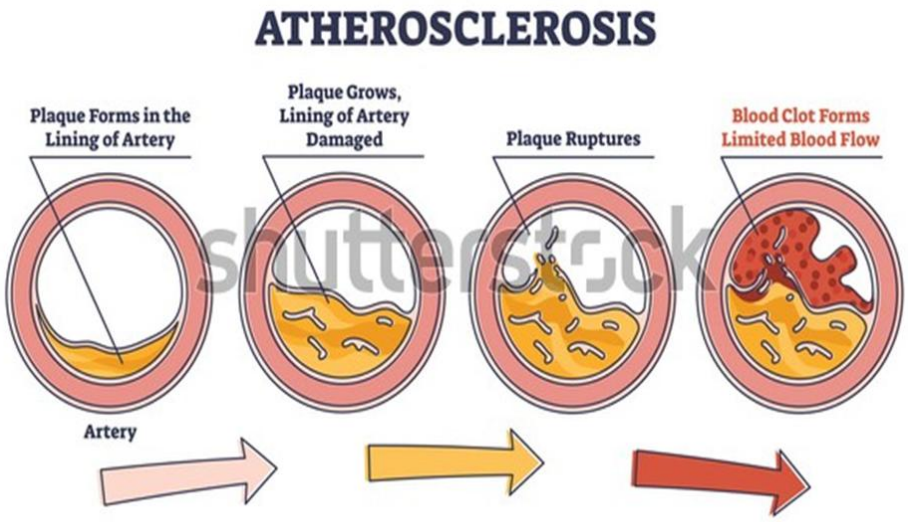


Figure 3: Atherosclerosis stages. (15, 16)

Myocardial Infarction (MI)(13)

A condition known as MI is brought on by partial or total blockage of blood and oxygen supplies in one or more cardiac arteries, which damages or kills heart cells. Atherosclerotic plaque rupture could be the cause of the blockage..

Ischemic stroke

Stroke ranks as the fourth most common cause of death. Strokes typically result from an artery being blocked by a blood clot or a fragment of atherosclerotic plaque that breaks free in a tiny blood vessel inside the brain. Lowering total cholesterol and low-density lipoprotein by 15% dramatically decreased the risk of the first stroke, according to numerous clinical trials..(13.4)

Other Complication include :(14)

- Peripheral artery disease
- Microvascular disease
- Sudden cardiac arrest
- Carotid artery disease

Classes of Medications Used To Treat Hyperlipidemia (17)

Classification:

1. HMG Co – A Reductase inhibitors (statins)
2. Lovastatin , Simvastatin , Pravastatin , Atorvastatin , Rosuvastatin
3. Bile Acid Sequestrants (Resin)
4. Cholestyramine , Colestipol
5. Activate lipoprotein lipase (Fibric acid derivatives)
6. Clofibrate, Gemfibrozil, Bezafibrate, Fenofibrate
7. Inhibit lipolysis and triglyceride synthesis
8. Nicotinic acid
9. Others
10. Ezetimibe, Gugu lipid.

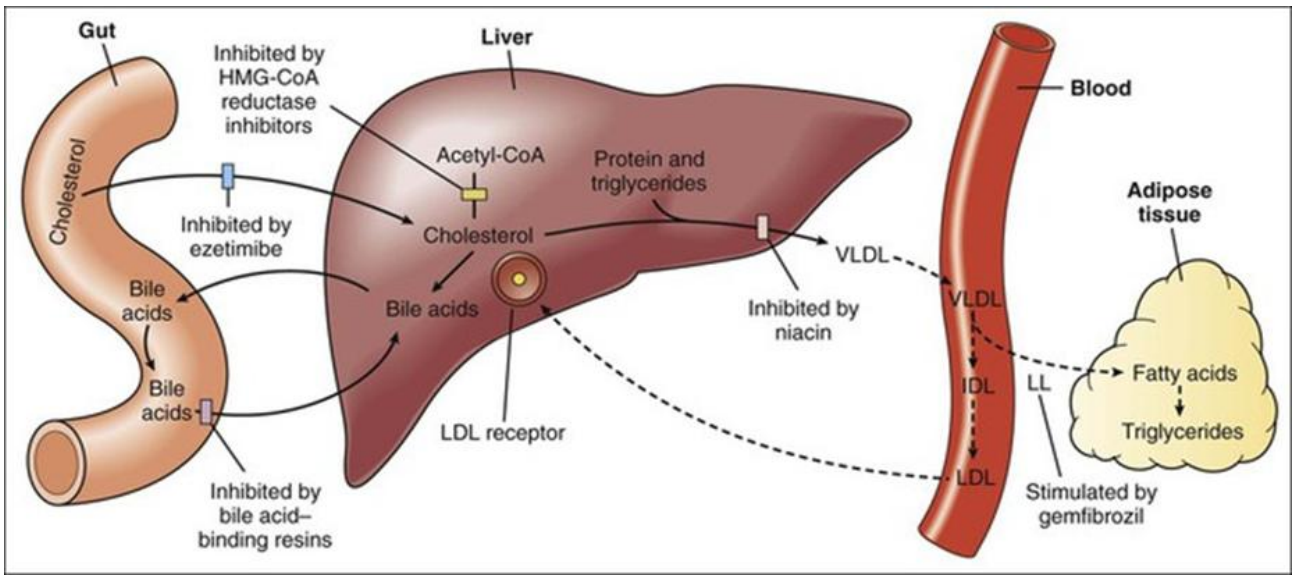
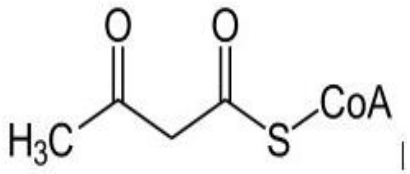


Figure 4: MOA Of Hyperlipidemic Agent (17)

Figure 5: Consequences of High Cholesterol (18)

1. Statins

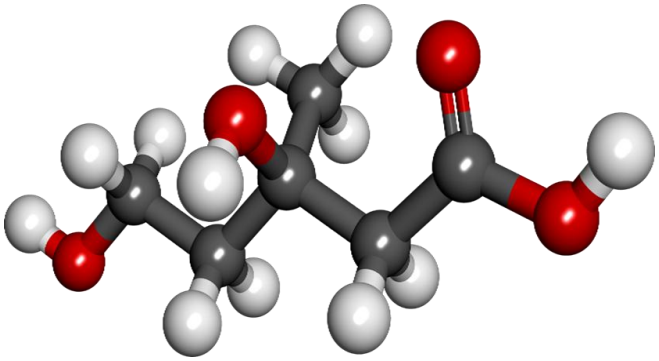
Mechanism of action (MOA) :19-23



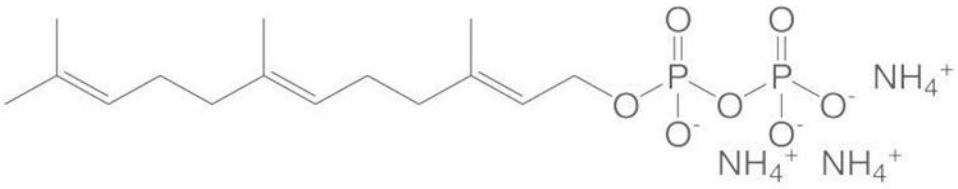
Aceto acetyl co-A (19)

HMG-CoA

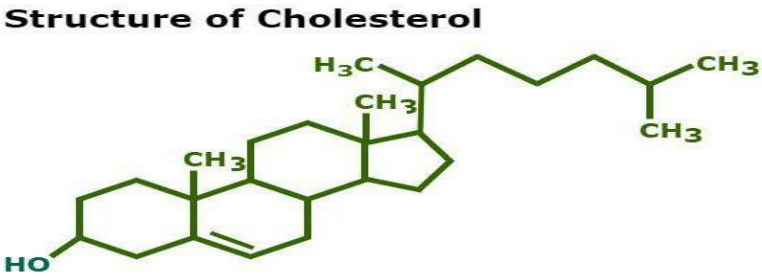
HMG Co - A Reductase



L – Mevalonate (21)



Farnesyl Pyrophosphate



Ex: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin [24]

Side effects

Headache, A hard time sleeping, Flushing of the skin, Muscle aches, Drowsiness, Dizziness, Belly cramping or pain.(25)

2. Bile acid sequestrants (26)

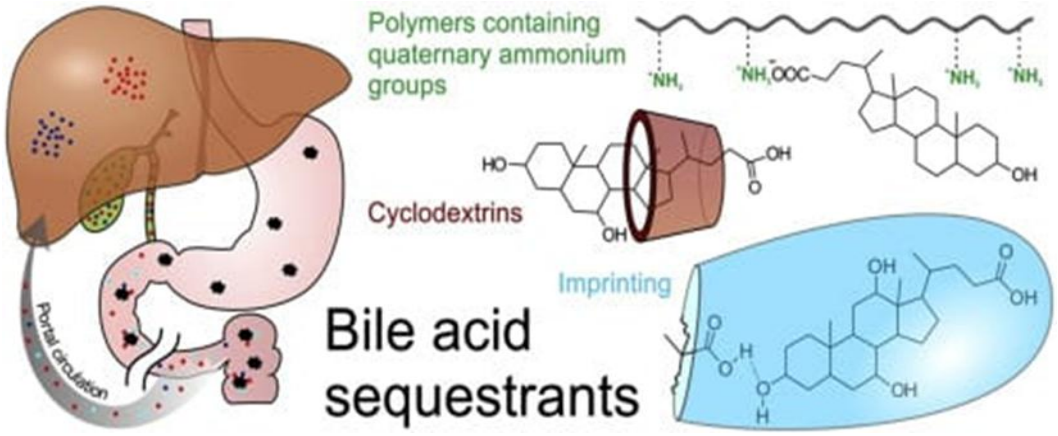


Figure 6: Bile acid sequestrants

Ex: Cholestyramine, Colesevelam, colestipol (27)

Side effects: Heartburn, Gas and bloating, Diarrhoea, nausea, Muscle aches and pains.(28)

3. Fibric Acid Derivatives

Fibrate are the class of antihyperlipidemic agent which are used to treat hyperlipidemia.(29)

MOA: Compared to plasma cholesterol, fibrates significantly lower plasma triglyceride levels. They have varying effects on LDL concentrations and considerably lower VLDL levels, which raise HDL levels..

Ex.

A. Benzafibrate :(30-31)

Benzafibrate is an antilipemic medication that reduces triglycerides and cholesterol. It raises high density lipoproteins while decreasing low density lipoproteins.

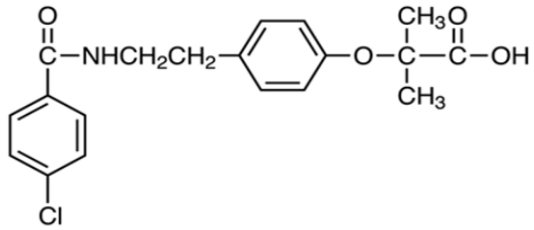


Figure 7: Benzofibrate

Sulphonamide

Mechanism of action :(32)

Chemotherapeutic drugs called antibiotics either inhibit or eradicate bacteria. In the synthesis of folic acid, which is necessary for bacteria to produce more DNA, sulphonamides are structural analogues and competitive antagonists of p-aminobenzoic acid (PABA). Because SN and PABA have similar structures, SN can prevent the formation of dihydrofolate and tetrahydrofolate, inhibit bacterial DNA growth, cell division, and replication, and replace PABA in the enzyme dihydropteroate synthetase, whose activity is crucial for folate production. Trimethoprim and SN medications work together to stop the production of tetrahydrofolate, which further prevents DNA replication. Because SN drugs prevent cell division, they are bacteriostatic rather than bactericidal

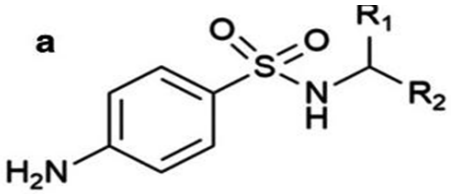


Figure 10: Sulphonamide

B. Clofibricacid:

Clofibric acid is a biologically active metabolite of the lipid-lowering drugs clofibrate, Eto fibrate and Theo fibrate[1][2] with the molecular formula C10H11ClO3.

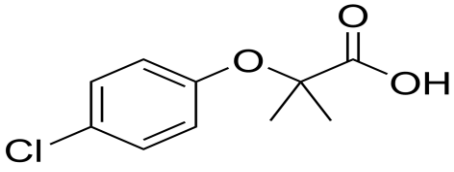


Figure 8: Clofibric acid (33)

Aluminiumclofibrate (34)

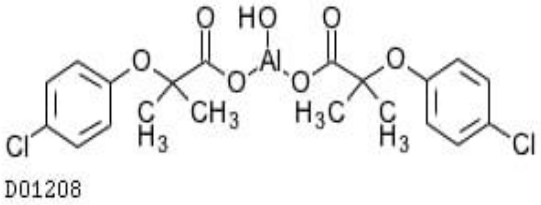


Figure 9: Aluminium Clofibrate

Mechanism of action:.(4,35)

Lipoprotein triglyceride lipolysis is increased by clofibrate's stimulation of extrahepatic lipoprotein lipase (LL) activity. LDLs become HDL, VLDLs become LDLs, and chylomicrons break down. A minor rise in lipid secretion into the bile and ultimately the intestine follows this. Additionally, clofibrate prevents apolipoprotein B, a VLDL carrier molecule, from being synthesized and encourages its clearance. In a number of tissues, including the liver and muscles, clofibrate activates the PPAR-a receptor. Eventually, this agonism results in altered gene expression, which raises HDL, decreases triglyceride secretion, increases beta-oxidation, and increases lipoprotein lipase activity

C. fenofibrate :(36)

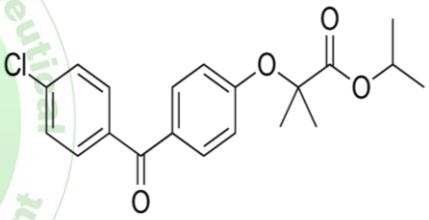


Figure 11: Finofibrate

Fenofibrate is used in conjunction with a low-fat diet, exercise, and occasionally other medications to lower blood levels of fatty substances like cholesterol and triglycerides and raise blood levels of HDL, a type of fatty substance..(37)

a. Choline fenofibrate:38

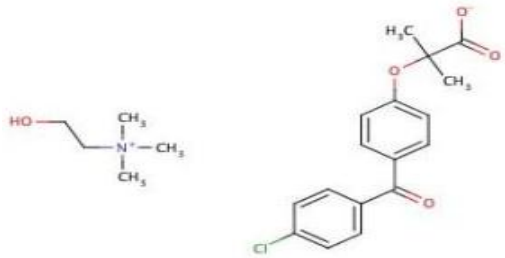


Figure 12 : Choline Finofibrate

Mechanism of action : (39)

Peroxisome proliferator-activated receptor alpha (PPAR-alpha), which is activated by fibrates like fenofibrate, increases lipoprotein lipase, stimulates the synthesis of high-density lipoproteins, and reduces the production of apolipoprotein C in the liver. Triglyceride-rich particle clearance and plasma catabolism are eventually enhanced by fibrates. Additionally, fibrates encourage the oxidation of fatty acids through acyl CoA synthetase and other

enzymes, which lowers the production of triglycerides. Plasma triglyceride and very low-density lipoprotein levels are ultimately decreased. Plasma triglyceride levels can be lowered by 30 to 60 percent when very low-density lipoprotein levels decline. Additionally, fenofibrate may help patients with thrombosis and gout by reducing fibrinogen levels and increasing uric acid excretion

Gemfibrozil:40

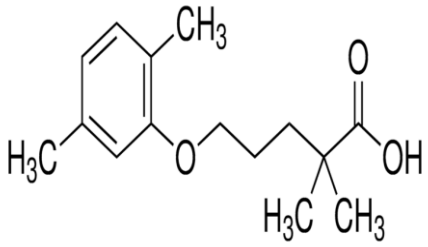


Figure 13: Gemofrozil

Gemfibrozil is useful medication for the reduction of triglycerides in patients with very high triglycerides serum levels. (41)

Combination therapy required: (42)

Statin + oil is safer and effective when TG is not so high.

Fibrates + cholesterol absorption inhibitors

Statin + Niacin

Statin + Fibrates

Non – Pharmacological Treatment:

1. Limit the amount of saturated fat consumed to less than 7–10% of total energy.
2. Cut your daily cholesterol intake to under 250 mg.
3. Consume low-fat foods and low-glycemic index carbohydrates to cut down on sources of cholesterol and saturated fat.
4. Eating fish, fruits, vegetables, and legumes.
5. Dietary fibre and fish oil supplements.
6. Reach your ideal weight and get more exercise and activity.
7. Cut back on or give up alcohol and quit smoking.

Drug delivery systems: (42-43)

A. Conventional Drug Delivery System Used for Hyperlipidemia

The most conventional approach to delivering antihyperlipidemic drugs is the non-invasive oral route, which involves taking the drug orally. This path, however, has a number of disadvantages. Drug concentrations tend to fluctuate, making it difficult to maintain a consistent therapeutic level. Additionally, the first-pass metabolic effect significantly reduces the bioavailability of many essential drugs. Drugs with a short half-life must be taken multiple times a day, which increases the likelihood of missed doses and results in poor patient adherence. Variable drug responses can also be caused by other factors like food intake, individual physiological differences, and disease conditions. Suboptimal biodistribution, low bioavailability, poor water solubility, limited site specificity, diminished therapeutic effect even at higher doses, and increased toxicity and side effects are all drawbacks of conventional dosage forms.

The creation of Novel Drug Delivery Systems (NDDS) is crucial to resolving these problems. The drug may be modified chemically or physically, encapsulated in lipid-based or polymeric vesicles, or its particle size reduced in these systems. NDDS helps get around the drawbacks of traditional drug delivery methods in addition to improving the pharmacological and biopharmaceutical flaws of conventional medications.

B. Novel drug delivery system:

A Novel Drug Delivery System (NDDS) is a cutting-edge approach to drug administration that improves drug efficacy, controls drug release to produce prolonged therapeutic action, enhances the pharmacological performance of active agents, boosts overall safety, and ultimately allows precise drug delivery to particular tissues. Three key requirements must be met for a medication to be administered successfully: accurate delivery to the targeted part of the body, appropriate release, and successful encapsulation. These systems are valuable because they can change pharmacokinetic behaviour and biodistribution. Tablets, eye drops, ointments, and injectable solutions are common forms of traditional drug administration. Many novel approaches to drug delivery have surfaced in recent years. These include chemically altering medications, encasing medications in pumps or polymer-based materials that are implanted into specific body parts, like under the skin or inside the eye, and trapping medications in tiny vesicles that can be injected into the bloodstream.Numerous delivery and targeting technologies are being developed to improve bioavailability and the percentage of drug that reaches the intended site, minimise negative side effects, and decrease drug breakdown and waste. Soluble polymers, lipoproteins, liposomes, microcapsules, cells and cell ghosts, microparticles made of non-soluble or biodegradable natural and synthetic polymers, and micelles are a few examples of drug carriers. By attaching particular antibodies that identify characteristics of the target area, these carriers can be made to degrade slowly, react to particular stimuli like pH or temperature, or even accomplish targeted delivery.Enhanced solubility and bioavailability, better pharmacokinetic profiles, prolonged drug release, better therapeutic effects at lower doses, fewer adverse reactions, protection from toxicity, increased pharmacological activity, improved stability, improved distribution within tissue macrophages, and protection of drugs from chemical or physical degradation are just a few of the many advantages that NDDS offers.

Different Novel Drug Delivery Systems:

- Oral Delivery Drug Delivery Systems.
- Parenteral and Implant Drug Delivery Systems.
- Pulmonary and Nasal Drug Delivery.
- Transmucosal Drug Delivery.
- Transdermal and Topical Drug.

Novel Drug Delivery Systems for Anti-Hyperlipidemic Drugs

Many anti-hyperlipidemic drugs have poor aqueous solubility, which leads to insufficient dissolution and, as a result, low bioavailability. Because of this, these medications frequently do not produce the intended therapeutic effect when taken in traditional dosage forms. Higher doses are needed to make up for this, which could have a number of undesirable side effects. Therefore, it is necessary to create dosage forms that maximize drug bioavailability while reducing side effects. Numerous innovative drug delivery systems that have shown increased bioavailability for these agents have been developed and evaluated as a result of ongoing research in this field. The following are a few cutting-edge delivery strategies for anti-hyperlipidemic medications:

1. Self-Micro Emulsifying Drug Delivery System
2. Ternary Solid Dispersions
3. Nanosuspension
4. Ion Exchange Resins
5. Nanosponge Drug Delivery
6. Nanoparticle Formulation
7. Mucoadhesive Microcapsules
8. Buccoadhesive Drug Delivery System
9. Gastric Floating Drug Delivery System
10. Pulsatile Drug Delivery System
11. Prodrug formulations

CONCLUSION:

Strong causal links between hyperlipidemia and ischemic heart disease, ischemic stroke, overall mortality, and its high Inforesights make it a serious health concern. Strong evidence also supports the effectiveness of lowering cholesterol in lowering hyperlipidemia-related morbidity and mortality. The treatment of hyperlipidemia involves the use of several drug classes. These classes vary not only in how they work but also in the kind and extent of lipid reduction. Modern antihyperlipidemic medications, including fibrates, bile acid sequestrants, nicotinic acid derivatives, statins, and cholesterol absorption inhibitors, are essential for reducing cholesterol levels and enhancing cardiovascular outcomes. Nevertheless, a number of these medications have short half-lives, low bioavailability, poor solubility, and dose-dependent adverse effects. The creation of Novel Drug Delivery Systems (NDDS) has shown promise as a solution to these problems. Self-microemulsifying systems, nanosuspensions, nanoparticles, nanosponges, buccoadhesive and mucoadhesive systems, floating formulations, and prodrugs are examples of advanced delivery platforms that have demonstrated great promise in improving the therapeutic efficacy of antihyperlipidemic agents. These cutting-edge systems increase bioavailability, maintain drug release, improve solubility, and lessen side effects, all of which contribute to safer and more efficient treatment options. All things considered, a comprehensive approach to controlling hyperlipidemia and averting atherosclerosis is offered by combining traditional therapy with cutting-edge drug delivery technologies. The creation of optimized formulations that enhance patient compliance, therapeutic results, and quality of life will be facilitated by further research in this area.

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