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THE ROLE OF ACTIVE PHARMACEUTICAL INGREDIENTS IN FORMULATION STRATEGIES FOR CHOLESTEROL-LOWERING MEDICATIONS

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ABSTRACT

Background: Cholesterol is a critical lipid required for various physiological functions, yet imbalances between high-density lipoprotein (HDL) and low-density lipoprotein (LDL) can lead to significant cardiovascular issues. **Objective:** This review aims to explore the role of active ingredients in the formulation strategies of cholesterol-lowering medications, focusing on their mechanisms of action, efficacy, and formulation considerations. **Methods:** A comprehensive literature review was conducted, analyzing various classes of anti- hyperlipidaemic drugs, including statins, bile acid sequestrants, and fibrates. The review highlights the chemical structures, pharmacological properties, and clinical implications of these active pharmaceutical ingredients (APIs). **Discussions:** The findings emphasize the importance of selecting appropriate active ingredients and formulation strategies to enhance drug efficacy, patient adherence, and overall treatment outcomes in managing hyperlipidaemia.

KEYWORDS: Cholesterol, Anti-hyperlipidaemic drugs, Lipid management, Atorvastatin, Rosuvastatin.

1. INTRODUCTION

- Cholesterol is a waxy substance made by animal liver and also supplied in diet through animal products such as meats, poultry, fish and dairy products[1]
- Cholesterol is needed in the body to insulate nerves, make cell membranes and produce certain hormones, and it is an important lipid in some membranes.
- Cholesterol plays a major role in human heart health. Cholesterol can be both good and bad. High-density lipoprotein (HDL) is good cholesterol and low-density lipoprotein (LDL) is bad cholesterol.
- When blood flow is restricted, angina (chest pain) can result. A heart attack will result when blood flow to the heart is severely impaired and a clot stops blood flow completely.
- When there is too much LDL cholesterol in blood, it is deposited inside the blood vessels, where it can build up to hard deposited and cause atherosclerosis, the disease process that underlies heart attacks.
- There are 102.3 million American adults who have total blood cholesterol values of 200 mg/dl and higher cholesterol.
- Cholesterol is measured in milligrams per decilitre of blood (mg/dl).
- A person's health cholesterol content is based on other risk factors such as age, gender, family history, race, smoking, high blood pressure, physical inactivity, obesity and diabetes.
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Etiology

High cholesterol can be caused by several factors, including

- **Diet:** High intake of saturated fats, trans fats, and dietary cholesterol can raise blood cholesterol levels.
- **Genetics:** Familial hypercholesterolemia is a genetic condition that can result in very high cholesterol levels.
- **Lifestyle factors:** Lack of physical activity, obesity, and smoking can contribute to elevated cholesterol levels.
- **Medical conditions:** Certain conditions, such as diabetes, hypothyroidism, and kidney disease, can affect cholesterol metabolism.
- **Medications:** Some medications can influence cholesterol levels, either raising or

lowering them.

Epidemiology

High cholesterol is a widespread issue

- **Prevalence:** A significant portion of the adult population has high cholesterol, with rates varying by age, sex, and lifestyle.
- **Risk factors:** Common risk factors include age, family history, diet, and lifestyle habits.
- **Geographic variation:** There are differences in cholesterol levels globally, often influenced by diet and lifestyle.

Symptoms

High cholesterol itself typically does not present symptoms. However, it can lead to serious health conditions, including

- **Atherosclerosis:** Buildup of cholesterol in the arteries, leading to heart disease and stroke.
- **Chest pain (Angina):** May occur if the heart does not get enough blood.
- **Heart attack:** A critical condition resulting from blocked blood flow to the heart.
- **Stroke:** Can occur if blood flow to the brain is interrupted.

1.1 Chemical structure of cholesterol

- Cholesterol is present in eukaryotes but not in most prokaryotes.
- The oxygen atom in its 3-OH group comes from O_2 (Figure 1).
- Cholesterol evolved after the earth's atmosphere became aerobic.
- The animal plasma membranes of eukaryotic cells are usually rich in cholesterol, whereas the membranes of their organelles typically have lesser amounts of this neutral lipid (Stryer, 1988).[1-4]

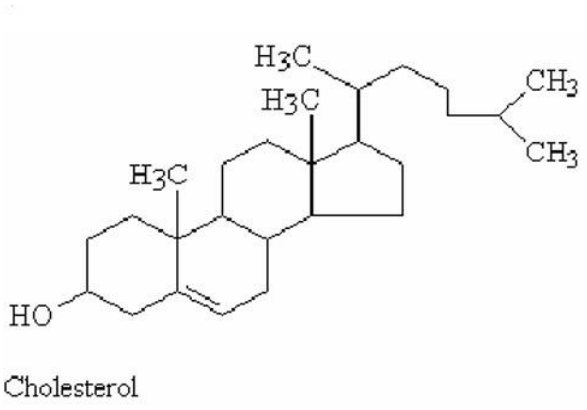


Figure 1.1: Chemical structure of cholesterol.[1-4]

1.2 Measurement

- Everyone age 20 years or more should have cholesterol measured at least once every 5 years.
- The best way to measure cholesterol is with a blood test called a lipid panel or lipid profile. You will need to fast (not eat) for 9 to 12 hours before your lipid panel. The test will determine the amounts of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in your blood, measured in milligrams per decilitre of blood (mg/dL). The Table classifies your lipid values.[5-6]

Classification of lipids Table 1: Classification of lipid.

Total cholesterol mg/dL	Level
Less than 200 200 to 239	Desirable Border line high
240 or more	High
LDL Cholesterol, mg/dL Less than 100	 Optimal
100 to 129 near	
Near optima/ above optimal 130 to 159 160 to 189	 Border line high High
190 or more **HDL cholesterol, mg/dL** Men, less than 40 Woman, less than 50	Very high Low Low
60 or more **Triglycerides ,mg/dL** Less than 150 150 to 199 200 to 499 500 or more	High Normal Border line high High Very high

1.3 Different types of anti-hyperlipidemic drugs[7]

- **HMG- co A reductase inhibitors (Statin)**

HMG-CoA reductase plays a critical role in cholesterol metabolism, serving as a target for statin drugs that help manage cholesterol levels and reduce the risk of heart disease. Its regulation is essential for maintaining balanced cholesterol levels in the body, example, Atorvastatin, Rosuvstatine.

- **Bile acid sequestrants (Resins)**

Bile acid sequestrants are effective agents in managing cholesterol levels by promoting the excretion of bile acids, leading to decreased cholesterol synthesis. They are particularly

useful in patients with elevated LDL cholesterol and can be a valuable part of a comprehensive lipid-lowering strategy, example, Cholestyramine, Colestipol.

- **Active lipoprotein lipase(Fibric acid derivatives)**

Active lipoprotein lipase, enhanced by fibric acid derivatives, plays a crucial role in lipid metabolism. Fibrates are effective in lowering triglycerides and raising HDL cholesterol, making them beneficial in managing dyslipidemia, particularly in patients at risk for cardiovascular disease and pancreatitis, example, Benafibrate, Fenofibrate.

- **Inhibit Lipolysis and Triglyceride synthesis**

Inhibiting lipolysis and triglyceride synthesis is vital for managing triglyceride levels and reducing the risk of metabolic disorders. Various medications, particularly fibrates and omega-3 fatty acids, target these processes effectively, offering a comprehensive approach to dyslipidemia management. Lifestyle changes further enhance treatment outcomes, example, Nicotinic acid.

- **Others**

Gugulipid: Gugulipid is an herbal supplement derived from the resin of the Comephorid Mukul tree, traditionally used in Ayurvedic medicine for its potential lipid-lowering effects.

Ezetimibe: Ezetimibe is a prescription medication used to lower cholesterol levels, specifically targeting the absorption of cholesterol in the intestines.

2. LITRATURE REVIEW

2.1 List of approved active pharmaceutical ingredient by CDSCO[8]

Table 2.1: List of approved active pharmaceutical ingredients by CDSCO.

Sr. No.	Drug name	Strength	Indication
1.	Atorvastatin + Fenofibrate	Each film coated tablet contains; atorvastatin calcium eq.to atorvastatin-10mg, fenofibrate BP (micronised)-160mg	By RMP- for the treatment of combined hyperlipidemia in patients with normal hepatic and renal function.
2.	Lovastatin	Each tab contains; lovastatin- 10mg,20mg,40mg.	Reduction of total LDL cholestrol in patients of primary hypercholesterolemia (type-II a & IIb hyperlipoproleinemia)
3.	Tolnaftate + Nystatin	Each gm contains; Tolnaftate-10mg, Nystatin- 100,000 Units	

4.	Atorvastatin	Each film coated tablet contains; atorvastatin calcium eq.to atorvastatin-10mg, 20mg, 40mg	As an adjunct diet to reduce elevated total cholesterol and triglyceride levels in patients with primary hypercholesterolemia and mixed dyslipidemia (type IIa & IIb)
5.	Cerivastatin tab	Each tablet contains; cerivastatin sodium-100mcg,200mcg,300mcg	By RMP- primary hypercholesterolemia type IIa, IIb resistant to diet.
6.	Choline Fenofibrate DR Capsule 45mg/135mg &DR Tablet 45mg/135mg	Each hard gelatin capsule contain: choline fenofibrate Eq. to fenofibric acid-45mg,135mg	For treatment of mixed lipidemia in combination with statin, severe hypertriglyceridemia
7.	Pravastatin 40mg	Each tab contains; Pravastatin sod. phEur. 40mg	As an adjunct to diet to reduce elevated total cholesterol, LDL- C, Apo-B TG levels and to increase HDL-C in patients with primary hypercholesterolaemia and mixed dyslipidaemia
8.	Fluvastatin	Fluvastatin sodium SR tablet-80mg	For secondary prevention of major adverse cardiac events in patients with coronary heart disease after coronary transcatheter therapy.
9.	Pitavastatin (1mg/2mg) Tablet	Each film coated tablet contains; pitavastatin calcium eq.to pitavastatin-1mg, 2mg	By RMP- for the treatment of familial hypercholesterolaemia
10.	FDC of Atorvastatin (10mg) + (375mg/500mg		For Hypercholesterolemia

2.2 Marketed formulation of anti-cholesterol drug

1. Atorvastatin

Table 2.2.1: Atorvastatin marketed formulation.

Formulation name	Atorvastatin 10mg[8]
Manufacturing company	Lipikind pharma pvt. Ltd.
No. of tablet in each strip	15
Price	42
Mechanism of action	Atorvastatin is a statin medication and a competitive inhibitor of the enzyme HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme reductase, which catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Atorvastatin acts primarily in the liver, where decreased hepatic cholesterol concentrations stimulate the upregulation of hepatic low-density lipoprotein (LDL) receptors,

	which increases hepatic uptake of LDL. Atorvastatin also reduces Very-Low-Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High- Density Lipoprotein Cholesterol (HDL-C).[10-14]
Direction	take this medicine in the dose and duration as advised by your doctor. Swallow it as a whole. Do not chew, crush or break it. Lipikind 10 Tablet may be taken with or without food, but it is better to take it at a fixed time.[9]
Use	To Reduce High cholesterol Prevention of heart attack
Product	 **Figure 2.2.1: Atorvastatin tablet.**

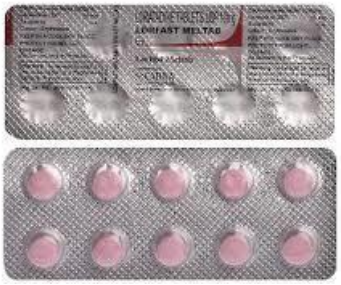
2. Rosuvastatin

Table 2.2.2: Rosuvastatin marketed formulation.

Formulation name	Rosuvastatin 10mg[16]
Manufacturing company name	Sun pharmaceutical industries Ltd.
No. of tablet in each strip	15
Price	293.28
Mechanism of action	catalyses the conversion of HMG-CoA to mevalonic acid and is the third step in a sequence of metabolic reactions involved in the production of several compounds involved in lipid metabolism and transport including cholesterol, low-density lipoprotein (LDL) (sometimes referred to as "bad cholesterol"), and very low-density lipoprotein (VLDL).[18-23]
Direction	Take this medicine in the dose and duration as advised by your doctor. Swallow it as a whole. Do not chew, crush or break it. Rosuvas 10 Tablet may be taken with or without food, but it is better to take it at a fixed time[17]
Use	To reduce High cholesterol and strock
Product	 **Figure 2.2.2: Rosuvastatin tablet.**

3. Lovastatin

Table 2.2.3: Lovastatine marketed formulation.

Formulation name	Lovadac 10mg[24]
Manufacturing company name	Cadila pharmaceuticals Ltd.
No. of tablet in each strip	10
Price	72.7
Mechanism of action	Lovastatin is a lactone which is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid and strong inhibitor of HMG-CoA reductase, a hepatic microsomal enzyme which catalyzes the conversion of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) to mevalonate, an early rate-limiting step in cholesterol biosynthesis. At therapeutic lovastatin doses, HMG-CoA reductase is not completely blocked, thereby allowing biologically necessary amounts of mevalonate to be available. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol, therapy with lovastatin would not be expected to cause an accumulation of potentially toxic sterols.[26-30]
Direction	Take this medicine in the dose and duration as advised by your doctor. Swallow it as a whole. Do not chew, crush or break it. Lovadac 10mg Tablet is to be taken with food.[25]
Use	To reduce High cholesterol Prevention of heart attack and stroke
Product	 **Figure 2.2.3: Lovastatin tablet.**

4. Fenofibrate

Table 2.2.4: Fenofibrate marketed formulation.

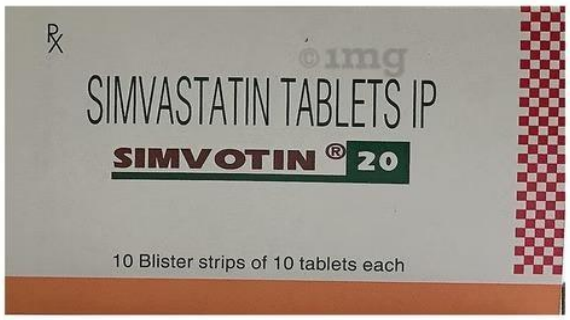
Formulation name	Fenofibrate tablet 160mg[31]
Manufacturing company name	USV Ltd.(Vapi Gujarat)
No. of tablet in each strip	10
Price	182.36
Mechanism of action	Fenofibrate activates peroxisome proliferator activated receptor alpha (PPARα), increasing lipolysis, activating lipoprotein lipase, and reducing apoprotein C- III. PPARα is a nuclear receptor and its activation alters lipid, glucose, and amino acid homeostasis. Activation of PPARα activates transcription of gene transcription and translation that generates peroxisomes filled with

	hydrogen peroxide, reactive oxygen species, and hydroxyl radicals that also participate in lipolysis. This mechanism of increased lipid metabolism is also associated with increased oxidative stress on the liver. In rare cases this stress can lead to cirrhosis and chronic active hepatitis.[33-39]
Direction	Take this medicine in the dose and duration as advised by your doctor. Swallow it as a whole. Do not chew, crush or break it. Lipicard 160 Tablet is to be taken with food[32]
Use	To reduce High cholesterol High triglyceride
Product	 **Figure 2.2.4: Fenofibrate tablet.**

5. Simvastatin

Table 2.2.5: Simvastatine marketed formulation.

Formulation name	Simvastatin 20 tablet[40]
Manufacturing company name	Sun pharmaceutical industries Ltd.
No. of tablet in each strip	10
Price	287.64
Mechanism of action	Simvastatin is a prodrug in which the 6-membered lactone ring of simvastatin is hydrolyzed *in vivo* to generate the beta,delta-dihydroxy acid, an active metabolite structurally similar to HMG-CoA (hydroxymethylglutaryl CoA). Once hydrolyzed, simvastatin competes with HMG-CoA for HMG-CoA reductase, a hepatic microsomal enzyme, which catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Simvastatin acts primarily in the liver, where decreased hepatic cholesterol concentrations stimulate the upregulation of hepatic low density lipoprotein (LDL) receptors which increases hepatic uptake of LDL. Simvastatin also inhibits hepatic synthesis of very low density lipoprotein (VLDL). The overall effect is a decrease in plasma LDL and VLDL[42-45]
Direction	Take this medicine in the dose and duration as advised by your doctor. Swallow it as a whole. Do not chew, crush or break it. Simvotin 20 Tablet may be taken with or without food, but it is better to take it at a fixed time[41]
Use	To reduce High cholesterol Prevention of heart attack and strock

Product	 **Figure 2.2.5: Simvastatin tablet.**

3. AIM AND OBJECTIVE

Aim

To evaluate the role of active ingredients in the formulation strategies of cholesterol-lowering medications, emphasizing their mechanisms of action, efficacy, and considerations for optimal patient treatment outcomes.

Objectives

1. To analyse the chemical structures and pharmacological properties of various classes of anti- hyperlipidaemic drugs, including statins, bile acid sequestrants, and fibrates.
2. To review the current literature on marketed formulations of anti-cholesterol drugs and their impact on lipid management.

4. CONCLUSION

This review underscores the pivotal role of active pharmaceutical ingredients in formulating effective cholesterol-lowering medications. By examining the various classes of anti-hyperlipidemic drugs, we see that each class—statins, bile acid sequestrants, and fibrates—has distinct mechanisms that contribute to lipid management. In summary, an integrated approach that combines pharmacological knowledge with individualized patient care is crucial for managing hyperlipidemia. Ongoing research and development of novel formulations and combination therapies will be vital in advancing cholesterol management and reducing cardiovascular disease risk.

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