AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A Review on the Pravastatin Drug

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ABSTRACT

Pravastatin is widely used antihyperlipidemic drug, exhibits poor aqueous solubility and low dissolution rate, which limit its oral bioavailability. The present study focuses on the design, development and evaluation of the pravastatin solid dispersion tablets prepared by the direct comparison method to enhance dissolution efficiency. Solid dispersions were characterized by using the FTIR, Melting point Analysis, and calibration studies, while the flow properties such as bulk density, tapped density, angle of repose, Carr's index were determined to ensure suitable compressibility.

Keywords: Statins, Pravastatin, Direct Compression method, Solid dispersion, Drug profile.

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Received 17 October 2025, Accepted 23 November 2025

Please cite this article as: Radha V *et al*., A Review on the Pravastatin Drug. American Journal of PharmTech Research 2025.

INTRODUCTION

Statins work by lowering low-density lipoprotein (LDL) cholesterol levels through the inhibition of the enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase. This enzyme catalyses the conversion of HMG-CoA into mevalonate, a key intermediate, and represents the rate-limiting step in the cholesterol biosynthesis pathway [1].

Pravastatin, 3-hydoxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin), is a lipid-regulating drug with actions on plasma lipids similar to those of simvastatin. Pravastatin is used in the treatment of hypercholesterolemia, particularly in the types II a and II b hyperlipoproteinemia's [2].

Pravastatin, unlike other statins, is relatively hydrophilic and does not appear to be appreciably metabolized by cytochrome P450 enzymes. Because of excellent first-pass uptake, all statins have a selective impact on the liver.[2]

Lipophilic statins are taken up by passive diffusion through hepatocyte cell membranes, where as hydrophilic statins are taken up by active diffusion via hepatocyte cell membranes. Pravastatin has been received FDA approval for the first time in 1991 to treat hypercholesterolemia. Pravastatin and rosuvastatin have a higher hepato selectivity and a lower capacity for peripheral cell absorption than lipophilic agents.

Hypercholesterolemia.

Hypercholesterolemia and atherosclerosis are leading causes of cardiovascular morbidity and mortality. Elevated blood cholesterol, particularly low-density lipoprotein cholesterol (LDL-C), plays a critical role in the development of atherosclerosis, which is a major contributor to coronary heart disease (CHD).[3]

Hyperlipidemia.

Hyperlipidemia—commonly described as elevated cholesterol levels in the blood—has emerged as one of the major contributors to cardiovascular disease worldwide. It plays a

Central role in the growing burden of heart-related illnesses and is now recognized as a leading cause of both morbidity and mortality in developed as well as developing nations.

Pathophysiology of hyperlipidemia.

Exogenous pathway (uptake of dietary lipids) Cholesterol excretion by enterohepatic circulation Patho-physiology of hyper-lipidemia Endogenous pathway (distribution of cholesteryl esters from liver to target cells) Denovo cholesterol biosynthesis Route for cholesterol recovery

PHYSICOCHEMICAL PROPERTIES:[4]

Drug profile:

Pravastatin is a widely prescribed medication classified as a statin, commonly used to lower cholesterol and prevent cardiovascular events like heart attacks and strokes. It works by blocking HMG-CoA reductase, an enzyme involved in cholesterol production, helping to reduce "bad" LDL cholesterol and triglycerides, while raising "good" HDL cholesterol levels. Pravastatin is often taken in combination with a healthy diet, exercise, and lifestyle changes to maximize its heart-protective benefits.

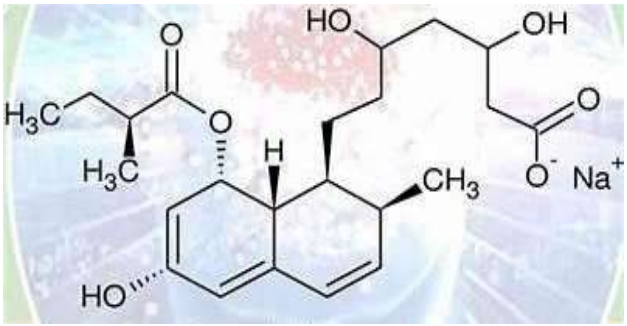

Figure 1: Structure of Pravastatin

Property	Description
Colour	White to off-white
Physical form	Crystalline powder
Odour	Odourless or almost odourless
Taste	Slightly bitter
Solubility	Freely soluble in water, Ethanol, Methanol, Hydrochloric acid (0.1N HCl); practically insoluble in chloroform and ether
Crystallinity	Crystalline in nature

Pharmacology.

Mechanism of action of the pravastatin.[5]

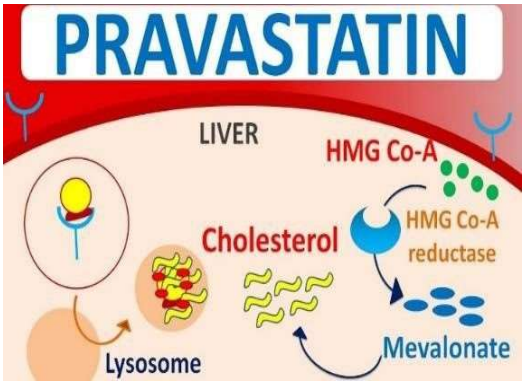

Figure 2: Mechanism of action of the pravastatin

The stepwise mechanism of the pravastatin is mentioned below:

Pravastatin Administration

↓

Inhibition of HMG-CoAReductase takes place, where the Pravastatin acts as a reversible competitive inhibitor of HMG-CoA reductase by sterically hindering the enzyme's active site, preventing the conversion of HMG-CoAto mevalonate.

This inhibition leads to decreased in tricellular cholesterol synthesis is in liver cells.

↓

Decreased Cholesterol Synthesis

↓

Increased LDL Receptor Expression which leads to Reduced liver cholesterol levels which cause the liver cells to increase the expression of LDL receptors on their surface.

↓

Decreased Blood LDL Levels leads to increased clearance of LDL leads to a reduction in blood LDL cholesterol levels.

↓

Secondary Effects where the Pravastatin. may also have anti-inflammatory effects and may stabilize plaques in blood vessels.

Table1: Effect of pravastatin on the lipid profile.[6]

Lipid parameter	Effect of pravastatin.
LDLC (Low-Density lipo protein cholesterol).	Decreases 20-40%
Total Cholesterol (TC).	Decreases
HDL-C(High-Density Lipoprotein Cholesterol).	Slightly increases.
Triglycerides (TC).	Decreases Slightly.

Pharmacokinetic Properties[7]

Pravastatin is administered orally as the sodium salt of the active compound. The drug has an oral bioavailability of 17%. Absolute oral bioavailability is ~17%**;** Tmax ~1–1.5 h**.** Food decreases AUC mode style but does not blunt LDL-Cowering**,** so timing with meals is flexibl**e.**

Absorption: Rapid, Tmax~1–1.5h.

Protein binding:*50%*

Metabolism: Unlike simvastatin/atorvastatin**,** pravastatin has minimal CYP450 metabolism. It depends on hepatic uptake via OATP1B1, undergoes limited isomerization/hydroxylation, and exhibits a first-pass hepatic extraction ratio~0.66 after IV dosing. This transporter-led disposition also explains several interactions.

Elimination and Excretion: After oral dosing, recovery is ~70% in feces and ~20% in urine**;** after IV dosing, elimination is roughly half renal / half non-renal**.** Terminal t½ ≈ 1.8 h.

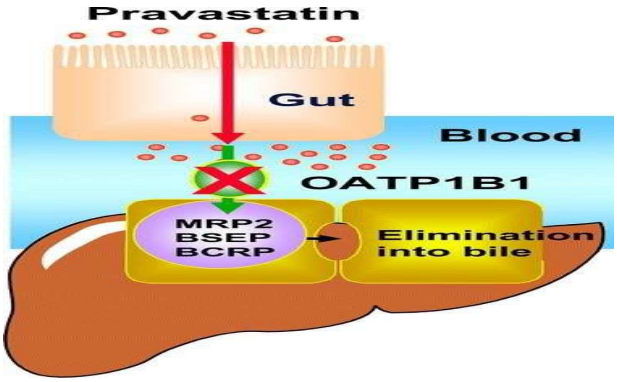

Figure 3: Excretion

Pharmacodynamic Properties[8]

Pravastatin inhibits the HMG-CoA reductase, this enzyme which catalyses the rate-limiting step within the cholesterol biosynthetic pathway. By inhibiting *de novo* cholesterol production and reducing in tricellular cholesterol stores, pravastatin stimulates the synthesis and activity of low-density lipoprotein (LDL) receptors, thereby enhancing the clearance of atherogenic LDL-cholesterol.

In vitro and *in vivo* data indicate that pravastatin exhibits hepatocellular tissue selectivity, with greatest inhibition of cholesterol synthesis occurring in the liver.

In hypercholesterolaemic patients, pravastatin produces consistent changes in total cholesterol, LDL-cholesterol, high density lipoprotein (HDL)-cholesterol and triglyceride levels; its effects on lipoprotein(a) are, however, variable.

Clinical Indications[10]

Therapeutic indications.

Coronary Artery Disease: The patients suffering from the myocardial infarction, in such cases pravastatin is indicated to reduce the risk for to Tal mortality, coronary heart disease death, the coronary event.

Cerebrovascular Disease: The patients with a history of coronary artery disease (i.e. either a myocardial infarction or unstable angina pectoris), pravastatin is indicated to reduce the risk of stroke or ischemic attacks.

How to administer.

Prior to administer of the pravastatin the patient should be allowed to be in the cholesterol lowering diet.

Secondary causes for hyper cholesterolaemia (e.g. obesity, poorly controlled diabetes, hypothyroidism, nephrotic syndrome) should be excluded and a lipid profile performed to measure Total-C, HDLC and TG.

Dose frequency.

Dose for Hyperlipidaemia

Initialdose:40 mg orally once a day.

Maintenancedose:40mgto 80mgorallyonceaday.

- Elderly or patients 5 with renal impairment, may require lower starting doses(e.g.,10mg once daily).
- Paediatric patients may require the Doses typically ranging from 10 to 40mg once daily.
- Pravastatin can be taken with or without food. Evening dose is mostly preferred due to the body's natural cholesterol production cycle.

Common adverse effects.

- Musculoskeletal pain (e.g., muscle aches, myalgia, arthralgia)
- Gastrointestinal issues: nausea, vomiting, abdominal pain, dyspepsia, constipation, diarrhoea.
- Hepatic (Liver)Effects.
- Various forms of hepatic injury like hepatitis, jaundice, pancreatitis, fulminant hepatic necrosis, and liver failure have been reported but remain exceptional in frequency.
- Muscle-Related Toxicity.
- Myopathy: Muscle pain, tenderness, or weakness sometimes accompanied by elevated creatine kinase (CK).

Metabolic Effects–Glucose & Diabetes.

Pravastatin can raise fasting blood glucose and HbA1c̄, with a slight increase in new-onset diabetes risk noted in certain patients. Still, cardiovascular benefits typically outweigh these metabolic risks.

Cognitive and Other Rare Effects.

Cognitive impairment: Rare cases of reversible memory loss, confusion, or amnesia, with no proven link to persistent cognitive decline or dementia.

Allergic reactions: Can include rash, pruritus, and very rarely anaphylaxis.

Risk Factors & Drug Interactions.

Higher risk of muscle-related adverse effects in the elderly (≥65), patients with renal impairment, hypothyroidism, or those on interacting medications.

METHOD OF PREPARATION OF PRAVASTATIN BY SOLID DISPERSION METHOD.

Solid Dispersion.

Solid dispersion technologies have shown promising potential in improving the oral absorption and bioavailability of drugs belonging to BCS Class II. Conventional approaches such as salt formation, particle size reduction, solubilization, and cyclodextrin complexation have been employed to enhance dissolution and thereby improve absorption and bioavailability of poorly water-soluble drugs. These techniques are often associated with certain limitations. Solid dispersion formulations provide greater flexibility through the use of diverse processing methods and excipients, making them a more versatile option for developing oral delivery systems of poorly soluble drugs. The solubility and bioavailability of such drugs can be further improved by converting them into the amorphous state. The mechanisms through which solid dispersions enhance solubility and dissolution include particle size reduction to the molecular level, transformation of the crystalline drug into its amorphous form, and improved wettability.

Classification of the solid dispersion.

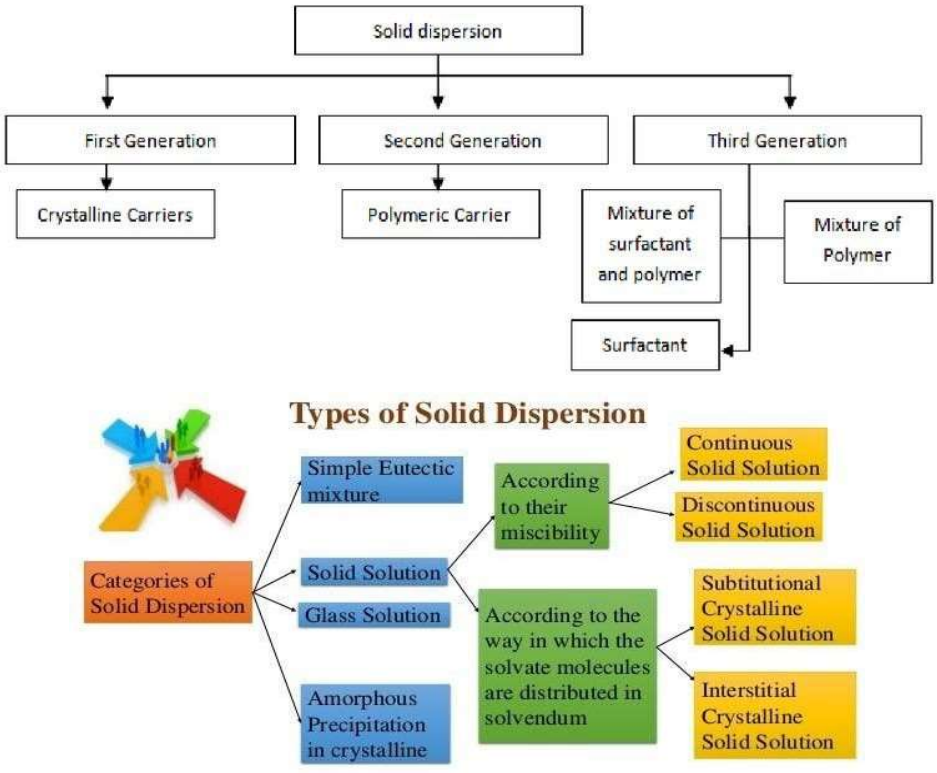

Figure 4: Types of solid dispersion

Methods for the Preparation of Solid Dispersions.

Several techniques are employed to prepare solid dispersion systems, which help improve the solubility and bioavailability of poorly soluble drugs. The commonly used methods include:

1. Melting method
2. Solvent method
3. Melting–solvent method (melt evaporation)
4. Hot-melt extrusion technique
5. Lyophilization (freeze-drying) technique
6. Melt agglomeration process
7. Incorporation of surfactants
8. Electrospinning method
9. Supercritical Fluid (SCF) technology.

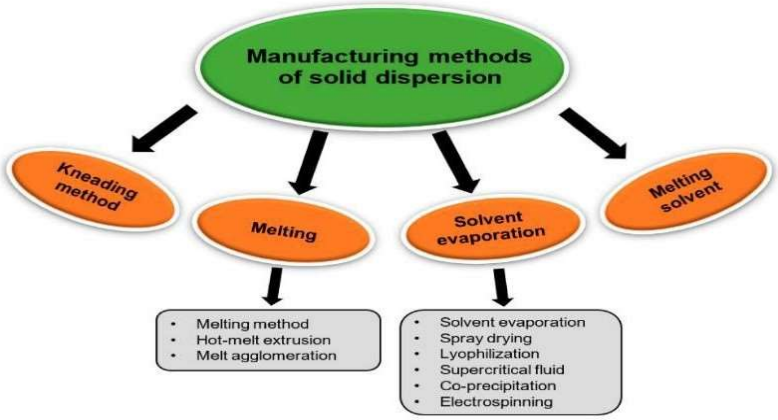

Figure 5: Methods for the Preparation of Solid Dispersions

Advantages of solid dispersion

- Faster drug dissolution and better absorption.
- Enhanced wettability.
- Supersaturation promotes absorption.
- Improved porosity enhances dissolution.
- Can be formulated as solid oral dosage forms.
- Alternative to salt or cocrystal methods. Etc.

Disadvantages of solid dispersion.

- Physical instability with time.
- Sensitive to heat and humidity.
- Sticky consistency complicates handling.
- Complex and costly production process.
- Reproducibility challenges. Etc.

DirectCompression.[13]

Direct compression is a tablet manufacturing process where powdered ingredients are blended and compressed directly into tablets without prior granulation steps. Composition of preliminary trails for pravastatin tablets was done through direct compression method All the ingredients were weighed required quantity of drug and excipients mixed thoroughly in a polybag. The blend is compressed using rotary tablet punching machine-8 station with 12 mm flat punch. Each tablet contains 40mg of pravastatin and other pharmaceutical ingredients.

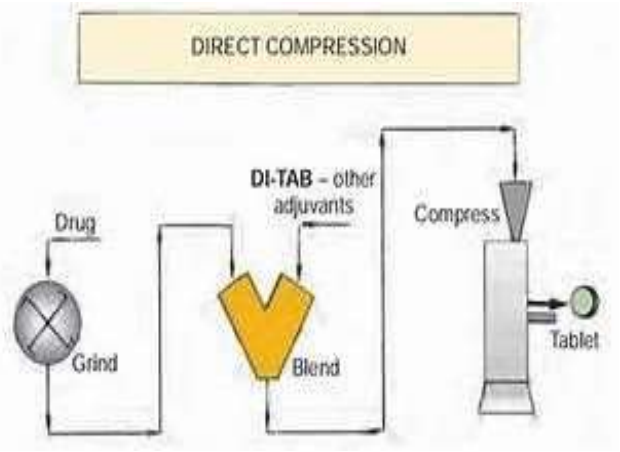

Figure 6: Direct compression

Advantages of Direct Compression.

- Cost-Effectiveness: Eliminates the need for granulation, reducing equipment, labour, and energy costs.
- Time Efficiency: Simplifies the manufacturing process, leading to faster production times.
- Enhanced Stability: Minimizes exposure to heat and moisture, preserving the stability of sensitive APIs. Etc.

Disadvantages of Direct Compression.

- Limited to Compressible Materials: Not suitable for APIs with poor compressibility.
- Risk of Segregation: Differences in particle size can lead to ingredient separation.
- Potential for Poor Flowability: Some formulations may exhibit inadequate flow properties. Etc.

EVALUATIONPARAMETERS

Precompression.

Studies before compression, the powder blend was evaluated for its micromeritic properties, including bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose.

Angle of repose.

The angle of repose was measured using the fixed funnel method. In this procedure, the powder blend was allowed to flow freely through a funnel positioned at a height of 2 cm above a flat surface.

The relationship between angle of repose and powder flow properties is presented in Table. Angle of Repose was calculated using the formula:

Tan θ = h/r, therefore $\boldsymbol{\theta = Tan^{-1} (h/r)}$..... **(1)**

Where,

θ is the angle of repose, **h** is the height of the pile in cm **r** is the radius in cm.

Bulk Density

Bulk density is the ratio of the mass of a powder sample to its bulk volume, expressed in g/cm³.. The bulk volume (V) was recorded, and the bulk density was calculated using the formula: Bulk density, $\boldsymbol{\rho_b = M / V}$ ..... **(2)**

Were,

M is the weight of powder

V is the volume of powder.

Tapped density.

Tapped density was determined using a tapped density apparatus The final or minimum volume (Vt) was noted, and the tapped density was calculated using the formula:

Tapped Density**,** $\boldsymbol{\rho t = M / Vt}$ ..... **(3)**

Were,

M is the weight of powder $\mathbf{V_t}$ is the tapped volume of powder

Carri's Index.

The compressibility index is a simple test to evaluate the bulk density and tapped density of a powder and the state at which it is packed down.

The formula for Carr's index:

Carr's Index (%) = [(TBD - LBD) / TBD] x 100… (6)

TBD = Tapped bulk density

LBD = Loose bulk density

Hausner's ratio.

Hausner's ratio measures the propensity of powder to be compressed and the flowability of powder.

Hausner's ratio= Tapped density/ Bulk density……

CLINICAL APPLICATIONS.

Treatment of Hypercholesterolemia and Dyslipidaemia.

- Primary hypercholesterolemia.
- Mixed dyslipidaemia.
- In patients with type 2 diabetes, pravastatin caused 18.4% reduction in total cholesterol, 22.2% reduction in LDL.

Primary Prevention of Coronary Heart Disease.

- Reduction in nonfatal MI or CHD death.
- Reduction in all-cause mortality.
- Fewer revascularization procedures.

Coronary Events Prevention in CAD Patients.

Pravastatin treatment diminishes risk of myocardial infarction, coronary death, and helps slow atherosclerosis, especially when combined with lifestyle changes.

Nephrotic Syndrome / Combined Hyperlipidemia

In nephrotic patients with hyperlipidemia, pravastatin increased LDL clearance and reduced cholesterol content per LDL and VLDL/IDL—but did not alter lipoprotein production rates.

Advantages.

Lowers LDL Cholesterol.

Pravastatin effectively reduces LDL cholesterol levels, which helps prevent atherosclerosis (hardening of arteries).

Cardiovascular Protection

Heart attacks

Strokes

Relatively Safe for Liver

- Compared to other statins, pravastatin is less metabolized by the liver (CYP450 enzymes), which makes it:
- Safer for patients with mild liver impairment.

Disadvantages.

less Potent

- Pravastatin is less potent than other statins (like atorvastatin or rosuvastatin).

Side Effects

- Although generally well-tolerated, it can cause:

- Muscle pain or weakness (myopathy) Liver enzyme elevation o Rarely, rhabdomyolysis (a serious muscle breakdown condition)

Pregnancy Risk

- Like all statins, contraindicated in pregnancy due to risk of fetal harm.

CONCLUSION

This review contains the importance of the Pravastatin which is a highly effective and well tolerated therapy for hypercholesterolemia, both alone and in combination. The current research shows that pravastatin is a safe and effective treatment for severe hypercholesterolemia. Pravastatin is also well-tolerated in various age groups when given in combination or alone. Individuals' TG and HDL-C levels are also influenced by their TG and HDL-C levels. It also explains the effect of the pravastatin on the lipid profile. Here the pravastatin is produced through the direct compression method. Pravastatin inhibits the HMG-CoA reductase, this enzyme which catalyses the rate-limiting step within the cholesterol biosynthetic pathway which is more effective.

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