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ROSUVASTATIN CALCIUM: A NEXT-GENERATION STATIN FOR CARDIOVASCULAR EXCELLENCE

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ABSTRACT

Rosuvastatin calcium is a powerful cholesterol level lowering agent it is important statin is widely use for management hyperlipidemia and reducing cardiovascular risk or disease this is calcium salt of rosuvastatin. Operates by inviting the enzyme HMG- COA reductase. a crucial component in cholesterol in the blood. Rosuvastatin calcium is a white crystalline powder that is poorly soluble in water commercially available for oral administration in tablet 5 mg ,10 mg ,20 mg and 40 mg strenght .

This overview examines the pharmacological properties of RC, including its mechanism of action, metabolic pathways, and clinical effectiveness in lowering cardiovascular risks. Beyond lipid-lowering, RC shows promising additional benefits, including anti-inflammatory and antioxidative effects, which may offer further protection against cardiovascular events. [1,2]

KEYWORDS: - *Rosuvastatin calcium, advanced age, coronary heart disease, hyperlipidemia, clinical efficacy rosuvastatin, cardiovascular risk, statins, low density lipoprotein cholesterolcy. [3]*

INTRODUCTION

Rosuvastatin calcium is a statin medication widely used for **lowering cholesterol** and managing cardiovascular risk. As an HMG-CoA reductase inhibitor, it works by blocking an enzyme involved in cholesterol synthesis in the liver, leading to a significant reduction in low-density lipoprotein (LDL) cholesterol and triglycerides while increasing high-density lipoprotein (HDL) cholesterol. These effects help slow the progression of atherosclerosis, a major cause of heart disease, stroke, and other cardiovascular events. First approved in the early 2000s, rosuvastatin quickly became a preferred choice in cholesterol management due to its potent lipid-lowering properties and favorable safety profile. It has demonstrated efficacy across various patient populations, including those with high cardiovascular risk, diabetes, and other comorbidities. Additionally, beyond its lipid-lowering capabilities, rosuvastatin has been shown to offer additional cardiovascular benefits, such as anti-inflammatory and endothelial-protective effects, which may contribute to its effectiveness in reducing cardiovascular events. [4]

The Coronary heart disease (CHD) is a comprehensive disease caused by coronary atherosclerosis, that is based on lumen stenosis or blockage, resulting in a series of pathologic changes such as ischemia and hypoxia of individual myocardium and then injury and necrosis. It is also called ischemic heart disease clinically [5]. Ischaemic heart disease (IHD) is the leading cause of mortality worldwide and constitutes a major health burden. According to World Health Organisation (WHO) statistics it accounts for 12.8% of deaths, with stroke and other cerebrovascular disease accounting for a further 10.8%. In the United Kingdom, data from the Health Surveys for England suggest that while mortality may be declining, cardiovascular disease morbidity continues to rise. Epidemiological studies have established a strong correlation between cholesterol and the incidence of cardiovascular disease. The associated morbidity and mortality is positively correlated to low density lipoprotein cholesterol (LDL-C) and inversely related to high density lipoprotein cholesterol (HDL-C). [5]

METHODOLOGY

- **DRUG NAME** :- Rosuvastatin Calcium**.**

1.Chemical Structure

IUPAC Name: (E)-7-[4-(4-Fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid calcium salt

Molecular Formula: $C_{22}H_{27}FN_3O_6S_2Ca$

Molecular Weight: Approximately 500.6 g/mol (for the calcium salt form)

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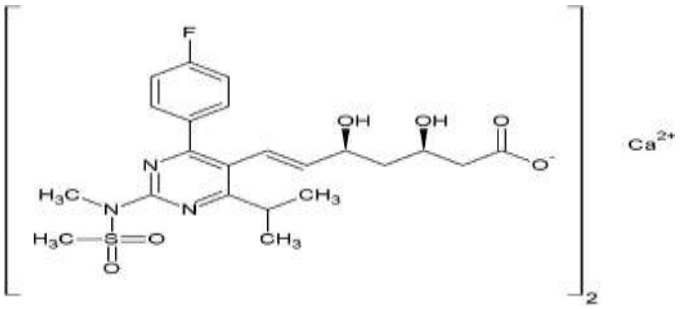
Stucture



2. Physical Properties
Appearance: Rosuvastatin calcium is typically a white to off-white powder.

Solubility: Poorly soluble in water, but more soluble in organic solvents like ethanol and methanol. Solubility can vary with pH.

pKa Values: Rosuvastatin calcium has a pKa of approximately 4.6, which affects its ionization and, therefore, its solubility and absorption profile.

Melting Point: It has a melting point in the range of 122-130°C.

3. Stability
Sensitivity to Light: Rosuvastatin calcium is sensitive to light and should be stored in opaque containers to avoid photodegradation.

pH Stability: It is stable in acidic to slightly basic pH conditions but may degrade in strongly basic environments.

Thermal Stability: It remains stable under moderate temperatures but should be stored in a cool, dry place to avoid degradation. [1,6]

Fig

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MECHANISM ACTION OF DRUG

HMG-CoA Reductase Inhibition: Rosuvastatin inhibits the enzyme HMG-CoA reductase, which plays a central role in cholesterol synthesis in the liver.

Increased LDL Receptor Activity: By reducing cholesterol production, rosuvastatin causes the liver to upregulate LDL receptors, which helps clear LDL (low-density lipoprotein) cholesterol from the bloodstream.

Reduction in Total Cholesterol and Triglycerides: This mechanism lowers LDL cholesterol levels, moderately reduces triglycerides, and raises HDL (high-density lipoprotein) cholesterol.[7]

PHARMACOLOGY

Rosuvastatin is a fully synthetic HMG-CoA reductase inhibitor. Other HMG-CoA reductase inhibitors are either natural, mevinic acid derived (lovastatin, simvastatin, pravastatin) or synthetic, heptenoic acid derived (atorvastatin, fluvastatin). [8]. Rosuvastatin belongs to a new generation of methane-sulphonamide pyrimidine and N-methane sulfonyl pyrrole-substituted 3, 5-dihydroxy-heptenoates. Although the characteristic statin pharmacophore remains similar to other statins, the addition of a stable polar methane-sulphonamide group provides low lipophilicity and enhanced ionic interaction with HMG-CoA reductase enzyme thus improving its binding affinity to this enzyme. [9,10]

Pharmacokinetics

Absorption: Rosuvastatin is absorbed orally with a bioavailability of about 20%.

Distribution: It has a half-life of around 19 hours and binds to plasma proteins, particularly albumin.

Metabolism: Only a small fraction of rosuvastatin is metabolized, primarily by the CYP2C9 enzyme in the liver. This low metabolism rate reduces the risk of drug interactions compared to other statins.

Excretion: Rosuvastatin is primarily excreted unchanged in the feces, with some excreted through the kidneys.

Pharmacodynamics

Rosuvastatin reduces LDL cholesterol levels by up to 50% or more, depending on the dose. It also decreases triglycerides and moderately increases HDL cholesterol**.**

It stabilizes atherosclerotic plaques, making them less likely to rupture and cause events like heart attacks or strokes. Additionally, rosuvastatin has anti-inflammatory effects on the vascular wall, which can reduce the risk of vascular disease progression. [11]

CLINICAL PHARMACOLOGY

General: In the bloodstream, cholesterol and triglycerides (TG) circulate as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into very-low-density lipoprotein (VLDI.), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) fractions that contain apolipoprotein B-100 (ApoB-100) and high-density lipoprotein (HDL) fractions . Cholesterol and TG synthesized in the liver are incorporated into VLDL. and secreted into the circulation for delivery to peripheral tissues. TG are removed by the action of lipases, and in a series of steps, the modified VLDL is transformed first into IDL and then into cholesterol-rich LDL IDL and LDL. are removed from the circulation mainly by high affinity ApoB/E receptors, which are expressed to the greatest extent on liver cells. HDL is hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

Epidemiologic, experimental, and clinical studies have established that high LDL. cholesterol (LDL-C), low HDL cholesterol (HDL-C), and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. In contrast, higher levels of HDL-C are associated with decreased cardiovascular risk. Like LDL cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. [12,13]

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DRUG- DRUG INTRACTION

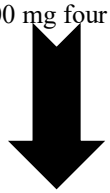
1) **Warfarin:** Combination of warfarin (25 mg) + rosuvastatin (40 mg)

Did not change warfarin plasma concentrations but **increased** the International Normalized Ratio (INR)

2) **Digoxin:** Combination of digoxin (0.5 mg) + Rosuvastatin (40 mg)

Resulted in no change to digoxin **plasma concentrations**.

3) **Erythromycin** Combination of Erythromycin (500 mg four times daily for 7 days) + Rosuvastatin (80 mg)



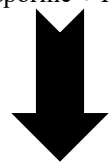
Decreased AUC and Cmax of rosuvastatin by 20% and 31%, respectively.

(Note -These reductions are not considered clinically significant.)

4) **Ketoconazole** Coadministration of ketoconazole (200 mg twice daily for 7 days) + Rosuvastatin (80 mg)

Resulted in no change in **plasma concentrations** of rosuvastatin

5) **Cyclosporine:** Coadministration of Cyclosporine + Rosuvastatin



Resulted in no significant changes in **cyclosporine** plasma concentrations.

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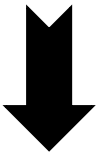
6) **Antacid** : Coadministration of an antacid (aluminum and magnesium hydroxide combination)

+ Rosuvastatin (40 mg)



resulted in a **decrease i**n plasma concentrations of rosuvastatin by 54%.

7) **Itraconazole:** Itraconazole (200 mg once daily for 5 days) **resulted** in a 39% and 28% increase in AUC of rosuvastatin after 10 mg and 80 mg dosing, respectively.

(Note -These increases are not considered clinically significant)

8) **Fluconazole**: Coadministration of fluconazole (200 mg once daily for 11 days) with rosuvastatin (80 mg) resulted in a 14% increase in AUC of rosuvastatin.

(Note This increase is not considered clinically significant). [12]

Common Side Effects
1. Myalgia (muscle pain)
2. Abdominal pain
3. Constipation
4. Headache
5. Dizziness
6. Nausea
7. Fatigue
8. Diarrhea
9. Pain in extremities
10. Back pain .

Less Common Side Effects :
1. Cognitive impairment
2. Memory loss
3. Confusion
4. Depression
5. Anxiety
6. Insomnia
7. Sleep disturbances
8. Asthenia (weakness)
9. Arthralgia (joint pain)
10. Muscle Pain **.** [14,15]

THE PROCES WHICH OBTAIN FROM ROSUVASTATIN BY SYNTHETICALLY METHOD
Chemical synthesis of rosuvastatin involves several steps:
Step 1: Synthesis of Intermediate 1
- Starting material: 3,5-Dihydroxy-7-methyloct-6-enoic acid
- Reaction: Protection of hydroxyl groups with tert-butyldimethylsilyl (TBDMS) chloride
- Product: 3,5-Bis-TBDMS-7-methyloct-6-enoic acid

Step 2: Synthesis of Intermediate 2
- Starting material: (3R,5S)-3,5-Dihydroxy-7-methyloct-6-enoic acid
- Reaction: Protection of hydroxyl groups with benzyl bromide
- Product: (3R,5S)-3,5-Dibenzyl-7-methyloct-6-enoic acid

Step 3: Coupling Reaction

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- Reactants: Intermediate 1 and Intermediate 2
- Reaction: Coupling reaction using lithium diisopropylamide (LDA)
- Product: 3,5-Bis-TBDMS-7-methyl-6-enoic acid-(3R,5S)-3,5-dibenzyl ester

Step 4: Hydrolysis
- Reactant: Coupling product
- Reaction: Hydrolysis using lithium hydroxide
- Product: Rosuvastatin acid

Step 5: Esterification
- Reactant: Rosuvastatin acid
- Reaction: Esterification using calcium chloride
- Product: Rosuvastatin calcium

Step 6: Purification
- Crystallization
- Filtration
- Drying

Final Product:
Rosuvastatin calcium (Crestor)

Reagents and Conditions:
- Solvents: Tetrahydrofuran (THF), dichloromethane (DCM), ethanol
- Temperature: -78°C to 25°C
- Pressure: Atmospheric
- Catalysts: LDA, lithium hydroxide
- Reagents: TBDMS chloride, benzyl bromide, calcium chloride

Yield and Purity:
- Overall yield: 50-60% - Purity: >99%. [16,17]

IDENTIFICATION TEST

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with rosuvastatin calcium RS or with the reference spectrum of rosuvastatin calcium.

B. Dissolve 20 mg in 25 ml of methanol, add 2 drops of methyl red indicator neutralise with 6 M ammonium hydroxide. Add 3M hydrochloric acid until the solution is acidic to the indicator. Add ammonium oxalate solution, a white precipitate is obtained.

Tests

Related substances. Determine by liquid chromatography (24.14)

Test solution. Dissolve 50 mg of the substance under examination in 100 ml of the mobile phase.

Reference solution (a). A 0.05 per cent w/v solution of rosuvastatin calcium RS in the mobile phase.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with mobile phase.

Chromatographic system

A stainless steel column 25 cm x 4.6 mm packed with octadecylsilane bonded to porous silica (5 µm),
mobile phase: a mixture of 50 volumes of 0.2 per cent w/v acetic acid in water, 25 volumes of acetonitrile and 25 volumes of methanol,
flow rate: 1 ml per minute,
spectrophotometer set at 248 nm,
injection volume: 20 µl.

Inject reference solution (a). The test is not valid unless the column efficiency is not less than 2000 theoretical plates and the tailing factor is not more than 2.0.

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.5 times the area of the peak in the chromatogram obtained with reference solution (b) (0.5 per cent) and the sum of areas of all the secondary peaks is not more than twice the area of the peak in the chromatogram obtained with the reference solution (b) (2.0 per cent). [1]

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THERAPEUTIC USE

Therapeutic Use	Description
Lowering LDL Cholesterol	Reduces levels of "bad" LDL cholesterol, which helps decrease cardiovascular risk.
Reducing Triglycerides	Lowers triglyceride levels, reducing the risk of heart disease.
Increasing HDL Cholesterol	Slightly raises "good" HDL cholesterol, providing added heart protection.
Preventing Atherosclerosis	Slows the progression of plaque buildup in arteries, helping to prevent blockages.
Reducing Risk of Heart Attack & Stroke	Lowers the likelihood of heart attack, stroke, and other cardiovascular events, especially in high-risk individuals.
Familial Hypercholesterolemia Treatment	Helps manage high cholesterol in people with genetic cholesterol disorders, like heterozygous and homozygous familial hypercholesterolemia.
Post-Surgery/Procedure Prevention	Used after procedures (e.g., angioplasty) to prevent complications related to plaque buildup in arteries.

..[18]

MARKETED PREPARATION ROSUVASTATIN CALCIUM

Brand Name	Manufacturer	Formulation	Strengths Available
Crestor	AstraZeneca	Tablets	5 mg, 10 mg, 20 mg, 40 mg
Rosulip	Cipla	Tablets	5 mg, 10 mg, 20 mg, 40 mg
Rozavel	Sun Pharmaceuticals	Tablets	5 mg, 10 mg, 20 mg, 40 mg
Rosuvas	Lupin	Tablets	5 mg, 10 mg, 20 mg, 40 mg
Roseday	Ranbaxy (now Sun Pharma)	Tablets	5 mg, 10 mg, 20 mg, 40 mg
Rosvin	Dr. Reddy's Laboratories	Tablets	5 mg, 10 mg, 20 mg, 40 mg
Rexlip	Zydus Cadila	Tablets	5 mg, 10 mg, 20 mg, 40 mg
Rosucrest	Torrent Pharmaceuticals	Tablets	5 mg, 10 mg, 20 mg, 40 mg
Rovista	Biocon	Tablets	5 mg, 10 mg, 20 mg, 40 mg
Rosutor	Abbott	Tablets	5 mg, 10 mg, 20 mg, 40 mg

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IN RESENTLY PROGREES WORKING OF ROSUVASTATIN CALCIUM

Other Dosage forms

- Capsules.
- Oral Suspension.
- Fixed-Dose Combination.
- Extended-Release tablet /capsule. (slower release)
- powder for oral Solution. (drinkable solution Powder dissolve in water).
- Combination products.

e.g - Amlodipine, valsartan.

- Multiple therapeutic effect.[19]

Innovative Formulation

-That Inhance patient compliance bioavailability. Or offer new diliver mechanisum.

- Orally Disintigrating Tablet (ODTs).
- Cheawable Tablet.
- Transdermal patch.
- Baccal or Sublingual Films
- Effervecent Tablet .
- Microspheres or Nanoparticles.[20]

Injection

-Rare

- Hyperlipidemia / patient who come take medication orally. [21]

Recent progress in the future research of Rosuvastatin calcium is focused on several promising areas:

1. Alternative Formulations: There is significant interest in developing new dosage forms, such as orally disintegrating tablets (ODTs) and lozenges, which could enhance patient compliance, particularly in individuals who have difficulty swallowing traditional tablets or capsules. Research is exploring optimal excipients, formulations for stability, and controlled- release properties, making it easier for patients to take their medication without compromising efficacy.[22]

2. Combination Therapies: Ongoing research is looking into combining Rosuvastatin with other drugs, particularly PCSK9 inhibitors (like evolocumab or alirocumab), to provide more potent cholesterol- lowering effects. These combinations are being tested for better outcomes in patients with high cardiovascular risk who do not respond adequately to statins alone. [23]

3. Expanded Cardiovascular Benefits: While Rosuvastatin is widely used for its lipid-lowering properties, studies are investigating its anti- inflammatory effects and its potential to stabilize atherosclerotic plaques. This could have a profound Impact on reducing heart attacks and strokes in high-risk individuals, even in those without high cholesterol levels. [24]

4. Personalized Medicine: Research into pharmacogenetics is looking at how individual genetic differences may affect Rosuvastatin's efficacy and side effect profile. For example, certain genetic markers may influence how well a person metabolizes the drug or their risk of developing adverse effects, such as muscle pain or elevated liver enzymes.[25]

5. Long-Term Safety: There is growing research into the long-term use of Rosuvastatin, particularly with regard to muscle-related side effects, kidney function, and the potential risk of diabetes. Studies aim to clarify the trade-offs between the benefits of reducing cardiovascular events and these risks, with a focus on safer usage patterns.[26]

Recent research on Rosuvastatin calcium has focused on improving its bioavailability, stability, and formulation for enhanced therapeutic effectiveness. Key advancements. include

1. Self-Nanoemulsifying Drug Delivery Systems (SNEDDS): Studies have shown that using SNEDDS to deliver Rosuvastatin significantly improves its bioavailability. These systems enhance absorption by promoting faster dissolution in the gastrointestinal tract. In one study, the Ros SNEDDS formulation demonstrated 1.7 times better. bioavailability compared to the standard Rosuvastatin form . [27 ,28]

2. Stabilization of Formulations: Rosuvastatin calcium is prone to degradation due to moisture, light, and acidic conditions. Recent efforts have focused on stabilizing the drug by using natural stabilizers like Xanthan Gum and Chitosan. These stabilizers help maintain the stability of the drug and improve dissolution rates. A formulation with Chitosan and Xanthan Gum showed more than 20% improvement in dissolution compared to commercial tablets .[27,28]

Recent research on the dosage forms of Rosuvastatin calcium:

1. Solid Dispersions for Enhanced Solubility: Researchers are developing solid dispersions to improve the solubility of Rosuvastatin, addressing bloavailability issues associated with its low water solubility.

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2. Capsule Dosage Forms: Capsules filled with solid dispersions, combined with excipients like lactose and magnesium stearate, are being explored for enhanced dissolution rates.
3. Advanced Drug Release Techniques: New techniques such as controlled-release formulations are under investigation to maintain therapeutic levels of Rosuvastatin over extended periods.
4. Stability and Bioavailability Improvement: Studies focus on improving the stability of Rosuvastatin under different conditions, with particular attention to dissolution profiles and content uniformity.
5. Nanotechnology-Based Formulations: Research is exploring nanoparticles and nanoemulsions to enhance the drug's absorption and reduce side effects.
6. Film-Coated and Novel Tablet Forms: There is ongoing work on film-coated tablets to improve the release profile and mask any taste-related issues
7. In Vitro Dissolution Studies: Researchers are conducting in vitro dissolution tests to ensure that the new formulations meet the desired release criteria under specific conditions

- **ABBREVIATION**
- RC: Rosuvalstin calcium
- LDL: Low Density Lipoprotein
- HDL: High Density Lipoprotein
- CHD: coronary heart disease
- ISD: Ischemic heart disease
- LDLC: Low Density Lipoprotein Cholesterol
- HDLC: High Density Lipoprotein Cholesterol
- TG: Triglycerides
- VLDL: Very low Density Lipoprotein
- IDL: Intermidiat Density Lipoprotein
- AUC: Area Under Curve
- TBDMC: Tert-Butyldimethylsilychloride
- THF: Tetrahydrofuran
- RS: Rosuvalstin

CONCLUTION

Rosuvastatin calcium a leading statin for optimal LDL-C reduction and cardiovascular risk mitigation, boasting an exemplary safety profile, making it a versatile and reliable treatment choice for diverse patient populations, including those with diabetes, renal impairment, and older adults, and those requiring intensive lipid management."

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