**IJPSR (2023), Volume 14, Issue 3** **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 July 2022; received in revised form, 29 August 2022; accepted 09 September 2022; published 01 March 2023

# ANALYTICAL METHODS FOR THE DETERMINATION OF STATIN DRUGS USED IN DYSLIPIDEMIA AND HYPERCHOLESTEROLEMIA

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**Keywords:**

Statins, Hypercholesterolemia, Drugs, Analytical methods

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**ABSTRACT:** Statins are the first line of defense in the treatment of dyslipidemia and hypercholesterolemia illness. HMG-CoA reductase inhibitors or statins are the most widely prescribed drugs for persons at risk of cardiovascular disease. Cardiovascular disease (CVD) is the leading cause of death and a major cause of morbidity around the world. Statins have the same mechanism of action, but their chemical structures, pharmacokinetic profiles, and lipid-modifying potency differ. Triglycerides, cholesterol, and low-density lipoprotein (LDL) levels in the blood are all known risk factors for vascular disease, but statin drugs help to increase high-density lipoprotein (HDL) levels in our bloodstream. Some of the drugs utilized include rosuvastatin, atorvastatin, simvastatin, and pravastatin. According to clinical data, rosuvastatin is the most effective drug for decreasing low-density lipoprotein cholesterol and triglycerides, followed by atorvastatin, simvastatin and pravastatin. A brief review of the analytical methods developed from 2001-2021 for the estimation of Antilipidemic drugs has been discussed in the present study. This study will help the researchers to develop better methods for this class of drugs.

**INTRODUCTION:** Around the world, cardiovascular disease (CVD) is the leading cause of death and a major cause of morbidity. A major goal of medical treatment is to lower high blood cholesterol, a risk factor for cardiovascular disease. Because statins lower blood cholesterol, they are the first-line treatment. All causes of mortality, coronary heart disease, and stroke events were reduced with statins as was for revascularization [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(3).1435-41

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(3).1435-41

It took several years for the causal link between blood cholesterol levels and the risk of coronary heart disease to be widely accepted. In 1970, scientists in atherosclerosis research were firmly convinced that cholesterol-lowering would work. Interest in pharmacological approaches began as early as the 1950s and ultimately led to the discovery of statins [2].

Clinical investigations were beginning to show the role of cholesterol in atherosclerosis, necessitating the creation of new drugs. In 1976, Japanese researcher Akira Endo identified three compounds from the fungus *Penicillium citrinum* that were able to block the 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA) enzyme in a mouse liver enzyme system, preventing cholesterol synthesis [3].

Because of their efficacy and safety profile, statins are the treatment of choice for hypercholesterolemia. They're also becoming more essential in managing cardiovascular risk in persons with quite low plasma cholesterol levels. Statins have the same mechanism of action, although they differ in chemical structures, pharmacokinetic profiles, and lipid-lowering potency. The chemical structures of statins govern their water solubility, which controls their absorption, distribution, metabolism, and excretion. Lipophilic statins are taken up by active carrier-mediated processes in the liver due to first-pass metabolism and passive diffusion. In contrast, hydrophilic medicines are taken up by active carrier-mediated processes [4].

In recent clinical trials, statins have been proven to lessen the risk of stroke in persons with vascular disease. According to several epidemiological studies, hypercholesterolemia is the most prominent risk factor for coronary heart disease in industrialized countries. 3 – hydroxyl – 3 –methyl-glutaryl coenzyme A reductase inhibitors (statins) have been proven to decrease coronary events in the primary and secondary prevention of coronary heart disease. Triglyceride, cholesterol, low-density lipoprotein, and high-density lipoprotein abnormalities are all known risk factors for vascular disease. Cholesterol and low-density lipoprotein has a direct relationship with the incidence of coronary heart disease, while high-density lipoprotein has an inverse relationship [5]. Furthermore, scientific research has revealed that rosuvastatin, followed by atorvastatin, simvastatin, and pravastatin, is the most effective medicine for decreasing LDL cholesterol. Statins (HMG-CoA reductase inhibitors) are among the most widely prescribed medications for persons at risk of cardiovascular events. However, statins are well tolerated by most patients [6].

**Statins used in Dyslipidemia and Hyper-cholesterolemia:** Astra-Zeneca produced rosuvastatin ($C_{22}H_{28}FN_3O_6S$), which was approved by the US Food and Drug Administration in 2003 [7]. It was created to help people with dyslipidemia and hypercholesterolemia. It's a novel HMG-CoA reductase inhibitor that stops cholesterol synthesis by inhibiting HMG-CoA reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of cholesterol [8-12]. It's sold under the brand name Rosuvas. In tablet form, act as Rosuvas, Rosulip-F, and other similar products. Spectrophotometry [8-13], HPLC [14-19], and LC-MS [20-23] have all been used to create analytical procedures for determining Rosuvastatin **Table 1.**

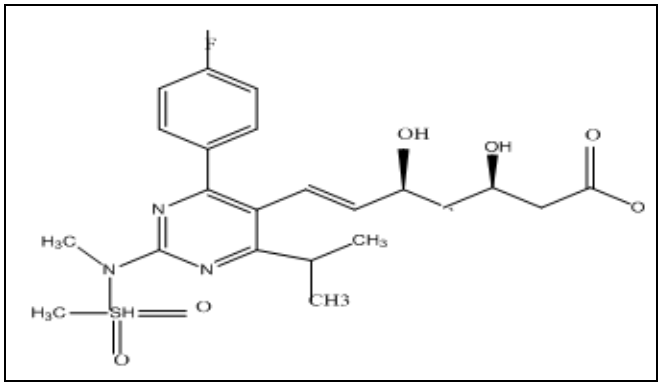


**FIG. 1: CHEMICAL STRUCTURE OF ROSUVASTATIN**

Bruce Roth invented atorvastatin ($C_{33}H_{35}FN_2O_5$) in 1985. Lipitor was approved by the Food and Drug Administration (FDA) in 1996 [24]. In treating hyperlipidemias, it is used to lower LDL cholesterol, apolipoprotein B, and triglycerides while increasing HDL cholesterol [25]. The enzyme (HMG-CoA) reductase catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis [26-29]. It's sold under the brand name Atorva. In tablet form, act as X'tor, Vasolip, and other similar drugs. Spectrophotometry [30-34], HPLC [25, 26, 28, 29, 31], MS [24, 35, 36], and GC/MS [37] have all been used to create analytical procedures for determining Atorvastatin **Table 2.**

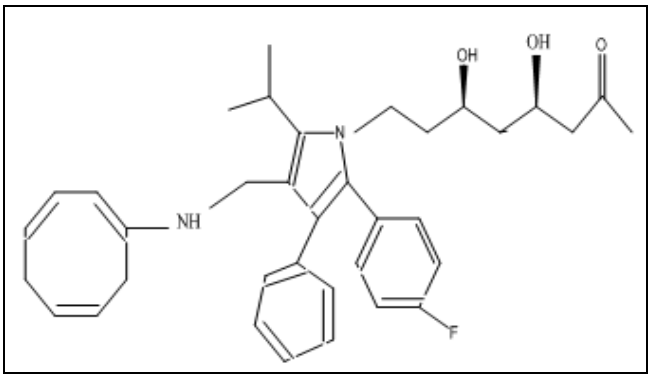


**FIG. 2: CHEMICAL STRUCTURE OF ATORVASTATIN**

Simvastatin **(**$C_{25}H_{38}O_5$) was discovered and developed at Merck in 1980. It was the first member of the statin class and a derivative of an

*Aspergillus terreus* fermentation product. This prodrug is metabolized to simvastatin hydroxy acid, a strong inhibitor of HMG CoA reductase, a crucial enzyme in cholesterol formation in the liver [38-40].

It's sold under the brand name Zocor. In tablet form, act as Simvas 10 and Starstat 10. Analytical approaches for determining Simvastatin have been included in HPLC [39-42], spectrophotometry [40, 43,] and LC-MS [44] **Table 3.**

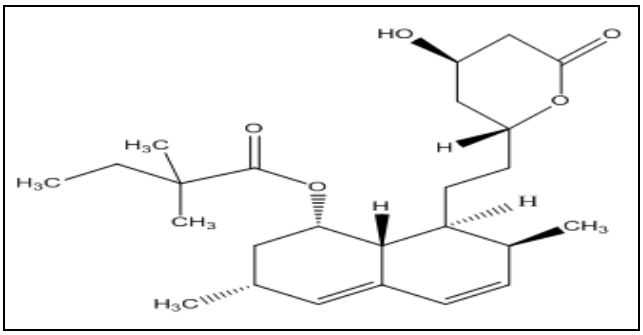


**FIG. 3: CHEMICAL STRUCTURE OF SIMVASTATIN**

Fluvastatin ($C_{24}H_{26}FNO_4$) is a white crystalline powder that inhibits the enzyme hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting step in cholesterol biosynthesis that transforms HMG-CoA to mevalonate [45-48].

It lowers plasma lipoprotein and cholesterol levels, which helps to prevent cardiovascular disease [49]. It is sold under the brand name Lescol XL. HPLC [45, 46], capillary electrophoresis [47,] and spectrophotometry [48-51] have all been used to create analytical procedures for determining Fluvastatin **Table 4.**

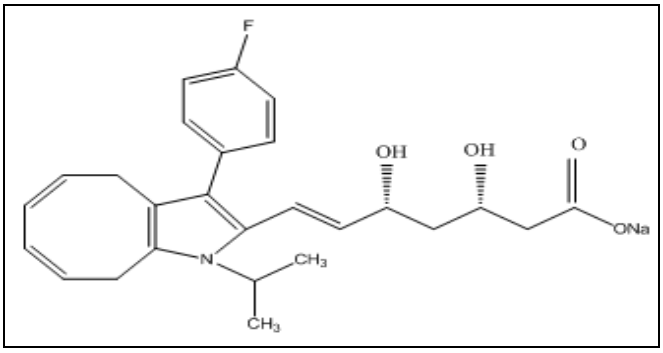


**FIG. 4: CHEMICAL STRUCTURE OF FLUVASTATIN**

During the compactin medication research phase, Sankyo Co., Ltd. (now Daiichi Sankyo) found pravastatin ($C_{23}H_{36}O_7$) as an active compactin metabolite in canine urine [53]. Blocking the cholesterol-producing enzyme HMG-CoA reductase reduces cholesterol production in the liver [54-56]. The drug pravastatin is used to treat hyperlipidemia and familial hypercholesterolemia. It's sold under the brand name Pravator. In pill form, it act as prastatin and pravator. HPLC [57, 58, 59, 61], capillary electrophoresis [54], LC-UV [55] and Spectrophotometry [56, 57, 60] were used to create analytical procedures for determining Pravastatin **Table 5.**

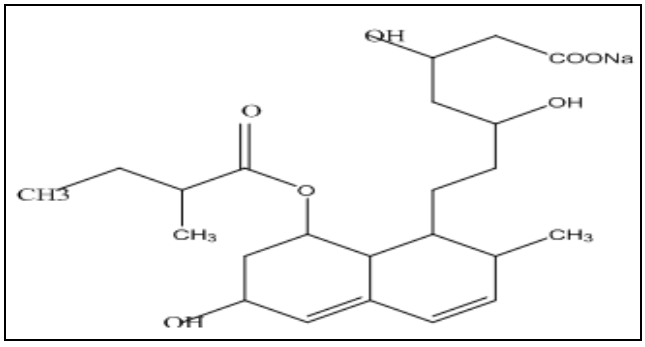


**FIG. 5: CHEMICAL STRUCTURE OF PRAVASTATIN**

**TABLE 1: A REVIEW OF ANALYTICAL METHODS FOR ROSUVASTATIN**

| Method | Mobile phase/ reagent | Column | References |
|---|---|---|---|
| Spectrophotometry | Methanol | | 8 |
| Spectrophotometry | Methanol | | 9 |
| Spectrophotometry (derivative) | Distilled water | | 10 |
| Spectrophotometry | Acetonitrile, Phosphate buffer (pH 9.8) | | 11 |
| Spectrophotometry | Methanol, Phosphate buffer | | 12 |
| Spectrophotometry | Methanol | | 13 |
| HPLC | Methanol: acetonitrile: water (40:40:20) | Thermo scientific C8 | 14 |
| HPLC | Acetonitrile: Phosphatebuffer (50:50) | C 18 | 15 |
| HPLC | Phosphate buffer (pH 2.5): Methanol: Acetonitrile (45:33:22) | Agilent Zorbax CYANO C 18 | 16 |
| HPLC | toluene: chloroform: n-butanol: formic acid (6:2:1.5:0.5) | C 18 | 17 |
| HPLC | Acetonitrile: water | ZORBAX EclipseC18 | 18 |
| HPLC | ACN: methanol: water (20:25:55), pH 3adjusted with phosphoric acid | C 18 | 19 |

| | | | |
|---|---|---|---|
| LC-MS | 0.1% formic acid: MeOH (20:80) | Phenomenex Kinetex C18 | 20 |
| LC-MS | 0.1% formic acid: acetonitrile (30:70) | C18 | 21 |
| LC-MS | ACN: formic acid (0.1%) (60:40) | Agilent Eclipse Plus ODS | 22 |
| LC-MS | Methanol: water (with 0.1% formic acid) | Poroshell 120 EC-C18 | 23 |

**TABLE 2: A REVIEW OF ANALYTICAL METHODS FOR ATORVASTATIN**

| Method | Mobile phase/ reagent | Column | References |
|---|---|---|---|
| Spectrophotometry | Methanol | | 30 |
| Spectrophotometry | Methanol | | 31 |
| FTIR spectroscopy | Methanol | | 32 |
| Spectrophotometry | Methanol | | 33 |
| Spectrophotometry | Methanol | | 34 |
| HPLC | Phosphate buffer (pH 4): Acetonitrile (90:10) | C 18 | 25 |
| HPLC | Cetrimide: acetonitrile (35:65) | Nucleodur C18 | 26 |
| HPLC | 0.025M phosphoric acid: acetonitrile (60:40) | C18 | 28 |
| HPLC | Acetonitrile: methanol: 0.1% formic acid (50:10:40) | C 18 | 29 |
| LC-Q-TOF-MS | ACN: aqueous 5mM ammonium formate solution | Zorbax Eclipse XDB-C18 | 35 |
| LC-MS | Acetonitrile 0.025M: $NaH_2PO_4$: buffer pH 4.5 (55:45) | C 18 | 24 |
| LC-MS | tertbutyl methyl ether: n-hexane (70:30) | Zorbax Eclipse XDB-C8 | 36 |
| GC-MS | Hexane: methanol (1:50) | Capillary column HP5-MS | 37 |

**TABLE 3: A REVIEW OF ANALYTICAL METHODS FOR SIMVASTATIN**

| Method | Mobile phase/reagent | Column | References |
|---|---|---|---|
| HPLC | Acetonitrile: phosphate buffer solution, pH 4 (25:75) | C 18 | 39 |
| HPLC | Ammonium acetate buffer (10 mM; pH 4.0): acetonitrile (40:60) | Symmetry C18 | 40 |
| HPLC | Acetonitrile: potassium dihydrogen phosphate buffer (pH 4) (75:25) | C18 | 41 |
| HPLC | Acetonitrile: water (pH 3.0 adjusted with ortho-phosphoric acid) (50:50) | Purospher Star C 18 | 42 |
| Spectrophotometry | Methanol | | 43 |
| Spectrophotometry | 0.25N NaOH | | 44 |
| LC-MS | 0.04% formic acid in water) and mobile phase B (acetonitrile) | Acquity UPLC BEH C18 | 45 |

**TABLE 4: A REVIEW OF ANALYTICAL METHODS FOR FLUVASTATIN**

| Method | Mobile phase/reagent | Column | References |
|---|---|---|---|
| HPLC | Acetonitrile:0.1% orthophosphoric acid (50:50) | C18 | 46 |
| HPLC | Acetonitrile: 0.02M potassium phosphate buffer (50: 50, v/v, pH 5) | Phenomenex LunaC18 | 47 |
| Capillary Electrophoresis | Methanol | fused-silica capillary | 48 |
| Spectrophotometry (difference method) | Methanol, 0.1N NaOH, 0.1N HCl | | 49 |
| Spectrophotometry (derivative method) | Methanol | | 50 |
| Spectrophotometry | Phosphate buffer 7.4 | | 51 |
| Spectrophotometry | NaOH | | 52 |

**TABLE 5: A REVIEW OF ANALYTICAL METHODS FOR PRAVASTATIN**

| Method | Mobile phase/ reagent | Column | References |
|---|---|---|---|
| HPLC | Acetonitrile (0.1%): diethylamine (50:50) | HYPERSIL C 18 | 57 |
| HPLC | Methanol: phosphate buffer (70:30%) | C 18 | 58 |
| HPLC | Water: acetonitrile: acetic acid(40:59:1) | Phenomex C 18 | 59 |
| HPLC | ACN: MeOH(0.08M): Orthophosphoric acid (23:20:57) | Hypersil ODS | 61 |
| Capillary Electrophoresis | borate buffer (pH 8.5): 10%acetonitrile | Fusedsilica capillary | 54 |
| LC-UV | Methanol: water(80:20): 85% *o*-phosphoric acid | Purospher Star, C18 | 55 |
| Spectrophotometry | Ethanol | | 56 |
| Spectrophotometry (derivative method) | Methanol | | 57 |
| Spectrophotometry | Methanol and acetonitrile | | 60 |

**CONCLUSION:** The present study has discussed a brief review of the analytical methods developed from 2001-2021 for estimating Antilipidemic drugs. This current review paper included thorough information on statins which includes their mechanisms, essential features, and analytical methods reported by various authors. This study will help the researchers to develop better methods for these classes of drugs.

**ACKNOWLEDGMENT:** We would like to express our sincere gratitude to Director Dr. H. P. Chettri and Principal Dr. N. R. Bhuyan, Himalayan Pharmacy Institute, for their continuous support and encouragement.

**Funding:** None

**CONFLICTS OF INTEREST:** There were no conflicts of interest declared by the authors.

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**How to cite this article:**
Tumung N, Jajo H, Bairagi S and Shrestha B: Analytical methods for the determination of statin drugs used in dyslipidemia and hypercholesterolemia. Int J Pharm Sci & Res 2023; 14(3): 1435-41. doi: 10.13040/IJPSR.0975-8232.14(3).1435-41.