3. REVIEW OF LITERATURE

3. REVIEW OF LITERATURE:

Several methods have been reported for the analysis of hyperlipidemic agents. Those include both classical and instrumental methods. The methods have been developed keeping in view the requirements. Consequently, certain methods are also focused on the analysis of the drug from biological fluids. Table 3.1–3.5 gives a brief account of some of the methods available in the literature for the analyzing the drugs in alone or for analyzing the drugs selected for the present investigations study.

Table: 3.1 List of reported methods for EZETIMIBE

Sr. No.	Method	Remarks	Ref.
1.	HPLC	A stability-indicating HPLC method was developed for analysis of the drug in the presence of the degradation products. Stationary Phase: C8 column; Mobile Phase: 0.02 M, ammonium acetate buffer, pH adjusted to 7.0 with ammonium hyroxide-acetonitrile; Mode of elution: Gradient; Flow rate: 1.5 ml/min; Detection wavelength: 250 nm; Linearity range: 5-500 µg/ml.	1
2.	RP-HPLC	For assaying ezetimibe in pharmaceutical dosage forms. Stationary phase: Kromasil 100 C18 column; Mobile Phase: water (pH 6.8, 0.05%, w/v 1-heptane sulfonic acid)-acetonitrile (30:70, v/v) ; mode of elution: Isocratic; Flow rate: 0.5 ml/min; Detection wavelength: 232 nm; Linearity range: 0.5 – 50 µg/ml.	2
3.	LC-MS/MS	A selective and high-sensitive assay to measure serum concentration-time profiles, renal and fecal elimination of ezetimibe in pharmacokinetic studies. Stationary phase: Xterra® MS, C18 column; Mobile phase: Acetonitrile-water (60:40,v/v); Mode of elution: Isocratic; Flow rate: 200 µl/min; Mean retention times: For ezetimibe and the internal standard were 2.5 and 2.4	3

		min, respectively. The MS/MS analysis was performed in the negative ion mode(m/z transition: Ezetimibe 408-271, internal standard 223-117). The validation ranges for Ezetimibe and total Ezetimibe were as follows: serum 0.0001 – 0.2 ng/ml; urine and fecal homogenate 0.025 – 10 ng/ml and 0.1 – 20 ng/ml, respectively.	
4.	LC-MS/MS	Validated method for quantification for free and total Ezetimibe in human plasma. Stationary phase: capcell C 18 column; Mode of elution: Gradient; Mobile phase: Acetonitrile-5mM ammonium acetate; Detection: Using tandem mass negative ionization by multiple reactions monitoring mode. The mass transition pairs of m/z 408->270.8 and m/z 414.5->276.8 were used to detect Ezetimibe and internal standard, respectively. Linearity ranges: 0.02 – 20 ng/ml for free ezetimbe and 0.25 – 250 ng/ml for total ezetimbe in human plasma.	4
5.	HPLC	Validated method for quantification of ezetimbe and metabolite(s) Stationary phase: Intersil C8 column; Mode of elution L Gradient; Mobile phase: 20 mM ammonium acetate adjusted to pH 7.0 with 1% aqueous ammonium hydroxide(A) and acetonitrile(B); Detection: photodiode array detector and radioactively detector; Linearity ranges: 0.02 – 10 ng/ml.	5
6.	LC-MS/MS	Plasma sample were assayed for unconjugated and total ezetimbe concentration. Stationary Phase: Spherisorb-ODS2 column 10 µm particle size; Mode of elution: Isocratic; Mobile phase: methanol: 0.025 M ammonium acetate in ration of 9:1 Detection: using tandem mass positive ion mode. The mass transitions monitored for ezetimbe were 329.3 to	6

		133.1 and for internal standard 434.2 to 216.1. Flow rate: 1.5 ml/min; Linearity ranges:1.00 to 100 ng/ml and 5.02 to 502 ng/ml for unconjugated and total ezetimbe, respectively.	
7.	SIAM RP-HPLC, combination with simvastatin.	SIAM method for simultaneous analysis of ezetimibe and simvastatin. Stationary phase: Lichrospher 100 C18 column; Mobile phase: Acetonitrile- water- methanol (60:25:15; v/v/v) pH adjusted 4.0 ± 1; Flow rate : 1.5 ml/min; UV detection wavelength : 238 nm; Linearity : 1- 80 µg/ml of simvastatin and 3-80 µg/ml of ezetimibe.	7
8.	HPTLC, combination with atorvastatin calcium.	Estimation of atorvastatin and ezetimibe simultaneously in combined dosage forms. Stationary phase: silica gel 60F254; Mobile phase: Chloroform -benzene -methanol-acetic acid (6:3:1:0.1; v/v/v/v); linearity: 0.8 – 4.0 µg/spot for atorvastatin and 0.1 -1.0 µg/spot for ezetimbe.	8

Table: 3.2 List of reported methods for PRAVASTATIN

Sr. No.	Method	Remarks	Ref.
1.	HPLC Combination with Lovastatin, Atorvastatin, Rosuvastatin, Simvastatin.	Analysis of five HMG-CoA reeducates inhibitors: pharmacological, Pharmacokinetic and analytical overview and development of a new method for use in pharmaceutical formulations analysis and in vitro metabolism study. Stationary Phase: Intertisl ODS 3V column; Mobile phase: 0.01 M ammonium acetate, pH 5.0 acetonitrile - methanol; Mode of elution: ternary gradient: Flow rate: 1 ml/min; Detection wavelength: 247 nm; Retention time: 28.5 min. Percentage recover: 89.6 – 105.6 % or its label's claim in the pharmaceutical formulations.	9

2.	HPLC combination with Lovastatin, Mevastatin and Simvastatin	Relative lipophilicities, solubility and structure pharmacological consideration. Stationary phase: Bondapak column; Mobile phase : Methanol- water- triethylamine- glacial acetic acid (50:50:0.1:0.1, v/v/v/v); Flow rate: 1.3 ml/min; UV Detection wavelength: 238 nm; Retention time: 17.5 min; LOD:10 ng/ml; LOQ: 25 ng/ml.	10
3.	HPLC and Capillary Electrophoresis	Determination in production media. Stationary phase: A. Particle column, B. Monolithic column and C. Silica capillary filled with borate buffer pH 9.3 containing 20mM SDS (MECK). All three methods successfully separate Pravastatin form interfering compounds (matrix, mevastatin and 6-epi Pravastatin); Runtime: Shorter than 1 min; Solvent consumptions: for method A,B and C were 132, 510 and 1.5 ml/h. the most sensitive was the method using particle column (LOD was about 10^{-5} mg/ml), followed by the system using monolith column (L0D was 0.0002 mg/ml and the MECK method LOD was about 0.02 mg/ml).	11
4.	HPLC	Determination in rat liver, solid phase extraction. Triamcinoline was internal standard. Stationary phase: Bond Elut C18 RP-Column; Mobile phase: 0.035 mM/L Na_2HPO_4 buffer, pH 3-acetonitile (155:42, v/v); Linearity range: 0.05 – 10 µg/ml; Detection limit: 13 ng/ml; Average extraction recovery: 80.8 %.	12
5.	HPLC	Estimation in human plasma and urine samples, automated solid phase extraction. Stationary phase: Rp-C18 column; Mode of elution: Isocratic; UV detection wavelength: 239 nm; linearity range: 1.9 – 200 and 1.9 – 2000 ng/ml in plasma and urine, respectively.	13

6.	HPLC-MS	Determination in human plasma. Extractive column: C18 column; Mode of elution: Isocratic; Detection: BY negative ion electrospray mass spectrometry; Linearity range: 0.25 – 300 ng/ml: Recovery: 90.5 %; Total runtime: Less than 2 min.	14
7.	Turbo ion spray LC-MS/MS with its derivatives.	For quantification of Pravastatin, Pravastatin-Bis, SQ-31906, SQ-31906-d5, and Pravastatin lactone in human serum samples. Detection: BY tandem mass spectrometry in the positive ion mode; Linearity range: 0.5 – 100 ng/ml. Method was also applied for stability study at different conditions.	15
8.	HPLC	For determination in plasma. Solid phase extraction column: Cyclohexyl bond elute cartridge; Stationary phase: Octyl matrix; Linearity range: 5- 200 µg/L; Coefficient of variation: less than 10%.	16
9.	HPLC-APCI/MS	For simultaneous determination with its main metabolites in human plasma. Isolation by solid phase extraction technique and detection by atmospheric pressure (negative ion) chemical ionization mass spectrometry (APCI-MS). Retention time: 2.1 min; Total runtime: 5 min; Linearity range: 0.625 – 80 ng/ml.	17
10.	HPLC	Biotransformation in human urine, plasma and feces. Stationary phase: Partisile10 ODS-3 C18 column; Mobile phase: 10mM potassium phosphate buffer, pH 7.2 and 5mM tetrabutyl ammonium hydrogen sulphate (25:75, v/v for 20 min than after 50:50,v/v); Flow rate: 4.0 ml/min; Injection volume: 500 – 1000 µl; UV detection wavelength: 245 nm; Retention time: 33 min.	18

11.	HPLC	Determination with its isometric metabolites in human urine. Detection by UV.	19
12.	HPLC	A method for the determination in plasma by using an immobilized antibody column extraction. A laser-induce fluorescence detector monitored the analyte after fluorogenic dramatization. Drug antibody was coupled to sepharose 4B and used as an extraction phase for sample cleanup and extraction of the drug. A plasma sample was applied to the column and washed with water, and the drug was eluted with methanol. A column switching techniques was utilized to remove excess reagents and byproducts. A He-Cd laser–induced fluorescence detector was applied to achieve and ultra sensitive determination. Detection limit: 2 pg/injection, which was 20 times more sensitive than the conventional fluorescence detection; Limit of quantitation: 100 pg/ml; An average coefficient of variations: Less than 8 % ; Linearity range : 1-100 ng/ml.	20
13.	HPLC	A method for the quantization of the HMG-CoA reeducates inhibitor Pravastatin in human plasma. Stationary phase: RP-C18 column; Detection: By UV detector; Recovery: 69.2 ± 6.7 % (mean ± S.D.) ; LOD: in aqueous solution was 0.4 ng; LOQ : IN plasma was 2 ng/ml.	21
14.	HPLC	Estimation of Pravastatin sodium. Stationary phase: Hypersil ODS C18 column; Mobile phase: methanol; Flow rate L 0.5ml/min; Detection: UV diode array detection. Retention time: 2.9 min.	22
15.	GC-MS	In serum. Limit of quantification: 0.5 µg/L for Pravastatin and its metabolites.	23

16.	GC-MS	In serum and Plasma Limit of quantification: 0.3 μg/L.	24
17.	HPTLC, also for simvastatin and rosuvastatin calcium.	For separation and quantization of simvastatin, Pravastatin sodium and rosuvastatin calcium. Stationary phase: silica gel 60F254; Mobile phase: Chloroform-methanol-toluene (6:2:2, v/v/v); LOD: 15, 9 and 8 ng/spot for simvastatin, Pravastatin sodium and rosuvastatin calcium respectively.	25

Table: 3.3 List of reported methods for ROSUVASTATIN

Sr. No.	Method	Remarks	Ref.
1.	HPLC Combination with Lovastatin, Atorvastatin, Pravastatin, Simvastatin.	Analysis of five HMG-CoA reeducates inhibitors: pharmacological, Pharmacokinetic and analytical overview and development of a new method for use in pharmaceutical formulations analysis and in vitro metabolism study. Stationary Phase: Intertisl ODS 3V column; Mobile phase: 0.01 M ammonium acetate, pH 5.0 acetonitrile - methanol; Mode of elution: ternary gradient: Flow rate: 1 ml/min; Detection wavelength: 247 nm; Retention time: 28.5 min. Percentage recover: 89.6 – 105.6 % or its label's claim in the pharmaceutical formulations.	9
2.	HPTLC, also for simvastatin and Pravastatin sodium.	For separation and quantitation of simvastatin, Pravastatin sodium and rosuvastatin calcium. Stationary phase: silica gel 60F254; Mobile phase: Chloroform-methanol-toluene (6:2:2, v/v/v); LOD: 15,9 and 8 ng/spot for simvastatin , Pravastatin sodium and rosuvastatin calcium respectively.	25
3.	HPLC-MS/MS	Quantification of N-desmethyl metabolite of rosuvastatin in human plasma. The assay-employing	26

		automated SPE followed by HPLC with positive electrospray tandem MS (HPLC-MS/MS). Linearity range for metabolites: 0.5 – 30 ng/ml; LOQ : 0.5.	
4.	HPLC-MS	Pharmacokinetics and pharmacogenetics. Plasma concentration of rosuvastatin and metabolites were determined by HPLC-MS.	27
5.	HPLC	Determination of rosuvastatin. Stationary phase: Xterraa RP C 18 column; Mobile phase: Acetonitrile – 0.02 M Potassium dihydrogen orthophosphate buffer, pH 3 (35:65; v/v); Flow rate : 1.5 ml/min; Detection wavelength: 242 nm; Linearity range: 8 -60 µg/ml; LOD : 0.03627 µg/ml.	28
6.	Microbore HPLC-MS.	Detection of rosuvastatin (Crestor™) in human plasma was investigated. Three microbore HPLC columns with internal diameters (i.d.) of 0.5, 1.0 and 2.0 mm were evaluated for column efficiency and mass sensitivity. Experiments with the 1.0 mm i.d. HPLC column were performed to determine the robustness of the microbore method for human plasma extracts after sample preparation using solid-phase extraction (SPE). Quantities of rosuvastatin of 0.3 pg on-column could be detected and cross-validation experiments demonstrated that the conventional and the microbore HPLC-MS/MS methods provided similar information on the concentration of rosuvastatin but with greatly reduced sample consumption using the microbore method.	29
7.	Spectrophoto-metric	Estimation in tablet formulation. Detection wavelength: 242 nm; Linearity: 4 – 24 µg/ml.	30
8.	LC-MS/MS	Estimation in human plasma.	31

	Combination with Fenofibric acid	Stationary phase: Xterra MS C-18 column; Mobile phase: 0.05M Formic acid; acetonitrile (45:55; v/v); Flow rate: 0.40 ml/min; Positive ion acquisition chromatographic run was used in the present method. LLOQ: 1.00 ng/ml; The application or the assay to clinical study confirmed the utility of the assay.	
9.	HPLC-MS	Estimation of rosuvastatin in human plasma using atorvastatin as internal standard. Stationary phase: Sphere ODS H-80 column; Mobile phase: 0.2% formic acid in water and acetonitrile (40:60; v/v); Flow rate: 1.0 ml/min; Positive ion mode 482 and 258 for rosuvastatin; Linearity: 1.0 ng/ml to 50.0 ng/ml.	32

Table: 3.4 List of reported methods for SIMVASTATIN

Sr. No.	Method	Remarks	Ref.
1.	SIAM RP-HPLC, combination with simvastatin.	SIAM method for simultaneous analysis of ezetimibe and simvastatin. Stationary phase: Lichrospher 100 C18 column; Mobile phase: Acetonitrile- water- methanol (60:25:15; v/v/v) pH adjusted 4.0 ± 1; Flow rate: 1.5 ml/min; UV detection wavelength : 238 nm; Linearity : 1- 80 µg/ml of simvastatin and 3-80 µg/ml of ezetimibe.	7
2.	HPLC Combination with Lovastatin, Atorvastatin, Pravastatin, Rosuvastatin.	Analysis of five HMG-CoA reeducates inhibitors: pharmacological, Pharmacokinetic and analytical overview and development of a new method for use in pharmaceutical formulations analysis and in vitro metabolism study. Stationary Phase: Intertisl ODS 3V column; Mobile phase: 0.01 M ammonium acetate, pH 5.0 acetonitrile	9

		- methanol; Mode of elution: ternary gradient: Flow rate: 1 ml/min; Detection wavelength: 247 nm; Retention time: 28.5 min. Percentage recover: 89.6 – 105.6 % or its label's claim in the pharmaceutical formulations.	
3.	HPLC combination with Lovastatin, Mevastatin and Simvastatin	Relative lipophilicities, solubilities and structure pharmacological consideration. Stationary phase: Bondapak column; Mobile phase : Metanol-wate-triethylamine-glacuak acetuc acud (50:50:0.1:0.1, v/v/v/v); Flow rate: 1.3 ml/min; UV Detecion wavelength: 238 nm; Retention time: 17.5 min; LOD:10 ng/ml; LOQ: 25 ng/ml.	10
4.	HPTLC, also for Pravastatin sodium and rosuvastatin calcium.	For separation and quantitation of simvastatin, Pravastatin sodium and rosuvastatin calcium. Stationary phase: silica gel 60F254; Mobile phase: Chloroform-methanol-toluene (6:2:2, v/v/v); LOD: 15,9 and 8 ng/spot for simvastatin , Pravastatin sodium and rosuvastatin calcium respectively.	25
5.	HPLC	Analysis of simvastatin in human plasma. Stationary phase: Lichrophere C18 column; Mobile phase: Acetonitrile – methanol (70:30; v/v); Mode of elution: Isocratic; Flow rate: 1.2 ml/min; Detection wavelength: 237 nm.	33
6.	Column switching HPLC	Determination of simvastatin and its metabolites in human plasma. Method A. Stationary phase: Bondesil CH column; Mobile phase: Methanol – water (80:20; v/v), Method B. Stationary phase: Capcell PaK C18 column; Mobile phase : Acetonitrile-water (80:20; v/v); Mode of elution: Isocratic; Flow rate: 1 ml/min; Detection wavelength: Florescence detection at excitation wavelength 360 nm and emission wavelength 430 nm;	34

		Retention time: 27.5 min; Limit of detection: 20 pg/ml.	
7.	HPLC, with its hydroxyl acid form.	Simultaneous determination of simvastatin and its hydroxyl acid form in human plasma. Stationary phase: C18 column; Mobile phase: Acetonitrile and water: Detection: By UV Detection.	35
8.	HPLC	Bioequivalence study of two formulations of tablet. Plasma concentration of simvastatin and its hydroxyl acid metabolite were analyzed by using LC/MS/MS.	36
9.	HPLC-MS/MS	Bioequivalence evaluation of two formulations (Simvast and Zocor) of tablets. Plasma concentration of simvastatin and β–hydroxy acid metabolite were analyzed by using LC/MS/MS.	37
10.	GC	Metabolic fate of 2,2-dimethyl-butyryl moiety of simvastatin in rats. Identification of metabolites by GC/MS.	38
11.	HPLC,USP	Method A. For detection of drug substance purity and potency. Stationary phase: C18 column; Mobile phase: Acetonitrile-dilute phosphoric acid (1 in 1000), (60:40; v/v); Flow rate: 3.0 ml/min; UV detection wavelength: 238 nm; Retention time: 1.0 min. Method B. For detection in tablets. Stationary phase: C18 column; Mobile phase: Acetonitrile buffer solution, (65:35, v/v); Flow rate: 1.5 min; UV detection wavelength: 238 nm.	39
12.	HPLC	**Method A**. For drug substance purity. Stationary phase: Spherisorb ODS column; Mobile phase: Acetonitrile- 0.025 M Sodium dihydrogen phosphate buffer, pH 4.5; Mode of elution: Isocratic and gradient; UV Detection wavelength: 238 nm. **Method B**. For measurement in tablets.	40

		Stationary phase: Hypersile ODS column; Mobile phase: Acetonitrile-wate (0.025 M sodium dihydrogen phosphate, pH 4.5), (60:40; v/v); Mode of elution: Isocratic; UV detection wavelength: 238 nm. **Method C.** For measurement in tablets. Stationary phase: Hypersil 5 μ ODS column; Mobile phase: 0.025 M Sodium dihydrogen phosphate, pH 4-acetonitile- methanol, (33:55:12; v/v/v); Mode of elution: Isocratic; UV detection wavelength: 230 nm. **Method D.** For drug substance potency. Stationary phase: Perkin-Elemer C18 CR column; Mobile phase: Acetonitrile – 0.1% v/v, phosphoric acid (50:50, v/v); Mode of elution: Isocratic; UV detection wavelength : 238 nm.	
13.	HPLC	For measurement of simvastatin and its metabolites in plasma. Stationary phase: Jones chromatography Apexl C18 column; Mobile phase: Acetonitrile-0.025 M Sodium acetate buffer; mode of elution: Gradient; UV detection wavelength: 238 nm.	41
14.	HPLC	For measurement of low levels of drug in fermentation broth. Stationary phase: PRP column; Mobile phase: Acetonitrile-aqueous ammonium phosphate, pH 6.1; Mode of elution: Gradient; UV detection wavelength : 260 nm.	42
15.	HPLC, combination with Lovastatin	Determination in pharmaceutical dosage forms. Stationary phase: Hichrome C18 column; Mobile phase: water-acetonitrile (30:70; v/v); Flow rate: 1.0 ml/min; Detection wavelength : 238 nm; Linearity range: 0.1 – 3.0 mg/ml; lOD : 29 ng/ml.	43

16.	HPLC, combination with Nicotinic acid.	Simultaneous determination in tablets. Stationary phase: C18 column; Mobile phase: 0.01 M KH_2PO_4 buffer-methanol (10:90; v/v); Mode of elution: Isocratic; Flow rate: 0.6 ml/min; Retention time: 4.6 min for simvastatin; Linearity range: 0.02 – 0.1 µg/ml.	44
17.	HPLC , combination with Lovastatin, mevastatin, Pravastatin.	Relative liophilicities, solubilities and structure pharmacological consideration. Stationary phase: Bondapak column; Mobile phase: Methanol- water- triethylamine-glacial acetic acid (50:50:0.1:0.1, v/v/v/v); Flow rate: 1.3 min/ml; UV detection wavelength: 238 nm.	45
18.	HPLC-MS/MS.	A method for the quantitative determination of the major statin drug simvastatin (SIM) and its metabolite simvastatin hydroxyl acid (SIMA). Detection was performed on an electrospray ionization triple quadruple mass spectrometer equipped with an ESI interface operated in positive and negative ionization mode. The multiple reaction-monitoring mode was used to provide MS/MS detection; Linearity range: 0.10 – 16.00 ng/ml and 0.10-16.00 ng/ml for SIM and SIMA, respectively; LOQ: 0.03 ng/ml and 0.02 ng/ml for SIM and SIMA, respectively.	46
19.	RP-HPLC	The aim of work was to establish conditions for paraoxonase 3 (PON3) activity determinations in human blood serum with simvastatin (SV) as a substrate. Stationary phase: LC 18 column; Mode of elution: Isocratic; Mobile Phase: Acetonitrile - phosphate buffer, pH 4.5 (70:30; v/v); Flow rate: 1.5 ml/min; Detection: Based on UV absorption at a wavelength of 239 nm was reliable for the simultaneous assay of SV. Linearity range: 0.5 –6µg/ml (1.194 -14.3	47

		nmol/ml); LOD and LOQ: for SV were 3.1and 10.4 ng/ml, respectively and in case of SVA, LOD and LOQ were 4.7 and 14.44 ng/ml for a 20 µl sample, respectively.	
20.	HPTLC	Identification of drug substances. Stationary phase: E. Merck silica gel 60 F254 HPTLC plate; Mobile phase: Cyclohexane- chloroform-isopropanol solution of 0.05% w/v butylated hydroxyl toluene (05:02:0.1; v/v/v); Detection: Visually under UV light at 238 nm or by spraying the developed plate with a dilute methanolic sulfuric acid solution and application of heat; Rf value: Approximately 0.4.	48
21.	Second derivative UV-spectroscopy	Determination in the table dosage for. UV measurement at 243 nm after carefully choosing zero-crossing technique of second derivative. This method eliminates the interference from absorbing excipients such as ascorbic acid, which often results in a bias of 2 – 10 %.	49
22.	First derivative UV-Specroscopy with Fluvastatin.	Quantitative determination in human serum and pharmaceutical formulations. UV measurement of their first derivative signals at 241.6, 245.9, 249.1 nm (for simvastatin) and 259.6 nm (for fluvastatin), respectively.	50
23.	Direct injection LC-MS/MS. With lovastatin and lovastatin acid.	Method was developed and validated for simultaneous determination of prodrug and its active drug in human plasma. Stationary phase: Oasis C18 column; Mobile phase: Acetonitrile- 3.0 M formic acid; Mode of elution: Gradient; Flow rate: 4.0 ml/min.	51
24.	Automated enzyme inhibition assay	Determination done of simvastatin in plasma and urine sample. The assay was performed on Tecan Genesis 150 and	52

	with radioactivity detection.	200 systems equipped with 8-probe and 96 well plates. Radioactivity was counted on a scintillation counter. Calibration ranges, 0.4 – 20, 2-50, and 5- 100 ng/ml, in human plasma and animal plasma and urine were validated.	
25.	LC-MS	Estimation was done for simvastatin and its hydroxyl acid in human plasma. Stationary phase: Kromasil C18 column; Mobile phase: Acetonitrile - 1mM ammonium acetate with pH 4.5 (75:25; v/v); Flow rate: 200 µl; LOQ: 50 pg/ml. The mass spectrometer was operated in the negative ion detection mode for 2 min and rest of analytical run with positive ion mode.	53
26.	LC-MS/MS	Determination of simvastatin and simvastatin acid in human plasma with solid phase extraction. Stationary phase: Phenomenex Synergic Max Rp Column; Mobile phase: Acetonitrile-methyl ammonium acetate 1 mM, pH 4.5 (80:20, v/v); Flow rate: 200 µl/min.	54
27.	Voltammetic	Estimation in tablet and serum samples. The electrochemical behavior studied in aqueous alcohol medium; Stationary phase: glassy carbon electron; Cyclic voltammetry studies showed one main, well defined, sharp oxidation peak between pH 2 and 8. Differential pulse and square wave voltammetric techniques: determination in 0.1 M H_2SO_4 and a constant amount of methanol (20%). Linearity range; $2x10^{-6} – 1x10^{-4}$M. LOQ: $2.71x10^{-7}$ M and $5.50x10^{-7}$M.	55
28.	Micellar electrokinetic chromato	Estimation in pharmaceutical dosage forms. Mode of experiment: cathodic mode; Temperature: 30C; voltage: 25kV; Pressure: 5 s! at 10 mbar; LOD :	56

	graphic method (MEKC), For lovastatin.	3.2 µg/ml; LOQ: 10.6 µg/ml.	
29.	LC/ESI/MS	Determination of simvastatin (I), using lovastatin (II) as internal standard. Stationary phase: C column; Mobile phase: methanol–water 18 (9:1). Detection: positive ionization mode. SIM mode (*m/z*: 441 and *m/z*: 427 for I and II, respectively); LOQ: 0.05 ng/ ml.	57

Table: 3.5 List of reported methods for Lovastatin

Sr. No.	Method	Remarks	Ref.
1.	HPLC Combination with Lovastatin, Atorvastatin, Pravastatin, Rosuvastatin.	Analysis of five HMG-CoA reeducates inhibitors: pharmacological, Pharmacokinetic and analytical overview and development of a new method for use in pharmaceutical formulations analysis and in vitro metabolism study. Stationary Phase: Intertisl ODS 3V column; Mobile phase: 0.01 M ammonium acetate, pH 5.0 acetonitrile - methanol; Mode of elution: ternary gradient: Flow rate: 1 ml/min; Detection wavelength: 247 nm; Retention time: 28.5 min. Percentage recover: 89.6 – 105.6 % or its label's claim in the pharmaceutical formulations.	9
2.	HPLC combination with Lovastatin, Mevastatin and Simvastatin	Relative lipophilicities, solubilities and structure pharmacological consideration. Stationary phase: Bondapak column; Mobile phase: Methanol–water-triethylamine-glacial acetic acid (50:50:0.1:0.1, v/v/v/v); Flow rate:	10

		1.3 ml/min; UV Detection wavelength: 238 nm; Retention time: 17.5 min; LOD:10 ng/ml; LOQ: 25 ng/ml.	
3.	HPLC, combination with Simvastatin	Determination in pharmaceutical dosage forms. Stationary phase: Hichrome C18 column; Mobile phase: water-acetonitrile (30:70; v/v); Flow rate: 1.0 ml/min; Detection wavelength : 238 nm; Linearity range: 0.1 – 3.0 mg/ml; LOD : 29 ng/ml.	43
4.	HPLC , combination with Simvastatin, mevasatin, Pravastatin.	Relative liophilicities, solubilities and structure pharmacological consideration. Stationary phase: Bondapak column; Mobile phase: Methnol- water- triethylamine- glacial acetic acid (50:50:0.1:0.1, v/v/v/v); Flow rate: 1.3 min/ml; UV detection wavelength: 238 nm.	45
5.	Direct injection LC-MS/MS. With simvastatin and simvastatin acid	Method was developed and validated for simultaneous determination of prodrug and its active drug in human plasma. Stationary phase: Oasis C18 column; Mobile phase: Acetonitrile- 3.0 M formic acid; Mode of elution: Gradient; Flow rate: 4.0 ml/min.	51
6.	Micellar electrokinetic chromatographic method (MEKC), with simvastatin.	Estimation in pharmaceutical dosage forms. Mode of experiment: cathodic mode; Temperature: 30C; voltage: 25kV; Pressure: 5 s! at 10 mbar; LOD : 3.2 µg/ml; LOQ: 10.6 µg/ml.	56
7.	HPLC, BP.	Estimation in tablet. Stationary phase: Silica gel; Mobile phase: Mixture of acetonitrile, buffer solution and methanol (5:3:1, v/v/v); Temperature : 45C ; Flow rate: 1.5 ml/min; Detection : 238 nm.	58

8.	HPTLC, USP,NF.	Estimation in tablet. Stationary phase: Silica gel; Mobile phase: Mixture of acetonitrile and 0.1% phosphoric acid solution(65:35, v/v); Flow rate: 1.5 ml/min; Solvent system : 0.05% w/v butylated hydroxytoluene in cyclohexane, chloroform and isopropyl alcohol. (5:2:1, v/v/v) UV detection wavelength: 238 nm.	59
9.	HPTLC	Estimation in tablet formulations. Stationary phase: silica gel G60 F254 TLC plate; mobile phase: Toluene-methanol (75:25, v/v); UV detection wavelength: 239 nm; Linearity range: 30 -180 µg/ml.	60
10.	Derivative Spectrophotometric methods, combination with ascorbic acid; quartering and gallic acid.	Method A. Second derivative zero crossing method; UV detection wavelength: 238.4 nm. Method B. First derivative bivariate Spectrophotometric, optimum pair of wavelengths was chosen for the determination of different binary mixtures. Linearity range: 3.20 -17.36 µg/ml, for both methods.	61
11.	CE and HPLC,EP.	Determination of lovastatin and its oxidation products. CE: Apparatus: Hewlett-packard HP 3D CE; Capillary : fused silica capillary; Injection: 40 mba, 10s; Voltage: 30kV; Temperature: 30C; Detection: 238 nm. HPLC: Stationary phase: Eurosphere C18 column; Mobile phase: Acetonitrile- 0.1% phosphoric acid; Flow rate: 1.5 ml/min; Mode of elution: Gradient; UV detection wavelength: 238 nm.	62

12.	HPLC and Raman spectroscopy	Determination of stability of lovastatin in solid state in the presence of Gallic acid. Raman Spectroscopy: Vibration mode: 1645 cm^{-}, Heated : 120 °C. HPLC: stationary phase: Zorbax C_g column; Mode of elution: Gradient; Mobile phase: Acetonitrile- 0.1% phosphoric acid; UV detection wavelength: 225.	63
13.	Super critical fluid chromatography.	Estimation of lovastatin. Stationary phase: Hypersil silica column; Mobile phase: Acetonitrile-methnol-water (55:12:33 v/v/v) pH 4 using phosphate buffer; Flow rate: 1.5 ml/min; UV detection wavelength: 230 nm.	64
14.	Capillary Zone Electrophoresis	Quantitative analysis of lovastatin (Lvt) in capsule of Monascus-Chinese. Eztraction: of 16% ethanol (v/v) in 60mM Gly-sodium hydroxide buffer, pH 10.5, 16 kV applied voltage, 238 nm detection wavelength with a capillary of 51 cm×75_m i.d (43 cm to detector). Calibration range: 4.0 to 240 g/mL LOD:0.73 g/ml ; LOQ:2.42g/mL.	65
15.	LC/ESI/MS, for atorvastatin, lovastatin, pravastatin and simvastatin	Four major statin drugs, atorvastatin, lovastatin, pravastatin and simvastatin. Mobile phase: methylammonium acetate as an additive; LOD: atorvastatin, lovastatin, pravastatin and simvastatin are 0.7, 0.7, 8.2 and 0.9 pg,respectively.	66
16.	Reversed-phase displacement chromatography	The purification of pravastatin, simvastatin and lovastatin in the sodium salt or lactone form and of mevastatin in the Lactone. Stationary phase: ODS C18; Mobile phases:	67

		water or mixtures of water–methanol and water–acetonitrile.	
17.	RP-HPLC	Analysis of secondary fungal metabolites mevinolin (also known as monacolin K, lovastatin or Mevacor) and fumagillin in fermentation broths. Mode of elution: Isocratic and gradient elution; Mobile phase: acetonitrile-aqueous phosphoric acid or acetonitrile-phosphate buffer; UV-photodiode array detection.	68
18.	LC	Determination of Lovastatin (mevinolin) and mevinolinic acid in fermentation liquids	69
19.	HPLC	Cyclosporin A (CSA) and lovastatin (LV) are lipophilic drugs. Mode of elution: isocratic; Mobile phase: acetonitrile and water in the proportions 70:30 and 80:20 with short retention times for CSA and LV; Stationary phase: Shim-pack C column; flow-rate: 2 ml /min UV detection wavelength: 215 nm at 70 8C for CSA. In the case of LV the flow-rate was 1 ml /min and detection was done at 238 nm at 25 8C; LOD: 250 and 10 ng/ml LOQ: 400 and 30 ng/ml for CSA and LV, respectively; Concentration range: 0.5–6 mg/ml for CSA and 0.05–0.4 mg/ml for LV.	70
20.	LC	Two quantitative determination of sibutramine HCl, using 4-chloro aniline and lovastatin as internal standards, respectively. The enantiomeric separation of sibutramine by chiral chromatography method has been described also.	71

		This method is capable of separating the two enantiomers with a selectivity of 1.4 and a resolution of 4.0. Both methods are found to be stability indicating and useful in the quality control of the bulk material.	
21.	LC/MS and LC/MS/MS	Quantitative determination in human plasma (Lovastatin) and cell supernatants (Arachidonic acid) and medium molecular weight (\2000 Da) endogenous peptides (Endothelins) in supernatants of human umbilical vein endothelial cell cultures is reported. Linear calibration curves and detection limits around 50 pg /ml were obtained in all three cases.	72
22.	FIA	A flow injection system with in-series ultraviolet and electrochemical detection for the simultaneous determination of lovastatin and butylated hydroxyanisole in a tablet	73

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