3. Review of Literature...
3. REVIEW OF LITERATURE

Following methods have been reported for the estimation of Atorvastatin calcium (ATV)

Jain et al \(^8\) described RP-HPLC method for simultaneous estimation of ATV and fenofibrate in tablet dosage form. The chromatographic separation was carried out using Luna \(C_{18}\) column as stationary phase and methanol: acetate buffer pH 3.7 (82:18, v/v) as mobile phase, at a flow rate of 1.5 ml/min. Detection was carried out at 248 nm. Retention time of ATV and fenofibrate were 3.02 and 9.05 min, respectively. The method was linear in the concentration range of 1-5 \(\mu g/ml\) for ATV and 16-80 \(\mu g/ml\) for fenofibrate.

Korany et al \(^9\) described determination of etofibrate, fenofibrate and ATV in pharmaceutical preparation and in plasma using differential pulse polarographic and square wave voltametric techniques by reduction at a dropping-mercury working electrode versus Ag/AgCl reference electrode. Limits of detection and quantitation for ATV were in the ranges of 0.037–0.21 and 0.12–0.71 \(\mu g/ml\), respectively.

Khedr et al \(^10\) described stability indicating HPLC assay of ATV with fluorescence detection. ATV and its degradation products were analyzed on stationary phase agilent Zorbax XDB \(C_{18}\) column using mobile phase acetonitrile: 0.02 M sodium acetate, pH 4.2 (45:55, v/v). The samples were monitored with fluorescence detector at 282 nm (excitation)/400 nm (emission). The photodegradation products were separated by silica gel thin-layer chromatography using double development with ethyl acetate: \(n\)-hexane: glacial acetic acid: methanol (40: 55:0.5:4.5, v/v/v/v) followed by (39:55:0.5:5.5, v/v/v/v). The method was linear over the concentration range of 10–1200 ng/injection for ATV.

Pasha et al \(^11\) described estimation of five HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin) using HPLC. Ternary gradient elution at a flow rate of 1 ml/min was employed using stationary phase an Inertsil ODS 3V column (4.6 x 250 mm, 5 \(\mu m\)) at ambient temperature. The mobile phase consisted of 0.01 M ammonium acetate (pH 5.0): acetonitrile: methanol.
Theophylline was used as an internal standard (IS). The detection was carried out at 237 nm. The retention time for ATV was 17.2 min.

Yadav et al.\textsuperscript{12} described HPTLC method for the determination of content uniformity of ATV tablets. The chromatographic estimation was carried out using precoated silica gel 60 F\textsubscript{254} as stationary phase with a mixture of benzene: methanol (7:3, v/v) as mobile phase. Detection of the spots were carried out at 281 nm. The limit of detection and limit of quantification for ATV were found to be 40 ng/spot and 200 ng/spot, respectively.

Zarghi A et al.\textsuperscript{13} described HPLC method for the determination of ATV in human plasma with UV detection and its application to pharmacokinetic study. Diltiazem was used as internal standard. The chromatographic estimation was performed with stationary phase Nucleosil C\textsubscript{8} column (125 x 4 mm i.d., 5 μm) using mobile phase sodium dihydrogen phosphate buffer: acetonitrile (60:40, v/v) adjusted to pH 5.5 at a flow rate of 1.5 ml/min with UV detection at 245 nm. The detection limit for atorvastatin was 1 ng/ml. The calibration curve was linear in the concentration range of 20-800 ng/ml.

Hermann et al.\textsuperscript{14} described determination of ATV and metabolites in human plasma with solid-phase extraction followed by LC-tandem MS. Sample preparation was carried out by solid phase extraction followed by separation of analytes on HPLC system with a mobile phase consisting of acetonitrile, water and formic acid. The detection limit was 0.06 ng/ml for atorvastatin and p-hydroxyatorvastatin, and 0.15 ng/ml for o-hydroxyatorvastatin.

Bahrami et al.\textsuperscript{15} described determination of ATV in human serum by RP-HPLC using UV detection. Chromatographic estimation was performed using stationary phase C\textsubscript{18} analytical column with a mobile phase consisting of sodium phosphate buffer (0.05 M, pH 4.0): methanol (33:67, v/v). ATV and the internal standard were detected by ultraviolet absorbance at 247 nm. The lower limits of detection and quantification were 1 and 4 ng/ml, respectively, and the calibration curves were linear over a concentration range of 4–256 ng/ml of ATV in human serum.
Gerber et al. described cell based screen of HMG-Co A reductase inhibitors and expression regulators using LC-MS.

Erk et al. described electrochemical methods for determination of ATV in pharmaceutical products and spiked human plasma. The methods were performed in Britton-Robinson buffer. Differential pulse and osteryoung square-wave adsorptive stripping voltammetric methods were applied at pH 2.0 and the methods were linear in the range of 35-460 and 60-620 nM, respectively, with LOD of 4 and 2 nM, respectively, and LOQ of 10 and 20 nM, respectively.

Koytchev et al. described bioequivalence study of atorvastatin tablets by LC-MS/MS method.

Altuntas et al. described LC determination of ATV in bulk drug, tablets and human plasma. LC was performed on stationary phase RP-Supelcosil C18 (5 µm, 15 cm x 4.6 mm i.d.) column using mobile phase consisting of acetonitrile: methanol: water (45:45:10, v/v/v), at a flow rate of 1.0 ml/min. The effluent was monitored by a UV detector at 240 nm. The method was linear in the concentration range of 0.5-86.0 µg/ml for ATV.

Miao et al. described determination of cholesterol lowering statin drugs (atorvastatin, lovastatin, pravastatin and simvastatin) in aqueous samples using LC-electrospray ionization tandem mass spectrometry. The instrumental detection limits of atorvastatin, lovastatin, pravastatin and simvastatin are 0.7, 0.7, 8.2 and 0.9 pg, respectively. A solid-phase extraction method was developed to enrich the analytes from aqueous samples. All of the statins were detected in an untreated sewage sample at 4-117 ng/l and in a treated sewage sample at 1-59 ng/l; atorvastatin was detected in a surface water sample at 1 ng/l.

Erturk et al. described HPLC method for the determination of ATV and its impurities in bulk drug and tablets. A gradient reverse-phase HPLC was performed using Luna C18 column as stationary phase with acetonitrile: ammonium acetate buffer (pH 4): tetrahydrofuran as mobile phase. Samples were eluted gradiently with the mobile phase at flow rate 1.0 ml/min and detected at 248 nm.
Erk et al \textsuperscript{22} described extractive spectrophotometric determination of ATV in bulk and pharmaceutical formulations. The procedures were based on the reaction between the drug and bromocresol green, alizarin red or bromophenol blue producing ion-pair complexes whose absorption could be measured at the optimum wavelengths. Beer's law was obeyed in the concentration ranges 5.0-53.0, 7.1-55.8 or 7.5-56.0 \(\mu\)g/ml with bromocresol green, alizarin red or bromophenol blue, respectively.

Jemal et al \textsuperscript{23} described quantitation of the acid and lactone forms of atorvastatin and its biotransformation products in human serum by HPLC with electrospray tandem mass spectrometry. Analysis was performed by HPLC on a 5 m YMC Basic column (5 cm \(\times\) 2.0 mm i.d.) as stationary phase using gradient elution (1 ml/min) with aqueous 5\% methanol containing 88\% formic acid (mobile phase A)/acetonitrile/methanol (19:1) containing 0.043\% 88\% formic acid (mobile phase B) and positive ion electrospray tandem MS detection operated in selected-reaction monitoring mode for the \([M + H]^+\) parent to daughter transition of each analyte (m/z listed for each transition). The calibration graph was linear from 0.5 - 200 ng/ml for all analytes.

Bullen et al \textsuperscript{24} described HPLC-tandem mass spectrometry assay for atorvastatin (I), ortho-hydroxyatorvastatin (II) and para-hydroxyatorvastatin (III) in human, dog and rat plasma. The analysis was performed by HPLC on a 4 \(\mu\)m YMC J'Sphere H80 column (15 cm \(\times\) 2 mm i.d.) as stationary phase with acetonitrile: 0.1\% acetic acid (7:3, v/v) as mobile phase (0.2 ml/min) and positive-ion electrospray tandem MS detection. The method was linear in the concentration range of 0.25-25 ng/ml for I-III.

Following liquid chromatographic methods have been reported for the estimation of Amlodipine besylate (AML) in pharmacopoeia and in combination with other drugs

Ramani et al \textsuperscript{25} described LC-ESI-MS/MS method for simultaneous quantitation of simvastatin acid, amlodipine and valsartan in human plasma. The instrument API-4000 LC-MS/MS was operated under the multiple reaction monitoring mode (MRM) using electrospray ionization. The chromatographic separation was performed with
stationary phase C₁₈ column, using mobile phase 0.02 M ammonium formate (pH 4.5): acetonitrile (20:80, v/v) at a flow rate of 0.5 ml/min. The retention time was 1.81, 1.12, 1.14 min for simvastatin acid, amlodipine and valsartan respectively.

Wei et al ²⁶ described determination of nicardipine and AML in human plasma using online solid phase extraction with a monolithic weak cation exchange column. The proposed method was linear over a range of 0.5-50.0 ng/ml for both analytes and the limit of detection (LOD) for each analyte was 0.2 ng/ml.

Dongre et al ²⁷ described simultaneous determination of metoprolol succinate and AML in pharmaceutical dosage form by HPLC. The chromatographic separation was performed on stationary phase Hypersil BDS cyano (250 mm x 4.6 mm, 5 μm) column using PDA detector. The mobile phase consisting of triethylamine (pH 3): acetonitrile (85:15, v/v) at a flow rate of 1.0 ml/min was used.

Vora et al ²⁸ described development and validation of a simultaneous HPLC method for estimation of bisoprolol fumarate and AML from tablets. Chromatographic separation was performed with stationary phase Luna C₁₈ column (50 x 4.6 mm) using mobile phase 25 mM ammonium acetate, pH 5: methanol (65: 35, v/v) at 0.8 ml/min flow rate. UV detection was performed at 230 nm. Retention time was 1.45 min and 3.91 min for bisoprolol and AML, respectively. The method was linear in the range of 8-33 μg/ml.

Sarkar et al ²⁹ described simultaneous determination of metoprolol succinate and AML in human plasma by LC-tandem mass spectrometry method and its application in bioequivalence study. The chromatographic separation was performed on a stationary phase basic C₁₈ column using mobile phase methanol: water containing 0.5% formic acid (8:2, v/v). HCTZ was used as internal standard. The protonated analyte was quantitated in positive ionization by multiple reaction monitoring with a mass spectrometer. The method was linear over the concentration range of 1-100 ng/ml for metoprolol succinate and 1-15 ng/ml for AML in human plasma.

BP 2007 ³⁰ reported LC method for the estimation of AML from bulk drug. The chromatographic separation was carried out on a stationary phase octa decylsilica gel
Kristoffersen et al 31 described simultaneous determination of 6 beta blockers (atenolol, sotalol, metoprolol, bisoprolol, propranolol and carvedilol), 3 calcium channel antagonists (diltiazem, amlodipine and verapamil), 4 angiotensin II antagonist (losartan, irbesartan, valsartan and telmisartan) and antiarrhythmic drug (flecainide) in post mortem whole blood by automated solid phase extraction and liquid chromatography mass spectrometry. Quantification was performed by RP-HPLC with positive electrospray ionization mass spectrometric detection (HPLC-MS).

Barman et al 32 described simultaneous HPLC determination of atenolol and AML in pharmaceutical dosage form. The chromatographic separation was performed with stationary phase ODS C18 (4.6 mm x 25 cm) column, using a mobile phase ammonium acetate buffer (pH 4.5 with glacial acetic acid): acetonitrile: methanol (35:30:35 v/v/v). The flow rate was maintained at 1.5 ml/min, column temperature was maintained at 40°C and detection was performed at 237 nm. The retention times for atenolol and AML were 1.5 and 3.4 min, respectively.

Naidu et al 33 described stability indicating RP-HPLC method for simultaneous determination of AML and benazepril hydrochloride from their combination drug product. The chromatographic separation was performed with stationary phase Zorbax SB C18 (5 µm, 250 mm x 4.6 mm) column using mobile phase phosphate buffer: acetonitrile (65:35, v/v, pH 7) and UV detection was performed at 240 nm using a photodiode array detector. The method was linear over the concentration range of 6-14 µg/ml for AML and 12-28 µg/ml for benazepril.

Valiyare et al 34 described HPLC determination of AML, losartan and ramipril in pharmaceutical formulations. The chromatographic separation was performed using stationary phase ODS C18 column with mobile phase acetonitrile: water: o-phosphoric acid at a flow rate of 1 ml/min. The detection was performed at 220 nm. The method
was linear in the concentration range of 30-70 \mu g/ml for AML. The limit of detection was 0.5 \mu g/ml for AML.

Kamble et al \cite{35} described HPLC method for simultaneous determination of lisinopril and AML from tablets. The chromatographic separation was performed using stationary phase ODS C_{18} column with a gradient elution using mobile phase 0.2% triethylamine in water (pH 3.5): methanol at a flow rate of 1 ml/min. Detection was performed at 215 nm. The method was linear in the concentration range of 0.025-0.25 mg/ml for AML.

Baranda et al \cite{36} described simultaneous determination of five 1,4-dihydropyridines (amlodipine, nitrendipine, felodipine, lacidipine and lercanidipine) in pharmaceutical formulation by HPLC-amperometric detection. The chromatographic separation was performed on a stationary phase Supelcosil LC C_{18} column using mobile phase acetonitrile: 10 mM acetate buffer (72:28, v/v) at a flow rate of 1 ml/min. The temperature was set at 30°C. The amperometric detector, equipped with a glassy carbon electrode was operated at +1100 mV versus Ag/AgCl in the direct current mode. The method was linear in the concentration range of 4.5-15 \mu g/ml.

Kulkami et al \cite{37} described HPLC method for determination of losartan potassium and AML in tablets. The chromatographic separation was performed on stationary phase Hypersil ODS C_{18} column with a mobile phase triethylamine in water (pH 3): acetonitrile (60:40, v/v) at a flow rate of 1 ml/min. The detection was performed at 240 nm. The retention time for AML and losapan were 4.7 min and 7.41 min respectively. Method was linear in the concentration range of 10-40 \mu g/ml for AML.

Zarapkar et al \cite{38} described simultaneous estimation of AML and losartan potassium in pharmaceutical dosage form by RP-HPLC. The chromatographic separation was performed using stationary phase YMC C_{18} ODS column with a mobile phase 50 mM KH_{2}PO_{4} buffer (pH 3): acetonitrile (60:40, v/v) at a flow rate of 1 ml/min. The detection was performed at 215 nm and retention time for AML was 4.19 min. The method was linear in the concentration range of 0.01-0.05 mg/ml for AML.
Rao et al.\textsuperscript{39} described RP-HPLC determination of AML and benazepril HCl in tablets. The chromatographic separation was carried out on stationary phase Prochrome C\textsubscript{18} column with a mobile phase 0.00134 M EDTA: acetonitrile: acetic acid (50:50:0.1, v/v/v) at a flow rate of 1 ml/min. Detection was performed at 238 nm with a retention time of 3.37 min for AML. The method was linear in the concentration range of 0.01-0.12 mg/ml for AML.

Gowri et al.\textsuperscript{40} reported simultaneous estimation of AML and benazepril from tablets by RP-HPLC. Chromatographic separation was achieved by ODS C\textsubscript{18} column as stationary phase and acetonitrile: methanol: triethylamine 0.05 M buffer (15:35:50, v/v/v, pH 3) as mobile phase. Mobile phase flow rate was maintained at 2ml/min and detection was performed at 237 nm.

Dhorda et al.\textsuperscript{41} described RP-HPLC determination of ramipril and AML in tablets. The chromatographic separation was carried out on a stationary phase Hypersil ODS C\textsubscript{18} column with a mobile phase water: acetonitrile: triethylamine (57:43:0.2, v/v/v, pH 3.2) at a flow rate of 1 ml/min. Caffeine was used as an internal standard. The detection was performed at 226 nm. The retention time for AML was 6.4 min. Method was linear in the concentration range of 0.1 – 0.3 mg/ml for AML.

Halkar et al.\textsuperscript{42} described simultaneous HPLC determination of AML and enalapril maleate from pharmaceutical preparation. The chromatographic separation was performed on stationary phase Hypersil ODS C\textsubscript{18} column with a mobile phase 0.025 M KH\textsubscript{2}PO\textsubscript{4}: acetonitrile (60:40, v/v, pH 3) at a flow rate of 1 ml/ min. Paracetamol was used as an internal standard. The detection was performed at 238 nm. The retention time for AML and enalapril were 10.69 min and 2.91 min respectively.

Patel et al.\textsuperscript{43} described simultaneous RP-HPLC estimation of six drugs (atenolol, amlodipine, nifedipine, nitrendipine, nimodipine and felodipine) for combined hypertensive therapy. The chromatographic separation was performed with stationary phase JASCO-metaphase ODS (250 x 4.0 mm, 5 \textmu m) column using mobile phase acetonitrile: 0.01 M KH\textsubscript{2}PO\textsubscript{4} (50:50, v/v, pH 4.5). The detection was performed at 250 nm. The method was linear in the concentration range of 25-3200 ng/ml for these drugs, with the detection limits at 15 ng/ml for AML.
Zarapkar et al. described simultaneous HPLC determination of AML and atenolol from pharmaceutical preparation. The chromatographic separation was performed using stationary phase C₁₈ column with a mobile phase 0.1% triethylamine pH 3.8: methanol (32:68, v/v) at a flow rate of 1 ml/min. The detection was performed at 238 nm. The retention time for AML was 6.4 min.

Following methods have been reported for the estimation of ATV and AML in combination

Mishra et al. described simultaneous estimation of ATV and AML from tablets using simultaneous equation method. Simultaneous equation method employed formation and solving of simultaneous equations using 246 nm and 360 nm as two analytical wavelengths. The method was linear in the concentration range of 5 – 30 µg/ml for both the drugs.

Sahu et al. described simultaneous spectrophotometric determination of AML and ATV in binary mixture using simultaneous equation method. Absorbance was measured at 238.2 and 246.6 nm corresponding to the absorbance maxima of AML and ATV in methanol, respectively. The method was linear in the concentration range of 5-30 µg/ml for both the drugs.

Chaudhrai et al. described stability indicating RP-HPLC method for the determination of ATV and AML from combined drug products. The method utilized a Lichrospher® 100 C₁₈, 5 µm, 250 mm×4.0 mm i.d. column as stationary phase, at ambient temperature. Mobile phase consisted of acetonitrile: 50 mM potassium dihydrogen phosphate buffer (60: 40, v/v, pH 3), effluent flow rate monitored at 1.0 ml/min, and UV detection was carried out at 254 nm. The method was linear in the range of 1-90 µg/ml and 1-80 µg/ml for ATV and AML, respectively. The limit of detection for ATV and AML were 0.4 and 0.6 µg/ml, respectively and the limit of quantification was 1.0 µg/ml for both drugs.

Sivakumar et al. described HPLC method with the aid of a chemometric protocol for the simultaneous analysis of AML and ATV in pharmaceutical formulations. The
mobile phase used was methanol: acetonitrile: 15 mM K$_2$HPO$_4$ buffer (pH 5.33) (10:42.08:47.92, v/v/v) and flow rate was maintained at 1.12 ml/min.

Mohammadi et al $^{49}$ described a stability-indicating HPLC assay for the simultaneous determination of ATV and AML in commercial tablets. Separation was carried out with Perfectsil Target ODS-3 (250 mm x 4.6 mm i.d., 5 μm) column as stationary phase using acetonitrile: 0.025 M NaH$_2$PO$_4$ buffer (pH 4.5) (55:45, v/v) as mobile phase at a flow rate of 1 ml/min and UV detection at 237 nm. The method was linear in the range of 2-30 μg/ml for ATV and 1-20 μg/ml for AML. The limits of detection were 0.65 μg/ml and 0.35 μg/ml for ATV and AML, respectively. The limits of quantitation were 2 μg/ml and 1 μg/ml for ATV and AML, respectively.

Khan et al $^{50}$ described simultaneous spectrophotometric determination of ATV and AML in tablets using simultaneous equation and dual wavelength method. Simultaneous equation method employed formation and solving of simultaneous equations using 245 nm and 363 nm as two analytical wavelengths. Dual wavelength method used the difference of absorbance value at 259.9 nm and 354 nm for estimation of ATV and absorbance at 363 nm for AML. Methanol (50%) was used as solvent. ATV and AML were found to be linear in the range of 0-40 μg/ml and 0-20 μg/ml, respectively.

Rajeswari et al $^{51}$ described RP-HPLC method for the simultaneous determination of ATV and AML in tablet dosage form. The mobile phase used was a mixture of acetonitrile: 0.03M phosphate buffer pH 2.9 (55:45, v/v). The detection of ATV and AML was carried out at 240 nm and 362 nm, respectively. The method was linear in the concentration range of 0.2 – 20 ng/ml for ATV and 0.1 – 20 ng/ml for AML.

Chaudhri et al $^{52}$ described simultaneous estimation of ATV and AML by HPTLC. The chromatographic separation was performed on stationary phase precoated silica gel 60 F$^{254}$ using mobile phase chloroform: toluene: methanol: acetic acid (7:3:3:0.3, v/v/v/v). Detection was performed densitometrically using a UV detector at 254 nm in absorbance mode. The Rf value for ATV and AML were 0.66 and 0.28, respectively. Linearity was in the range of 100- 1000 and 100 – 1500 ng/spot for ATV and AML,
respectively. The limit of detection and quantitation for ATV were 30 and 80 ng/spot, respectively and for AML were 45 and 92 ng/spot respectively.

Following methods have been reported for the estimation of Ezetimibe (EZT)

Dalmora et al 53 described stability indicating micellar electrokinetic chromatographic method for the determination of EZT in pharmaceutical formulations. The method was carried out on a fused-silica capillary (50 μm i.d.; effective length, 40 cm). The background electrolyte consisted of a 25 mM borate buffer and 25 mM anionic detergent SDS (pH 9.75)/methanol (90:10, v/v). The capillary temperature was maintained at 35°C, the applied voltage was 30 kV; the injection was performed using a pressure mode at 50 mbar for 5 s, with detection at 232 nm. The method was linear in the concentration range of 2-150 μg/ml of EZT.

Sharma et al 54 described UV and three derivative spectrophotometric methods for determination of EZT in tablet formulation. For UV spectrophotometry, the quantitative determination of the drug was carried at 233 nm and the method was linear in the concentration range of 6-16 μg/ml for EZT. For the first, second and third derivative spectrophotometric methods the drug was determined at 259.5 nm, 269 nm and 248 nm with the linearity ranges of 4-14 μg/ml, 4-14 μg/ml and 4-16 μg/ml respectively.

Akmar et al 55 described RP-HPLC method for estimation of EZT in bulk and pharmaceutical formulations. The chromatographic estimation of EZT was achieved using acetonitrile: 0.02 M potassium dihydrogen orthophosphate buffer (72:28 v/v) as the mobile phase with UV detection at 232 nm and C8 kromasil 5 μ column as stationary phase. The flow rate was maintained at 1 ml/min.

Basha et al 56 described concurrent determination of EZT and its phase I (ezetimibe ketone, EZM-K) and II (ezetimibe glucuronide, EZM-G) metabolites by HPLC with UV detection. The chromatographic analysis was performed using stationary phase C18 column by gradient elution consisting of 0.05 M formic acid: acetonitrile: methanol: water as mobile phase at a flow rate of 1.0 ml/min. The detection was performed at 250 nm. Nominal retention times of internal standard, EZM-G,
ezetimibe ketone glucuronide (EZM-KG), EZT and EZM-K were 9.39, 24.23, 27.82, 29.04 and 30.56 min, respectively.

Singh et al \textsuperscript{57} described stability indicating HPLC method for analysis of the drug in the presence of the degradation products. The analysis was performed using stationary phase C\textsubscript{8} column with mobile phase 0.02 M ammonium acetate buffer (pH 7.0): acetonitrile. The detection was carried out at 250 nm.

Imran et al \textsuperscript{58} described stability indicating UV spectroscopic method for the estimation of EZT and carvedilol. 20\% v/v acetonitrile in triple distilled water was used as solvent. The linearity range for EZT and carvedilol were 2-50 \( \mu\)g/ ml and 2-20 \( \mu\)g/ ml at 232 nm and 238 nm, respectively. The detection and quantitation limits were 0.4 \( \mu\)g/ ml and 1.3 \( \mu\)g/ ml respectively for EZT.

Li et al \textsuperscript{59} described LC-negative ion electrospray tandem mass spectrometry method for quantification of EZT in human plasma. The chromatographic separation was performed on stationary phase C\textsubscript{18} column, and the plasma extract was eluted with a gradient mobile phase consisting of acetonitrile and 5 mM ammonium acetate. The analyte was detected using negative ionization by multiple reaction monitoring mode. The mass transition pairs of \textit{m/z} 408.5 \( \rightarrow \) 270.8 and \textit{m/z} 414.5 \( \rightarrow \) 276.8 were used to detect ezetimibe and internal standard, respectively. The assay exhibited linear ranges from 0.02- 20 ng/ml for free EZT and 0.25 to 250 ng/ml for total EZT in human plasma.

Oswald et al \textsuperscript{60} described LC-MS/MS method for the quantification of EZT in human serum, urine and feces in healthy subjects genotyped for SLCO1B1. The chromatographic estimation was performed using stationary phase XTerra\textsuperscript{®} MS, C\textsubscript{18}, (2.1 mm \( \times \) 100 mm, 3.5 \( \mu\)m) column with acetonitrile: water (60:40, v/v) as mobile phase at 200 \( \mu\)l/min flow rate. The MS/MS analysis was performed in the negative ion mode (\textit{m/z} transition: EZT 408–271, internal standard 223–117). The linearity ranges for EZT and total EZT were as follows: serum 0.0001–0.015 \( \mu\)g/ml and 0.001–0.2 \( \mu\)g/ml; urine and fecal homogenate 0.025–10 \( \mu\)g/ml and 0.1–20 \( \mu\)g/ml, respectively.
Oliveira et al. described LC-tandem mass spectrometry method for the determination of EZT in plasma and pharmaceutical formulations. EZT and etoricoxib (internal standard) were extracted from the plasma by liquid-liquid extraction and separated on stationary phase C_{18} column (50 × 3.0 mm I.D.) with acetonitrile: water (85:15, v/v) as mobile phase. Detection was carried out by positive electrospray ionization in multiple reaction monitoring (MRM) mode. The chromatographic separation was obtained within 2.0 min and was linear in the concentration range of 0.25–20 ng/ml for free EZT and of 1–300 ng/ml for total EZT.

Sistla et al. described HPLC method for the determination of EZT in pharmaceutical dosage forms. Isocratic elution of EZT was achieved using stationary phase Kromasil 100 C_{18} column with mobile phase water (pH 6.8, 0.05%, w/v 1-heptane sulfonic acid): acetonitrile (30:70, v/v). The flow rate was 0.5 ml/min and the analyte monitored at 232 nm. The method was linear in the concentration range of 0.5–50 µg/ml for EZT.

Following methods have been reported for the estimation of EZT and ATV in combination

Seshachalam et al. described HPLC method for simultaneous determination of ATV and EZT in pharmaceutical formulations. The mobile phase used was 0.01 M ammonium acetate buffer (pH 3): acetonitrile (50:50, v/v). The detection was carried out at 254 nm. The retention times of EZT and ATV were 15.5 and 19.3 min, respectively. The method was linear in the concentration range of 4–400 µg/ml for ATV and 5–500 µg/ml for EZT. The limit of detection for ATV and EZT were 1.25 µg/ml and 1.48 µg/ml, respectively.

Dhaneshwar et al. described densitometric method for the estimation of ATV and EZT as bulk drug and in tablet dosage forms. Chromatographic separation was performed using silica gel 60 F_{254} as stationary phase, with toluene: methanol 8:2 (v/v) as mobile phase. Densitometric evaluation of the separated zones was performed at 240 nm. The $R_f$ values were 0.23 and 0.39 for ATV and EZT, respectively. The method was linear in the range of 0.4–2.4 µg/zone for both ATV and EZT.
Chaudhari et al \(^6^5\) described stability indicating RP-LC method for simultaneous determination of ATV and EZT from their combination drug products. The method utilized LiChrospher 100 C\(_{18}\) (250 x 4.0 mm id, 5 \(\mu\)m) column as stationary phase at ambient temperature. The mobile phase used was acetonitrile: water: methanol (45: 40: 15, v/v/v) with apparent pH adjusted to 4.0 with a flow rate of 1.0 ml/min and UV detection at 250 nm. The response was linear over the concentration range of 1-80 \(\mu\)g/ml for both the drugs.

Sonawane et al \(^6^6\) described simultaneous spectrophotometric estimation of ATV and EZT in tablets using Q-absorbance equation. The method involved, the absorbance measurement at 235.5 nm (iso-absorptive point) and 246.0 nm (\(\lambda_{\text{max}}\) of ATV), in methanol. The method was linear in the concentration range of 5-25 \(\mu\)g/ml for both the drugs.

Chaudhari et al \(^6^7\) described HPTLC method for the simultaneous estimation of ATV and EZT. The separation was carried out on stationary phase precoated silica gel 60 F\(_{254}\) using mobile phase chloroform: benzene: methanol: acetic acid (6.0:3.0:1.0:0.1, v/v/v/v). The detection was carried out at 250 nm. The calibration curve was found to be linear in the concentration range of 0.8-4.0 \(\mu\)g/spot for ATV and 0.1-1.0 \(\mu\)g/spot for EZT. The limit of detection and the limit of quantification for ATV were found to be 170 ng/spot and 570 ng/spot respectively, and for EZT 20 ng/spot and 70 ng/spot respectively.

Sonawane et al \(^6^8\) described UV-spectrophotometric and RP-HPLC method for the simultaneous determination of ATV and EZT in pharmaceutical dosage form. UV spectrophotometric method was based on formation of simultaneous equation at 232.5 nm and 246.0 nm in methanol. The method was found to be linear in the range of 5 – 25 \(\mu\)g/ml for both the drugs. RP-HPLC method was based on separation of the two drugs using Luna C\(_{18}\) column as stationary phase. Linearity was obtained in the concentration range of 8-22 \(\mu\)g/ml for both the drugs.
Following pharmacopoeial methods have been reported for the estimation of Aspirin (ASP)

BP 2007 \textsuperscript{69}, IP 1996 \textsuperscript{70} reported titrimetric method for the estimation of ASP in bulk drug and in pharmaceutical dosage form. ASP was titrated with excess of 0.5 N sodium hydroxide. Excess sodium hydroxide was back titrated with 0.5 N hydrochloric acid using phenolphthalein as an indicator.

BP 2007 \textsuperscript{71}, IP 1996 \textsuperscript{70} reported titrimetric method for the estimation of ASP and caffeine in tablet dosage forms. The combination product was treated with sodium citrate and boiled under reflux condenser. The liberated salicylic acid was titrated with 0.5 N sodium hydroxide using phenolphthalein as an indicator.

USP 2004 \textsuperscript{72} reported titrimetric method for the estimation of ASP in bulk drug. ASP was titrated with excess of 0.5 N sodium hydroxide. Excess sodium hydroxide was back titrated with 0.5 N sulphuric acid using phenolphthalein as an indicator.

USP 2004 \textsuperscript{72} reported spectrophotometric method for the estimation of ASP in capsule dosage form. The estimation was performed at 280 nm.

USP 2004 \textsuperscript{72} reported LC method for the estimation of ASP in tablet dosage form. The chromatographic separation was performed with stationary phase octa decylsilane column (4 mm X 30 cm) using mobile phase sodium 1-heptane sulfonate: acetonitrile (85:15, v/v, pH 3.5). The flow rate was maintained at 2 ml/min and detection was performed at 280 nm.

Following method has been reported for the estimation of ATV and ASP in combination

Manoj et al \textsuperscript{73} described RP-HPLC method for simultaneous estimation of ATV and ASP from capsule formulation. Chromatographic estimation was carried out on a stationary phase Hypersil C18 column (5 μm) in isocratic mode with mobile phase 50 mM KH2PO4: acetonitrile: methanol (30:50:20, v/v/v). The flow rate was 1 ml/min and effluents were monitored at 254 nm. The retention time of ATV and ASP were
2.48 and 5.23 min respectively. ATV and ASP were linear in the range of 11.2 – 56 μg/ml and 75-375 μg/ml respectively.

**Following pharmacopoeial methods have been reported for the estimation of Nicotinic acid (NIC).**

BP 2007 \(^{74}\) reported titrimetric method for the estimation of NIC in bulk drug. NIC was titrated with 0.1 M sodium hydroxide using phenolphthelain as an indicator.

USP 2004 \(^{75}\) reported estimation of NIC in bulk drug by spectrophotometric method. The absorbance was measured at 262 nm.

USP 2004 \(^{75}\) reported estimation of NIC in tablet dosage form by LC method. The chromatographic separation was performed on stationary phase octa decylsilane column (4 mm X 30 cm) using 0.005 M sodium 1-hexanesulfonate: methanol: acetonitrile: glacial acetic acid (78:14:7:1, v/v/v/v) as mobile phase. Detection was carried out at 262 nm and flow rate was maintained at 1.3 ml/min.

IP 1996 \(^{76}\) reported titrimetric method for the estimation of NIC in bulk drug and in tablet dosage form. NIC was titrated with 0.1 M sodium hydroxide using phenol red as an indicator.

**Following method has been reported for the estimation of ATV and NIC in combined dosage forms**

Nirmal et al \(^{77}\) described formulation of bilayer tablets of ATV and NIC and performed its evaluation using HPLC.

**Following methods have been reported for the estimation of Simvastatin (SMV)**

Ramani et al \(^{78}\) described LC-ESI-MS/MS method for simultaneous quantitation of simvastatin acid, amlodipine and valsartan in human plasma. The instrument API-4000 LC-MS/MS was operated under the multiple reaction-monitoring mode (MRM) using electrospray ionization. Chromatographic separation was performed using mobile phase consisting of 0.02 M ammonium formate (pH 4.5):acetonitrile (20:80,
v/v) at a flow rate of 0.50 ml/min with a C_{18} column as stationary phase. The retention time was 1.81, 1.12, 1.14 min for simvastatin acid, amlodipine and valsartan respectively. The method was linear in the range of 0.5-50 ng/ml for valsartan and 0.2-50 ng/ml for simvastatin acid and amlodipine, respectively.

Ali et al \cite{79} described HPLC method for the simultaneous analysis of SMV and tocotrienols in combined dosage forms. Analytes were monitored by UV detection at 238 and 295 nm for SMV and tocotrienols, respectively, using a gradient methanol/water elution. Calibration curves for tocotrienols and SMV were linear in concentration range of 20-80 µg/ml and 1-10 µg/ml respectively.

BP 2007 \cite{80} reported LC method for the estimation of SMV from bulk drug. The chromatographic separation was carried out on a stationary phase octa decylsilica gel column (3 µm) using gradient elution system with different proportions of solution A [(acetonitrile: 0.1% phosphoric acid (50:50)] and solution B (0.1% phosphoric acid in acetonitrile) as mobile phase. The flow rate was maintained at 3 ml/min and detection was performed at 238 nm.

Barett et al \cite{81} described HPLC-MS/MS method for simultaneous determination of SMV and simvastatin hydroxy acid (SMVA) in human plasma. Detection was performed on an electrospray ionization triple quadrupole mass spectrometer equipped with an ESI interface operated in positive and negative ionization mode. The linearity was observed in the concentration range of 0.10-16.00 ng/ml for SMV and 0.10-16.00 ng/ml for SMVA. The limit of quantitation was 0.03 ng/ml for SMV and 0.02 ng/ml for SMVA.

Suchoka et al \cite{82} described RP-HPLC determination of paraoxonase 3 activity (PON3) in human blood serum with SMV as a substrate. Separation of SMV and SMVA (simvastatin dihydroxy acid) was performed on stationary phase C_{18} column by isocratic elution with acetonitrile: KH_{2}PO_{4} buffer of pH 4.5 (v/v, 70:30) as a mobile phase at flow rate of 1.5 ml/min. Detection was carried out at 239 nm. The method was linear in the range of 0.5-6 µg/ml for SMV. Limits of detection (LOD) and quantitation (LOQ) for SMV were 3.1 and 10.4 ng/ml, respectively.
Corah et al described estimation of SMV by differential pulse and square wave voltammetric techniques in tablets and serum samples. Estimation of SMV was performed in 0.1 M H$_2$SO$_4$ and a constant amount of methanol (20%), in supporting electrolyte with a detection limit of 2.71 x 10$^{-7}$ M and 5.50 x 10$^{-7}$ M for differential pulse and square wave voltammetric methods, respectively.

Alveraz-Lueje et al described stability indicating LC method for the estimation of SMV. The chromatographic estimation was performed on stationary phase C$_{18}$ column using mobile phase acetonitrile: 28 mM phosphate buffer solution, pH 4 (65:35, v/v) at a flow rate of 1 ml/min. The detection and quantification limits for SMV were 9.1 x 10$^{-7}$ and 2.8 x 10$^{-6}$ M, respectively. The degradation of SMV fitted to pseudo-first order kinetics.

USP 2004 reported LC method for the estimation of SMV in bulk drug. Chromatographic estimation was performed on stationary phase octa decylsilane column (4.6 mm X 33 mm) using mobile phase acetonitrile: dilute phosphoric acid (50:50, v/v). Flow rate was maintained at 3 ml/min and detection was performed at 238 nm.

USP 2004 reported LC method for the estimation of SMV in tablet dosage form. Chromatographic estimation was performed on stationary phase octa decylsilane column (4.6 mm X 25 cm) using mobile phase acetonitrile: monobasic sodium phosphate buffer pH 4.5 (65:35, v/v). Flow rate was maintained at 1.5 ml/min and detection was performed at 238 nm.

Kim et al described determination of SMV in human plasma by column switching HPLC with UV detection. SMV was extracted in diethyl ether from plasma. The residue was dissolved in mobile phase I [acetonitrile-20 mM potassium phosphate buffer (45:55, v/v, pH 5.6)] and the solution was injected into a pre-column. The analytes fractionated in pre-column were concentrated on the top of an intermediate C$_{18}$ column. The concentrated SMV was separated to the analytical column with a mobile phase II [acetonitrile-20 mM potassium phosphate buffer (65:35, v/v, pH 5.6)], using a UV detector at the wavelength of 238 nm. SMV was eluted at 28.7 min and calibration curve was linear in the concentration range of 0.5-20 ng/ml of SMV.
Godoy et al. described LC method for determination of SMV in drug substance. The chromatographic estimation was performed with stationary phase Chromolith C_{18} monolithic column (100 x 4.6 mm) using mobile phase acetonitrile: 0.03 M phosphate pH 4.5 buffer (70:30, v/v) at a flow rate of 3 ml/min. The detection was performed at 238 nm and the retention time for SMV was 1.47 min.

Miao et al. described determination of cholesterol lowering statin drugs (atorvastatin, lovastatin, pravastatin and simvastatin) in aqueous samples using LC-electrospray ionization tandem mass spectrometry. The instrumental detection limits of atorvastatin, lovastatin, pravastatin and simvastatin are 0.7, 0.7, 8.2 and 0.9 pg, respectively. A solid-phase extraction method was developed to enrich the analytes from aqueous samples.

Yang et al. described determination of SMV in human plasma by liquid chromatography coupled with electrospray ionization mass spectrometry. The stationary phase used was C_{18} column with a mobile phase consisting of methanol: water (9:1, v/v). Detection was performed on an atmospheric pressure ionization single quadruple mass spectrometer equipped with an ESI interface and operates in positive ionization mode.

Erk et al. described spectrophotometric method for determination of SMV and fluvastatin in human serum and pharmaceutical formulations. SMV and fluvastatin were determined by measurement of their first derivative signals at 241.6, 245.9, 249.1 nm (for SMV) and 259.6 nm (for fluvastatin), respectively. Calibration curves were linear in the ranges of 12.0-28.0 µg/ ml for SMV and 10.0-28.0 µg/ ml for fluvastatin.

Srinivasu et al. described determination of lovastatin and SMV in pharmaceutical dosage form by MEKC. Lovastatin and SMV were separated using an electrolyte system consisting of 12% acetonitrile (v/v) in 25 mM sodium borate buffer pH 9.3 containing 25 mM sodium dodecyl sulphate (SDS) with an extended light path capillary (48.5 cm x 50 µm i.d). A limit of detection was 3.2 µg/ ml and a limit of quantitation was 10.6 µg/ ml for both the drugs.
Grahek et al. described chromatographic purification of pravastatin, simvastatin and lovastatin and mevastatin. The mobile phases consisted of water or mixtures of water-methanol and water-acetonitrile. Six different displacers were used. Chromatographic purification was performed on a column packed with silica-based octadecyl phase.

Wang et al. described second derivative UV spectrophotometric determination of SMV in its tablet dosage form. The estimation was performed at zero crossing point at 243 nm.

Tan et al. described estimation of SMV in human plasma by HPLC. Chromatographic estimation was performed on Lichrospher C18 column as stationary phase using acetonitrile: water (70:30, v/v) as mobile phase. The flow rate was 1.2 ml/min. Simvastatin was quantified by UV at 237 nm. The method was linear in the concentration range of 0.25-50.0 μg/ml of SMV.

Ochiai et al. described determination of SMV (I) and its active metabolite (II) in human plasma by column-switching HPLC with fluorescence detection after derivatization with 1-bromoacetylpyrene. A plasma sample spiked with internal standards was applied to a C8 solid-phase extraction column. A fluorescent derivative was prepared by esterification of II with 1-bromoacetylpyrene in the presence of 18-crown-6 for both fractions. The pyrenacyl ester of II obtained was purified on a phenylboronic acid solid-phase extraction column, and was measured by column-switching HPLC with fluorescence detection. The calibration curves for both I and II were linear in the concentration range of 0.1-10 ng/ml.

Carlucci et al. described simultaneous determination of SMV and its hydroxy acid form in human plasma by HPLC with UV detection. The procedure was linear from 20-1000 ng/ml for SMV and from 25-1000 ng/ml for SMV hydroxy acid, respectively.

Serajuddin et al. described relative lipophilicities, solubilities and structure pharmacological consideration of HMG Co A reductase inhibitors: pravastatin,
lovastatin, mevastatin and simvastatin. The apparent octanol-water partition coefficients (Po/w) and aqueous solubilities for four HMG-CoA reductase inhibitors were compared.

**Following methods have been reported for the estimation of SMV and EZT in combination**

Dhaneshwar et al\(^9\) described densitometric analysis of SMV and EZT as bulk drugs and in tablet dosage form. Chromatographic separation was performed on aluminium backed silica gel 60 F\(_{254}\) plates as stationary phase with toluene: 2-propanol (8:2, v/v) as mobile phase. Estimation was carried out at 240 nm. The drugs were resolved with Rf value 0.48 and 0.53 for SMV and EZT, respectively. The method was linear in the range of 0.4 -2.0 µg per spot for SMV and EZT.

Dixit et al\(^9\) described stability indicating HPTLC method for determination of EZT and SMV. The method uses aluminum backed silica gel 60F\(_{254}\) TLC plates as stationary phase with n-hexane: acetone 6:4 (v/v) as mobile phase. Densitometric analysis of both drugs was carried out in absorbance mode at 234 nm. The Rf values for SMV and EZT were 0.39 and 0.50, respectively. The method was found to be linear in the range of 200–1,600 ng/ band. The limits of detection and quantitation were 25 and 150 ng/ band, respectively.

Chaudhari et al\(^1\) described stability indicating RP-LC method for simultaneous determination of SMV and EZT from their combination drug products. The method utilizes a LiChrospher 100 C\(_{18}\) (250 x 4.0 mm id, 5 µm) column as stationary phase at ambient temperature. The mobile phase used was acetonitrile: water: methanol (60:25:15, v/v/v) with apparent pH adjusted to 4.0. Mobile phase flow rate was maintained at 1.5 ml/min and detection was carried out at 238 nm. The method was linear over the range of 1-80 and 3-80 µg/ ml for SMV and EZT, respectively.

Oliveira et al\(^1\) described simultaneous LC determination of EZT and SMV in pharmaceutical product. The stationary phase used was Synergi fusion C\(_{18}\) column (150 mm x 4.6 mm id). The mobile phase consists of 0.03 M phosphate buffer, pH 4.5: acetonitrile (35: 65, v/v), flow rate was 0.6 ml/min, and detection was made using...
a photodiode array detector at 234 nm. The method was linear in the concentration range of 0.5-200 μg/ml for both the drugs.

Rajput et al. described simultaneous spectroscopic estimation of EZT and SMV in tablet dosage forms using first order derivative zero-crossing method. The dA/dA was measured at 265.2 nm for EZT and 245.4 nm for SMV. The method was found to be linear in the range of 5-40 μg/ml for EZT and 5-80 μg/ml for SMV. The limit of detection was 0.39 and 0.12 μg/ml for EZT and SMV, respectively. The limit of quantification was 1.10 and 0.4 μg/ml for EZT and SMV, respectively.

Following methods have been reported for the estimation of Nebivolol hydrochloride (NEB).

Kachhadia et al. described stability indicating HPLC method for determination of NEB in tablet formulation. Chromatographic separation was achieved with stationary phase Phenomenex Luna C8 column (250 mm x 4.6 mm id, 5 μm) using mobile phase acetonitrile: pH 3.5 phosphate buffer (35:65, v/v) at a flow rate of 1.0 ml/min. Detection was performed at 280 nm using a photodiode array detector. The method was linear in the concentration range of 40-160 μg/ml.

Kamila et al. described UV spectrophotometric method for estimation of NEB in bulk and pharmaceutical formulation. The absorbance was measured at 282 nm. The method was linear in the concentration range of 5-50 μg/ml for NEB.

Patel et al. described RP-HPLC and HPTLC methods for the estimation of NEB in tablet dosage form. Lichrospher-100 C-18 (200×4.6 mm i.d., 5 μm) column was used for the HPLC as stationary phase in isocratic mode with mobile phase consisting of 50 mM KH₂PO₄ buffer (pH 3.0):acetonitrile: (45:55, v/v/v). The flow rate was 1.0 ml/min and effluent was monitored at 282 nm. The retention time was found to be 3.76 min for NEB. Camag system with stationary phase precoated silica gel 60F254 and mobile phase consisting of ethyl acetate: toluene: methanol: ammonium hydroxide (1:6:2:0.1 v/v/v/v) were used for HPTLC method. The detection of spot was carried out at 282 nm. The Rf value was found to be 0.33. The method was linear over the concentration range of 10-150 μg/ml for HPLC and 100-600 ng/spot for HPTLC method.
Ramkrishna et al.\textsuperscript{106} described quantification of NEB in human plasma by liquid chromatography coupled with electrospray ionization tandem mass spectrometry. The analyte was estimated using stationary phase Waters C\textsubscript{18} column by isocratic elution with water: acetonitrile: formic acid (30:70:0.03, v/v/v) as mobile phase and analyzed by mass spectrometry in the multiple reaction monitoring mode. The chromatographic runtime was 2 min and the weighted (1/x\textsuperscript{2}) calibration curves were linear over the range of 50-10,000 pg/ml for NEB. The limit of detection and lower limit of quantification in human plasma were 10 and 50 pg/ml, respectively.

Ali et al.\textsuperscript{107} described enantiomeric separation of metoprolol, tetratolol, tolamolol, nebivolol, etodolac on cellulose tris (3,5-ichlorophenylcarbamate) chiral stationary phase using HPLC. The mobile phase used was 2-propanol at 0.5 ml/min with detection at 220 nm. The separation factor for these drugs were in the range of 1.24-3.90.

Aboul-Enein et al.\textsuperscript{108} described HPLC enantiomeric resolution of NEB on normal and reversed amylose based chiral phases. The columns used were Chiralpak AD and Chiralpak AD-RH. The mobile phases used were pure ethanol and 1-propanol. The flow rates used were 0.5, 1.0 and 1.5 ml/min.

Following pharmacopoeial methods have been reported for the estimation of Hydrochlorothiazide (HCTZ).

USP 2004\textsuperscript{109} reported LC method for the estimation of HCTZ from bulk drug. The chromatographic separation was carried out on a stationary phase octa decylsilane column (3.5 \textmu m) using gradient elution system with different proportions of solution A (acetonitrile: methanol (3:1)] and solution B (0.5% formic acid in water) as mobile phase. The flow rate was maintained at 1 ml/ min and detection was performed at 275 nm.

USP 2004\textsuperscript{109} reported LC method for the estimation of HCTZ in tablet dosage form. The chromatographic separation was performed on a stationary phase octa decylsilane column (4.6 mm X 25 cm) using mobile phase 0.1 M monobasic sodium phosphate:
acetonitrile (9:1, v/v, pH 3). The flow rate was maintained at 2 ml/min and detection was performed at 254 nm.

IP 1996\textsuperscript{110} reported non-aqueous potentiometric method for the estimation of HCTZ in bulk drug. Pyridine was used as solvent and 0.1 M tetrabutyl ammonium hydroxide was used as titrant. End point was determined potentiometrically.

BP 2007\textsuperscript{111}, IP 1996\textsuperscript{110} reported spectrophotometric method for the estimation of HCTZ in tablet dosage form. Estimation was performed at 273 nm using 520 as $A_{1%}$.

BP 2007\textsuperscript{112} reported non-aqueous potentiometric method for the estimation of HCTZ in bulk drug. Dimethyl sulfoxide was used as solvent and 0.1 M tetrabutyl ammonium hydroxide was used as titrant. End point was determined potentiometrically.

Following methods have been reported for the estimation of NEB and HCTZ in combination

Bhat et al\textsuperscript{113} described HPTLC method for simultaneous determination of NEB and HCTZ from tablets. The mobile phase consisted of ethyl acetate: methanol: ammonia (8.5: 1:0.5, v/v/v) and the detection was performed at 280 nm.

Meyyanathan et al\textsuperscript{114} described RP-HPLC method for simultaneous estimation of NEB and HCTZ in tablets. Chromatographic separation was carried out using stationary phase Phenomenex Gemini C\textsubscript{18} (25 cm x 4.6 mm i.d., 5 μ) column with a mobile phase consisting of acetonitrile: 50mM ammonium acetate, pH 3.5 (70:30, v/v) at a flow rate of 1.0 ml/min. Detection was carried out at 254 nm. Probenecid was used as an internal standard. The retention times of probenecid, NEB and HCTZ were 13.05, 3.32 and 4.25 min, respectively. The method was linear in the concentration range of 2 -10 μg/ml for NEB and 2.5 – 12.5 μg/ml of HCTZ.
Review of Literature

Following methods have been reported for the estimation of Rabeprazole sodium (RAB).

Vasu et al 115 described identification of degradation products in stressed tablets of RAB by HPLC-hyphenated techniques. Three unknown impurities of RAB were formed in the formulated drug under the stress conditions, with relative retention times (RRTs) 0.17, 0.22 and 0.28. The Impurity-I (0.17 RRT) was isolated using preparative HPLC and characterized by NMR and MS. The other two impurities, Impurity-II (RRT 0.22) and Impurity-III (RRT 0.28) were characterized by HPLC-hyphenated techniques, LC-NMR and high-resolution LC-MS.

Moneeb et al 116 described chemometric determination of RAB in presence of its acid induced degradation products using spectrophotometry, polarography and anodic voltammetry at a glassy carbon electrode. The UV absorbances were recorded in 0.1 M NaOH within the wavelength range 220-340 nm. The polarograms and anodic voltamograms were recorded in Britton-Robinson buffer (pH 8.0) within the potential range -500 to -1508 and 400 to 1192 mV at 6 mV intervals with a pulse amplitude of -100 and 50 mV, sweep rate of 15 and 10 mV/s and pulse interval of 0.4 and 0.6 s, respectively.

Rahman et al 117 described quantitative analysis of RAB in commercial dosage forms by two spectrophotometric methods. Method 1 is based on the reaction of drug with 3-methyl-2-benzothiazolinone hydrazono hydrochloride (MBTH) in the presence of ammonium cerium (IV) nitrate in acetic acid medium at room temperature to form red-brown product with absorption maxima at 470 nm. Method 2 utilizes the reaction of RAB with 1-chloro-2,4-dinitrobenzene (CDNB) in dimethyl sulfoxide (DMSO) at 45°C to form yellow colored Meisenheimer complex with an absorption maxima at 420 nm. The linearity was obtained in the concentration ranges of 14-140 and 7.5-165 µg/ml for methods 1 and 2, respectively.

Sabnis et al 118 described RP-HPLC method for simultaneous determination of RAB and domeperidone in combined tablet dosage form. Chromatographic estimation was performed on Jasco HPLC system using stationary phase HiQ SiL octadecysilane C18 column (250 x 4.6 mm id) with mobile phase acetonitrile: 0.1 M ammonium acetate (50: 50, v/v) and paracetamol as an internal standard. The detection was performed
using a UV detector at 280 nm. The method was linear in the concentration range of 1.0-10.0 and 0.5-5.0 μg/ml for RAB and domperidone respectively.

Patel et al described HPTLC determination of RAB and domperidone in capsule dosage form. The chromatographic estimation was carried out on stationary phase silica gel 60 F\textsubscript{254} using ethyl acetate: methanol: benzene: acetonitrile (30:20:30:20, v/v/v/v) as mobile phase. Quantitation was carried out with UV detection at 287 nm over a concentration range of 400-1200 ng/spot and 600-1800 ng/spot for RAB and domperidone, respectively.

Raval et al described HPTLC method for determination of ondansetron in combination with omeprazole or RAB in solid dosage form. The separation was carried out by TLC using stationary phase precoated silica gel 60 F\textsubscript{254} and a mixture of dichloromethane: methanol (9:1, v/v) as a mobile phase. Detection of spots was carried out at 309 nm and 294 nm for ondansetron with omeprazole and ondansetron with RAB combinations, respectively. The method was linear in the concentration range of 0.1-0.5 μg/spot for three drugs.

Syed et al described spectrophotometric determination of certain benzimidazole proton pump inhibitors including RAB. The method involved reaction of RAB with iron (III) and subsequent reaction with ferricyanide under neutral condition which yields Prussian blue product with maximum absorption at 720-730 nm. The method was linear in the concentration range of 200-3200 ng/ml for RAB.

Shao et al described liquid chromatographic mass spectrometry analysis and pharmacokinetic studies of a novel rabeprazole formulation, sterile powder for injection, in dogs and rats.

Garcia et al described dissolution test for RAB in coated tablets using RP-HPLC. The optimum dissolution conditions were paddle at 75 rotations per minute (rpm) stirring speed, HCl 0.1 M and borate buffer pH 9.0 as dissolution medium for acidic and basic steps, respectively.
Saudagar et al 124 described first order derivative, simultaneous equation and area under the curve methods for estimation of domperidone and RAB in tablet dosage form. In first order derivative method, estimation was performed by zero crossing method at 302 nm for domperidone and 257 nm for RAB. The simultaneous equation was developed at 284 nm and 252.5 nm in 0.1 M HCl.

Garcia et al 125 described capillary electrophoresis method for analysis of RAB in a pharmaceutical dosage form. The conditions used were a bare fused silica capillary with 48.0 cm length and 75 μm id; a 10mM sodium tetraborate buffer (pH 9); a diode array detector set at 291 nm; hydrodynamic injection (50 mbar/5 s); and a voltage of 20 kV. The method was linear in the concentration range of 5.0-40.0 μg/ ml of RAB. The limits of detection and quantitation were 1.29 and 3.91 μg/ ml, respectively.

Gupta et al 126 described spectrophotometric simultaneous estimation of amoxycillin trihydrate and RAB in combined dosage form using simultaneous equation method. Simultaneous equation was developed at two wavelengths 247 nm and 292 nm.

Mehta et al 127 described RP-HPLC method of estimation of RAB in bulk and it tablet dosage form. Chromatographic estimation was performed using stationary phase ODS C18 column (250 X 4.6 mm) with mobile phase methanol: water (90:10, v/v) at a flow rate of 1 ml/min. Detection was performed at 282 nm using diode array detector and retention time of RAB was 3.49 min. The limit of detection and limit of quantification were 0.6 and 2 μg/ ml, respectively.

Garcia et al 128 described liquid chromatographic method for determination of RAB in coated tablets. The chromatographic estimation was performed on stationary phase Hypersil C8 column (250 x 4.6 mm, 5 μm) using mobile phase acetonitrile: water (35:65, v/v) at a flow rate of 1.0 ml/min, and a diode array detector set at 282 nm. The method showed linearity in the concentration range of 10-70 μg/ ml of RAB. The quantitation limit was 2.43 μg/ ml, and the detection limit was 0.80 μg/ ml.

Radi et al 129 described voltametric method for the determination of RAB in tablet dosage form. The method uses Britton Robinson buffer solution (pH 8.0) as
supporting electrolyte. The method was linear in the concentration range of $1.0 \times 10^{-6}$ to $2.0 \times 10^{-5}$ M of RAB with a limit of detection of $4.0 \times 10^{-7}$ M.

Following methods have been reported for the estimation of Itopride hydrochloride (ITC).

Ptacek et al.\textsuperscript{130} described determination of ITC in human plasma by HPLC with fluorimetric detection. Chromatographic estimation was performed using stationary phase an octadecylsilica column (55 mm x 4 mm, 3 μm particles) with mobile phase acetonitrile: triethylamine: 15 mM KH$_2$PO$_4$ (14.5:0.5:85, v/v/v, pH 4.8). The run time was 3 min. The fluorimetric detector was operated at 250/342 nm (excitation/emission wavelength). Naratriptan was used as the internal standard. The limit of quantitation was 9.5 ng/ml.

Ma et al.\textsuperscript{131} described determination of ITC in human plasma by RP-HPLC with fluorescence detection using levofloxacin as the internal standard (IS). Chromatographic separation was performed within 7.0 min using stationary phase Hypersil ODS C$_{18}$ (250mm X 4.6mm, 5 microm) column and an isocratic mobile phase 0.1mol/l ammonium acetate: methanol (30:70, v/v) flowing at 1.1 ml/min. The excitation and emission wavelengths were 304 and 344 nm, respectively. The method was linear in the concentration range of 5-1000 ng/ml of ITC. The lower limit of quantitation (LLOQ) was 5 ng/ml.

Lee et al.\textsuperscript{132} described determination of ITC in human plasma by liquid chromatography coupled to tandem mass spectrometric detection, using sulpiride as an internal standard (IS). Acquisition was performed in multiple reactions monitoring (MRM) mode, by monitoring the transitions: m/z 359.5>166.1 for ITC and m/z 342.3>111.6 for IS, respectively. Analytes were chromatographed on stationary phase YMC C$_{18}$ column by isocratic elution with 1 mM ammonium acetate buffer: methanol (20: 80, v/v; pH 4.0) as mobile phase. Total run time was 2 min for LC-MS/MS.

Smitha et al.\textsuperscript{133} described extractive spectrophotometric determination of ITC in bulk drug and pharmaceutical formulations. The method involved formation of colored chloroform extractable complex of drug with bromocresol green in acidic medium.
The complex had an absorption maxima at 419.8 nm. The method was linear in the concentration range of 2-10 µg/ml of ITC.

Dighe et al.\textsuperscript{134} described determination of ITC in bulk and its pharmaceutical preparation by HPLC. Chromatographic estimation was performed on a stationary phase Cosmosil C\textsubscript{18} column (150 X 4.6 mm) with a mobile phase 0.05 M potassium dihydrogen orthophosphate buffer: methanol (55:45, v/v) containing 0.1% heptane sulphonic acid at a flow rate of 1 ml/min. Detection was performed at 214 nm. The method was found to be linear in the range of 0.5 -10 µg/ml of ITC.

Kaun et al.\textsuperscript{135} described HPLC and HPTLC method for determination of ITC in the presence of its degradation products. HPLC estimation was carried out on a stationary phase Kromasil column [C\textsubscript{18} (5-µm, 25 cm x 4.6 mm)] using a mobile phase methanol: water (70:30, v/v, pH 4) with UV detection at 258 nm. The flow rate was 1.0 ml/min. HPTLC separation was achieved on stationary phase silica gel 60 F\textsubscript{254} using toluene:methanol:chloroform:10% ammonia (5.0:3.0:6.0:0.1, v/v/v/v) as mobile phase at 270 nm.

Singh et al.\textsuperscript{136} described quantitation of ITC in human serum by RP-HPLC with fluorescence detection (excitation at 291 nm and emission at 342 nm). Chromatographic estimation was obtained within 12.0 min using a stationary phase YMC-Pack ODS column (250 mm x 4.6 mm, 5 µm) and mobile phase consisting of a mixture of 0.05% tri-fluoro acetic acid in water: acetonitrile (75:25, v/v) flowing at a flow rate of 1.0 ml/min. The method was linear in the range of 14.0-1000.0 ng/ml of ITC. The lower limit of quantitation (LLOQ) was 14.0 ng/ml.

Following methods have been reported for the estimation of RAB and ITC in combination

Suganthi et al.\textsuperscript{137} described simultaneous HPTLC determination of RAB and ITC from their combined dosage form. The stationary phase used was precoated silica gel G 60 F\textsubscript{254} plate with solvent system of n-butanol: toluene: ammonia (8.5:0.5:1, v/v/v) and detection was carried out densitometrically at 288 nm. The Rf value for RAB and ITC were 0.23 and 0.75, respectively. Linearity was in the range of 40-200 ng/spot and 300-1500 ng/spot for RAB and ITC. The limit of detection and limit of
quantification were 10 and 20 ng/spot for RAB and 50 and 100 ng/spot for ITC, respectively.

Heralgi et al\textsuperscript{138} described spectrophotometric method for the estimation of RAB and ITC in capsule formulations using simultaneous equation. The equation was developed at 283 nm and 258 nm in phosphate buffer (pH 7.4).

Gandhi et al\textsuperscript{139} described RP-HPLC method for simultaneous determination of RAB and ITC in capsule dosage form. Determination was performed on Jasco HPLC system using stationary phase HIQ SIL C\textsubscript{18} column with mobile phase methanol: 0.385% ammonium acetate (75:25, v/v) and diclofenac sodium as internal standard. The detection was performed at 280 nm. The method was linear in the range of 1-5 \( \mu \text{g/ml} \) for RAB and 7.5-37.5 \( \mu \text{g/ml} \) for ITC respectively.

Sabnis et al\textsuperscript{140} described spectrophotometric simultaneous determination of RAB and ITC in capsule dosage form by ratio spectra derivative spectrophotometry. The estimation of RAB was carried out at 231 nm (minima) and ITC was carried out at 260 nm.

Pattanayak et al\textsuperscript{141} described simultaneous spectrophotometric estimation of RAB and ITC by Q-absorbance method and simultaneous equation method. Simultaneous equation was developed at 284 nm (A\text{max} of RAB) and at 258 nm (A\text{max} of ITC) in methanol. The absorption ratio (Q-value) was determined at 266.6 nm (Iso-bestic point) and 284 nm (A\text{max} of Rabeprazole Sodium).