2.1 LITERATURE REVIEW

There are many methods available for the analysis of drug acting as antihypertensive agent. Those include both classical and instrumental methods. But more popular methods are:

- High Performance Liquid Chromatography
- UV-Visible Spectroscopy
- Thin layer Chromatography

Many methods have been developed & Validated for Active drug & estimation of Active drug in their formulation form, using HPLC, UPLC, UV etc.

- **Patil P.R, et al. (2009)** developed spectrophotometric method for simultaneous estimation of Ramipril and Amlodipine. For this, simultaneous equation method is used. The method involved measurement of absorbance at two wavelengths, 210 nm and 238 nm, \( \lambda_{\text{max}} \) of Ramipril and Amlodipine respectively for concentration range of 15- 35 µg/ mL and 5- 25 µg/ mL for Ramipril and Amlodipine respectively.

- **Mehulkumar P, et al. (2009)** Developed method for Simultaneous Spectroscopic Estimation of Amlodipine Besylate and Olmesartan Medoximil by derivative spectroscopic method in Tablet Dosage Form where ZCP: 239 nm of AMLO and 255 nm of OLME, Solvent: Methanol: water (1:4), Range: 2.5- 30 µg/ml of AMLO and 4- 32 µg/ml of OLME was taken as a method parameter.


- **Kamble N, et al. (2004)** developed method for determination and validation of second derivative UV-spectrophotometric method for simultaneous determination of lisinopril and amlodipine from tablet dosage form using ZCP: 256 nm of AMLO and 216 nm of LIS, Methanol is used as solvent over range of 5- 30 µg/ml of AMLO and 10-60 µg/ml of LIS.

- **Singhvi I, et al. (1998)** developed Visible spectrophotometric methods for estimation of amlodipine besylate form tablets using extractive colorimetry method which involve formation complex with Bromocresol green (BCG),
Bromophenyl blue (BPB) and Methylene blue (MB), $\lambda_{\text{max}}$: 409 nm for BCG and BPB, 668.2 nm for MB Solvent: chloroform over a range of 10-80 $\mu$g/ml.

- **Ravi S Sankar, et al. (1997)** developed RP-HPLC methods for simultaneous estimation of Amlodipine besilate and atenolol in tablet by using Phosphate buffer (pH 5.5): Acetonitrile (50:50) as a mobile phase and column used spherisorbC$_8$, 250 x 3.9 mm id over a Range of 1-5 $\mu$g/ml for Amlodipine, 10-50 $\mu$g/ml for Atenolol. Detection was done at 225 nm.

- **Fernandesa N, et al. (2008)** developed UV spectroscopic methods for the simultaneous estimation of atenolol and indapamide in their combined dosage form. First method employs formation and solving of simultaneous equation using 246.4 nm and 266 nm as two wavelengths for formation of simultaneous equations. Second method was dual wavelength method, in which two wavelengths were selected for each drug in a way so that the difference in absorbance is zero for another drug. Atenolol has equal absorbance at 246.4 nm and 254.2 nm, where the differences in absorbance were measured for the determination of indapamide; similarly differences in absorbance at 266 nm and 270.2 nm were measured for the determination of atenolol. These methods obey Beer’s law in the concentration range 100 to 350 and 5 to 17.5 $\mu$g/mL for atenolol and indapamide, respectively.

- **Legorburu MJ, et al. (1999)** developed HPLC method with amperometric detection for the determination of the diuretic indapamide using a $\mu$Bondapak C$_{18}$ column is developed. The mobile phase consists of an acetonitrile–water mixture (45:55, 5mM) in KH$_2$PO$_4$–K$_2$HPO$_4$ (pH 4.0). The compound is monitored at +1200 mV with an amperometric detector equipped with a glassy carbon working electrode. Percentages of recovery are 88.3 ± 5.6 and 82.9 ± 7.8 for liquid–liquid and solid–liquid extraction, respectively over the concentration range from 25 to 315 ng/mL with a reproducibility in terms of relative standard deviation of 4% for a concentration level of 0.5 $\mu$g/mL and a quantitation limit of 1 ng/mL.

- **Harlikar J N, et al. (2003)** developed HPLC method for simultaneous determination of Indapamide, Perindopril, Ramipril and Trandolapril from bulk drug and pharmaceutical formulation using a mobile phase consisting of 0.05M ammonium acetate (pH 2.5) and acetonitrile in volume ratio of 70:30 at a flow rate of 1.0 ml/ minute. A supelco C-18, (3, 33 x 4.6 mm) column was
used as stationary phase. Quantitation was performed using UV detector at 215 nm.

- **Stefan RI, et al. (2002)** two types of flow systems were selected for the simultaneous assay of \(S\)- and \(R\)-perindopril (pdp): flow injection analysis (FIA) and sequential injection analysis (SIA). The SIA system was more efficient, because of the highest precision and accuracy, and the lower consumption of sample and buffer. The amperometric biosensors used as detectors in the flow systems were based on \(L\)- and \(D\)-amino acid oxidase (AAOD). The linear concentration ranges are in the nmol l\(^{-1}\) range, from 120 pmol l\(^{-1}\) to 40 nmol l\(^{-1}\) (3 × S.D.), with very low detection limits.

- **Kondo T, et al. (2007)** has developed method for characterization of conjugated metabolites of a new angiotensin II receptor antagonist, candesartan cilexetil, in rats by liquid chromatography/electrospray tandem mass spectrometry following chemical derivatization. In this method column C18 used for separation. The chromatographic parameters as mobile phase combination reported as Acetonitrile and water (0.05% triethylamine and 0.05% acetic acid), also calibration curve range reported as 5–500 ng/ ml.

- **Himabindu V, et al. (2007)** has developed Stability-Indicating LC Method for Candesartan Cilexetil by using CN column (250 mm \(\times\) 4.6 mm), 5 \(\mu\)m, mobile phase Phosphate buffer ( pH 3.0): Acetonitrile (50:50) with detection wavelength 210 nm.

- **Xiaoshan Z, et al. (2002)** determined the content of candesartan cilexetil by using HPLC. The ODS column was used and mobile phase content Acetonitrile: Phosphate buffer (pH- 3.2) (80:20). The detection wavelength was 252 nm. The calibration curve range reported as 0.5 ~ 2.5 \(\mu\)g.

- **Luo J, et al. (2004)** determined candesartan cilexetil and its related substances by using HPLC. The mobile phase was prepared as KH2PO4 mixing with triethylamine (pH -5.8) : Acetonitrile (48:52) and C18 column used with flow rate 1.0 ml/min. The wavelength was selected as 210 nm.

- **Chitlange SS, et al. (2008)** developed Reverse Phase High Performance Liquid Chromatographic (RP-HPLC) method for simultaneous estimation of Amlodipine besylate (AMLB) and Valsartan (VAT) on RP C-18 Column (Kromasil, 250 x 4.6 mm) using acetonitrile: phosphate buffer (0.02M, pH 3.0), (56:44 v/v) as mobile phase at a flow rate of 1.0 ml/min and the detection
wavelength was 234 nm. The retention time for AMLB and VAT was found to be 3.07 and 6.20 min, respectively.

- **Shah NJ, et al. (2009)** developed HPTLC method for the simultaneous estimation of valsartan and hydrochlorothiazide in combined dosage forms. The stationary phase used was precoated silica gel 60F 254. The mobile phase used was a mixture of chloroform: methanol: toluene: glacial acetic acid (6:2:1:0.1 v/v/v/v). The detection of spots was carried out at 260 nm. The method was validated in terms of linearity, accuracy, precision and specificity. The calibration curve was found to be linear between 300 to 800 ng/spot for valsartan and 100 to 600 ng/spot for hydrochlorothiazide. The limit of detection and the limit of quantification for the valsartan were found to be 100 and 300 ng/spot respectively and for hydrochlorothiazide 30 and 100 ng/spot respectively.

- **Tarte PS, et al. (2008)** developed a simple, accurate, precise and economical procedure for simultaneous estimation of Nebivolol hydrochloride and Hydrochlorothiazide in two component tablet dosage. The method is based upon determination of Nebivolol at 281 nm and Hydrochlorothiazide at 272 nm, in aqueous methanol (20% v/v). Nebivolol hydrochloride and Hydrochlorothiazide at their respective $\lambda_{\text{max}}$ 281.0 nm and 272.0 nm shows linearity in the concentration range of 5-35 $\mu$g/ml and 10-70 $\mu$g/ml respectively.

- **Dash P, Das SN, et al. (2009)** a simple UV spectrophotometric method was developed for the determination of Hydrochlorothiazide and ramipril in pure and its pharmaceutical formulations. Hydrochlorothiazide (HYD) exhibits $\lambda_{\text{max}}$ at 212nm and Ramipril (RAM) at 226nm in methanol respectively and obeyed linearity in the concentration range of 1.25-40 mg/ml and 0.5-16 mg/ml. Drugs obey linearity within the concentration range of 1.25-40$\mu$g/ml and 0.5-16$\mu$g/ml for HYD and RAM respectively. The percentage recovery values of pure drug from the analyzed formulation were in between 98.156-100.011% and 98.958-100.015% for HYD and RAM respectively.

- **Patil UP, et al. (2009)** Three accurate, precise, sensitive and economical procedures for simultaneous estimation of Atorvastatin Calcium and Telmisartan in tablet dosage form have been developed. The methods employed were absorbance correction method (I), first order derivative
spectroscopic method (II) and duel wavelength method (III). The first method employs wavelength 328 nm for direct estimation of Telmisartan where Atorvastatin Calcium shows nil absorbance. Estimation of Atorvastatin Calcium is carried out after correction for absorbance of Telmisartan at 241 nm. The second method is based on first order derivative spectroscopy. Wavelengths 297 nm and 241.8 nm were selected for the estimation of the Atorvastatin Calcium and Telmisartan, respectively. In the third method, Atorvastatin Calcium was determined by plotting the difference in absorbance at 258 and 291 nm (difference is zero for Telmisartan) against the concentration of Atorvastatin Calcium. Similarly for the determination of Telmisartan, the difference in absorbance at 225 and 252 nm (difference is zero for atorvastatin calcium) was plotted against the concentration of Telmisartan. Both the drugs obey Beer’s law in the concentration range 5-30 µg/ml. The results of analysis have been validated statistically and by recovery studies.

- **Barot TG, et al. (2009)** A simple and accurate methods to determine Indapamide, in pure powder form, were developed and validated using liquid chromatography (LC). The LC separation was achieved on a Inertsil ODS 3V, 5µm, 150 x 4.6 mm, 5µ in the isocratic mode using Mixture of 7 volume of acetoinitrile, 20 volume of Tetrahydrofuran and 73 volumes of a 1.5g/l solution of Triethylamine adjusted pH 2.8 with ortho-phosphoric acid at a flow rate of 1.4 ml/min. the methods were performed at 305 nm; In LC method, quantification was achieved with PDA detection over the concentration range of 80 to 120 µg/ml.

- **Ivanovic D, et al. (2007)** developed chromatographic method for simultaneous determination of hydrochlorothiazide (HCTZ), lisinopril (L), and their impurities in pharma-ceuticals. Chlorothiazide (CTZ) and disulfonamide (DSA), as potential impurities in hydrochlorothiazide, and diketopiperazine (DKP), as an impurity of lisinopril, were analyzed. The optimum separations were achieved by gradient elution on a 4.6 mm x 20 mm, 3.5 µm particle size, C18 column. The mobile phase was a gradient prepared by mixing 7:93 (v/v) acetonitrile 25 mM potassium dihydrogen phosphate, pH 5, and 50:50 (v/v) acetonitrile 25 mM potassium dihydrogen phosphate pH 5 in different ratios.
The flow rate was 1.0 mL min\(^{-1}\). UV detection was performed at 215 nm. Methylparaben was used as internal standard.

- **Chaudhari BG, *et al.* (2007)** Developed and validate a stability indicating reverse-phase HPLC method for the simultaneous estimation of atorvastatin (ATV), and amlodipine (AML) from their combination drug product. The proposed RP-HPLC method utilizes a Lichrospher® 100 C\(_{18}\), 5mm, 250mm x 4.0mm i.d. column, at ambient temperature, optimum mobile phase consisted of acetonitrile and 50mM potassium dihydrogen phosphate buffer (60 : 40, v/v), apparent pH adjusted to 3±0.1 with 10% phosphoric acid solution, effluent flow rate monitored at 1.0 ml/min, and UV detection at 254 nm. ATV, AML, and their combination drug product were exposed to thermal, photolytic, hydrolytic, and oxidative stress conditions, and the stressed samples were analyzed by proposed method. The described method was linear over the range of 1-90m g/ml and 1-80m g/ml for ATV and AML, respectively. The mean recoveries were 99.76 and 98.12% for ATV and AML, respectively. The limit of detection for ATV and AML were found to be 0.4 and 0.6m g/ml, respectively and the limit of quantification was 1.0m g/ml for both drugs. The average percentage drug release was found to be more than 70% within 30 min for both drugs.