REVIEW OF LITERATURE:

Literature survey reveals that different pharmaceutical drugs are adopted for development and analytical method validation of pharmaceutical products.

Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results;

There are various medicinal Drugs which are used singly or in combination with other drugs in Formulations, the assay of these Drugs are given in different pharmacopeia, This method includes HPLC is one of them this HPLC method is more accurate and can be used for samples in Micro liters as follows.

For the research work number of research paper were studied which was based on the subject. There review is as follows-

Akteruzzaman, et. al., 2012, was done Development and Validation of RP-HPLC Method for Simultaneous Estimation of Metformin Hydrochloride and Rosiglitazone in Pharmaceutical Dosage Forms. Chromatographic separation was carried out on Luna C18 (4.6x250mm, 5 ) using the mobile phase comprising sodium dihydrogen phosphate buffer (pH 3.5) and acetonitrile in the ratio of 60:40 (v/v) at a flow rate of 0.7 ml/min. The injection volume was 20 l at 230 nm and at ambient temperature. Linearity for Metformin Hydrochloride and Rosiglitazone was in the range of 12-25 g/mL with correlation coefficient values 0.999 for both samples. The % recovery was obtained as 96.40%, 95.84 and 97.93% for MET and 99.84%, 100.47 and 102.75% for ROSI. All experimental results were within the range of the acceptability for precision and accuracy, which indicated that the developed method was sensitive enough and accurate for qualitative, quantitative and simultaneous analysis of MET and ROSI.

Abdussaleem., et.al., 2010, was done Analytical Method Development and Validation of Losartan Potassium and Atenolol in Combined Dosage Form by RP-HPLC method. The chromatographic separation was carried on C18 column (Phenomenex C18, 5 , 250mm x 4.6mm). Mobile phase using Triethylamine: Acetonitrile: Methanol in the ratio of 50:30:20(pH adjusted to 4.0 with phosphoric acid) as a mobile phase at a flow rate of 1.2ml/min and detection at 235nm. Recoveries from combined dosage form were
between 98 and 102%. The method was successfully validated in accordance to ICH guidelines acceptance criteria for linearity, accuracy, precision, specificity, robustness.

**Blessen, et. al., 2011**, was done Development and Validation of Atenolol and Amlodipine Besylate by using RP-HPLC method. The chromatographic Separation was carried on ODS C18, 5 um, 250 mm x 4.6 mm column with mobile phase, Buffer: Acetonitrile: Methanol (4:3.5:2.5 v/v/v), flow rate was 1.0 ml/min, inject10 μl volume and run 10 min on wavelength 225 nm..Buffer was prepared with Triethylamine and adjusted pH to 3.0 with Ortho-Phosphoric Acid. The recoveries obtained for Atenolol was 100.1% and for AB was 100.4% respectively. Linearity response was established over the concentration range of 50-150 g/ml for AT and 5-15 g/ml for AB. The results of proposed method were validated as per ICH guidelines. This method can be used for the routine quality control of both drugs in combination in tablet dosage form.

**Bhusari, et.al., 2012**, was done Validated HPLC Method for Simultaneous Quantization of Amlodipine Besylate, Atenolol and Aspirin in Bulk Drug. The separation was carried on Thermo Hypersil BDS–C18 (250 mm × 4.6 mm, 5.0 μ) mobile phase containing methanol: 10 mM phosphate buffer with pH 7.0 adjusted with ortho phosphoric acid (70: 30) at flow rate of 1 mL/min using UV detection at 235 nm. Linearity, accuracy and precision were found to be acceptable over the concentration ranges of 2-12 g/ml for Amlodipine Besylate, Atenolol and 4-24 g/mL for Aspirin, respectively. The method was validated for precision, robustness and recovery. The limit of detection (LOD) and limit of quantization (LOQ) was 0.5 g/mL and 1 g/mL for Amlodipine Besylate and Atenolol and 1 g/mL and 2 g/mL for Aspirin, respectively. Statistical analysis.

**Chandra, et. al., 2011**, Validated RP-HPLC Method for Ramipril and Metoprolol Tartarate in Bulk and Tablet Dosage Form. The chromatographic separation was carried on Hypersil C18, 150 mm x 4.6 mm, 5 m with mobile phase acetonitrile: methanol:10mM Acetate buffer (30: 50: 20 v/v) and pH adjusted to 5 ± 0.1 with triethanolamine was used. The flow rate was 1.0 mL/min and absorbance at 210 nm. Linearity for Metoprolol Tartarate and Ramipril was in the range of 5-25 and 0.5-2.5 g/mL with correlation coefficient values 0.9998 for both, the percentage recovery obtained was 101.82 and 100.22 %, respectively The method can be used for estimation of combination of these drugs in combined dosage form.
Chheta, et. al., 2009, was done Development And Validation Of A Stability indicating HPLC Method For Atenolol And Hydrochlorothiazide In bulk drug and tablet formulation. The separation was carried on a Hypersil-BDS C18 column (250X4.6mm i.d., 5 mm). The mobile phase was 25mM phosphate buffer (PH 3±0.05): acetonitrile (85:15, v/v) at 0.7 mL/min and the UV detector at 227 nm. Linearity, accuracy and precision were found to be acceptable over the concentration ranges of 4-48 g/ml and 1-12 g/ml for ATN and HCZ, respectively. The optimized methods proved to be specific, robust and accurate for the quality control of ATN and HCZ in bulk drug and pharmaceutical formulations.

Dwivedi, et. al., 2011, was done Development and validation of a RP-HPLC Method for Atenolol (AT) and Nitrendipine (NT) in tablet Dosage Form. The separation was carried on Phenomenox C18 (4.6x250mm, 5 μ) with mobile phase mixture of methanol: acetonitrile: water (40:40:20 v/v) (pH adjusted to pH 3.0 using orthophosphoric acid) was used. Flow rate of 1.5 ml/min and the wavelength at 235 nm. The method was validated in terms of linearity, accuracy, precision, and specificity, limit of detection and limit of quantization. Linearity for AT and NT were found in the range of 30-70 g/ml and 6-14 g/ml, respectively. The percentage recoveries for AT and NT ranged from 99.05-100.51% and 99.14-101.60%, respectively. The method was found to be robust and can be successfully used to determine the drug content of marketed formulations.

Gupta, et. al., 2011, was done Validated Reverse Phase HPLC Method for Simultaneous Estimation of Atorvastatin and Atenolol in Tablets. The separation was carried on ODS, C18 (250 x 4.6 mm i.d., 5 μ) column with a mixture of Acetonitrile, and Phosphate buffer (pH 4.5±0.05 adjusted with ortho phosphoric acid) in the ratio 72:28 (v/v) as mobile phase at a flow rate of 1.0 mL min-1 at 238 nm. The linear over the concentration ranges of 4–20 g mL-1 and 20–100 g mL-1 respectively. Validation studies revealed the method is specific, rapid, reliable and reproducible. Stability or stress studies was carried out for the high recovery and low relative standard deviation confirm the suitability of the method for determination of Atorvastatin and Atenolol in tablets.

Havaldar, et. al., 2010, was done Simultaneous Estimation of Metformin Hydrochloride, Rosiglitazone and Pioglitazone Hydrochloride in the Tablets Dosage Form. The separation was carried on Zorbax C8 column of 150×4.6 x 5 μm particle size and
ammonium dihydrogen phosphate buffer adjusted to pH 3.0 using diluted ortho phosphoric acid and acetonitrile (65:35 v/v) as eluent at a constant flow rate of 0.7 ml per min. UV detection was performed at 215 nm. This method is simple, rapid and selective and can be used for routine analysis of antidiabetic drugs in pharmaceutical preparation.

**Jain, et.al., 2011,** was done Development and Validation of a RP-HPLC method for the simultaneous estimation of Atenolol and Lercanidipine hydrochloride in Pharmaceutical dosage forms. Chromatographic separation was carried on Luna C18 column (5 μm, 150mm x 4.60mm) and ACN/phosphate buffer (60:40, v/v, pH 3.6) as mobile phase, at a flow rate of 0.5ml/min. Detection was carried out at 235 nm. Linearity for ATL and LER were in the range of 50-250 mg/ml and 10- 50 mg/ml respectively. Parameters such as linearity, precision, accuracy, recovery, specificity and ruggedness are studied as reported in the ICH guidelines. Developed method was found to be accurate, precise, selective and rapid for simultaneous estimation of ATL and LER in tablets.

**Khan, et. al., 2012,** was done Determination and Method development for assay of Losartan potassium and Hydrochlorothiazide drugs in solid dosage form by reverse phase C18 column (Zorbax CN (250mm x 4.6mm) 5 μ). The mobile phase using Triethylamine: Acetonitrile: Methanol in the ratio of 33:27:40(pH adjusted to 7.0 with phosphric acid) at a flow rate of 1.0ml/min and detection at 270nm. Validation revealed the method is specific, rapid, accurate, precise, reliable, and reproducible. Linearity of LOS and HCTZ were found in the range of 70%-130% concentration ranges for both the drugs. and recoveries were between 98 and 102%. The method can be used for estimation of combination of these drugs in combined dosage form.

**Madhukar, et. al., 2011,** was done an Analytical Method Development and Validation of Metformin Hydrochloride By RP-HPLC. The separation was carried out on C18, 5 μ, 250mm x 4.6mm column. A mobile phase comprising 10m.mol 1-Octane Sulfonic acid: Acetonitrile in the volume ratio of (80:20) was developed. The detection was carried out using a PDA detector set at a wavelength of 232nm. The method was linear over the concentration range of 1-250 g/ml and get the correlation (r2) 0.9995, showed good recoveries (100.25 - 101.13%), the assay were 99.4% and 99.94% respectively. The method can be used for quality control assay of Metformin Hydrochloride.
Medaharitha, et. al., 2012, was done Method Development and Validation for the Simultaneous estimation of Atenolol (AT) and Hydrochlorothiazide (HZ) in tablet dosage form by RP-HPLC method. The separation was carried ODS C18 column (4.6x 150 x5 m) using water and methanol (50:50v/v) as mobile phase and pumped at rate of 0.8ml/min and using UV-Visible detector at 230nm. The linearity was found in the range of 50-150 μg/ml and shows a correlation coefficient of 0.999. This study concluded that the proposed method was found to be accurate, reproducible, and consistent and could be effectively used for the routine analysis of these drugs in marketed formulations.

Pavan, et. al., 2012, was done Development and Validation of RP-HPLC Method for Benfotiamine and Metformin hydrochloride in Tablet Dosage Form. The separation was carried on Luna C18 (4.6x250mm, 5 ) with mobile phase acetonitrile: methanol: water: 0.1% OPA (40:20:35:5 %v/v). The flow rate was 1.0 ml/min with detection at 249 nm. The linearity was found to be in the range of 5–35 μg/ml for Benfotiamine and for Metformin Hydrochloride 50–200 μg/ml. The proposed method is accurate with 99.1% - 100.17% recovery for Benfotiamine and 99.31% -100.44% for Metformin Hydrochloride. The method can be used for the estimation of dosage form in routine analysis.

Pansare, et. al., 2013, was done Assay method development and validation for simultaneous estimation of Amiloride Hydrochloride (AML) and Furosemide (FUR) tablet by RP-HPLC method. The separation was carried on Kromasil C18 (250×4.6mm, 5 ) column. The mobile phase consisted of 0.005M. Hexane-1-Sulfonic acid sodium salt in water and methanol (50:50v/v) pH 4.0 by 1M acetic acid as eluent, at a flow rate of 1ml/min. Detection was carried out at wavelength 361nm. Linearity was established by over the concentration range of 2.5 to 7.5 μg/ml for AML with correlation coefficients (r2) 0.9997 and 20 to 60 μg/ml for FUR with correlation coefficients (r2) 0.9992. The percentage recovery obtained for AML and FUR were 99.42% and 99.67% respectively. The method has been validated as per ICH guideline and successfully applied to estimation of AML and FUR in tablet dosage form.

Pankaj, et.al., 2011, was done Development and Validation of a RP-HPLC Method For Simultaneous Determination of Atenolol and Aspirin in Fixed dose combinations. The separation was carried on Luna, C18 (250 x 4.6 mm i.d., 5 ) column and phosphate buffer (pH adjusted to 4.5 with ortho phosphoric acid): Methanol (85:15 v/v) as eluent, at
a flow rate of 0.8 ml/min. UV detection was performed at 239.5 nm. Linearity, accuracy, and precision were acceptable in the ranges (20-100 g/ml) for Aspirin and (10-50 g/ml) for Atenolol. The % recovery for Atenolol and Aspirin is 99.17 and 99.75 respectively. The result of the studies showed that the proposed RP-HPLC method is simple, rapid, precise and accurate, which can be used for the routine determination of Atenolol and Aspirin in bulk and in its pharmaceutical dosage forms.

**Rao, et al., 2011,** was done Development and Validation of RP-HPLC method for the Determination of Hydrochlorothiazide and Eprosartan in Bulk and Pharmaceutical Dosage Form. The separation was carried on Eclipse XBD-C18 (5 m, 150mm × 4.6mm I.D.) column. The mobile phase was a mixture of buffer (20mM KH2PO4) and methanol in the ratio of 80:20 v/v. The flow rate was set at 1.0 ml/min and UV detection at 225nm. Validation parameters such as linearity, accuracy, precision, and robustness, limit of detection (LOD) and limit of quantification (LOQ) were evaluated as per ICH guidelines. The proposed method was successfully applied for the quantification of bulk and active pharmaceutical present in tablet dosage form.

**Safeer, et al., 2010,** was done Analytical Method Development and Validation of Amlodipine and Hydrochlorothiazide in Combined Dosage Form by RP-HPLC. The separation was carried on C18, 5, 250mm x 4.6mm. Using Mobile phase Triethylamine: Acetonitrile: Methanol in the ratio of 50:25:25(pH adjusted to 3.0 with Orthophosphoric acid) at a flow rate of 2.0ml/min and detection at 235nm. Recoveries were between 98 and 102%. The method can be used for estimation of combination of these drugs in combined dosage form.

**Syed, et al., 2011,** was done A validated RP-HPLC method for the determination of Propranolol and Valsartan in bulk drug and gel formulation. The separation was carried on Hypersil ODS C-18 column (250 x 4.6 mm, I’d., 5 m particle size) with isocratic flow with UV detector. The mobile phase at a flow rate of 1.0 mL/min consisted of acetonitrile, methanol, and 0.01 M disodium hydrogen phosphate (pH 3.5) in the ratio of 50:35:15 v/v. Results: A linear response was observed over the concentration range 5-50 μg/mL of Propranolol and the concentration range 4-32 μg/mL of valsartan. Limit of detection and limit of quantization for Propranolol were 0.27 μg/mL and 0.85 μg/mL, and for valsartan were 0.45 μg/mL and 1.39 μg/mL, respectively. The method was
successfully validated in accordance to ICH guidelines acceptance criteria for linearity, accuracy, precision, specificity, robustness.

Tulja Rani, et.al., 2011, was done Development of an RP-HPLC Method for the Simultaneous Estimation of Propranolol Hydrochloride and Diazepam in Combined Dosage form. The Chromatographic separation was carried out on Waters C18 (250 ×4.6 mm 1’d, 5 µ) column using acetonitrile: 0.4 % potassium dihydrogen ortho phosphate (adjusted to pH 3.52 with ortho phosphoric acid) in the ratio of 60:40 v/v as eluent. The flow rate was 1 ml/min and effluent was detected at 229 nm. The linearity range was 2-24 μg/ml and 0.25- 3.0 μg/ml for Propranolol hydrochloride and diazepam, respectively. Percentage recoveries for Propranolol hydrochloride and diazepam were 100.03 and 99.72 %, respectively. All the analytical validation parameters were determined and found in the limit as per ICH guidelines, The developed method is also found to be precise and robust for the simultaneous determination of Propranolol hydrochloride and diazepam in tablet dosage forms.

The efficient development and validation of analytical methods are critical elements in the development of pharmaceuticals. Success in these areas can be attributed to several important factors, which in turn will contribute to regulatory compliance. Experience is one of these factors both the experience level of the individual scientists and the collective experience level of the development and validation department.