Literature Review

Zoesta A.R. et. al. \(^{(1)}\), has developed an assay for the quantitation of dipyridamole in human plasma using a reversed-phase C18 microbore HPLC column. Chromatography was carried on a 5 µm ODS Hypersil C18 microbore column (2 mm I. D. × 10 cm) using an acetonitrile-water (48:52, v/v) mobile phase containing 20 mM \( \text{Na}_2\text{HPO}_4 \) and 50 mM sodium dodecyl sulfate adjusted to pH 2. The eluant was monitored at 305 nm.

Janet H Bridle et. al. \(^{(2)}\), has developed an HPLC method for the assay and chromatographic purity assessment of dipyridamole raw material and capsule product. A mobile phase composing of methanol: aq 200 mM pentane sulphonic acid, sodium salt, [70:30 v/v], triethylamine added [2ml/L] and was then adjusted to pH 3.0 with phosphoric acid. The mobile phase was pumped through an octadecylsilated-silica column, being held at 60° C, at a flow rate of 1.5ml/min. Detection was made at 288nm.

Zhang J et. al. \(^{(3)}\), has performed development and subsequent validation of an isocratic high-performance liquid chromatographic (HPLC) procedure employing ultraviolet (UV) detection for the determination of degradation products in Dipyridamole Injection. The development of this assay involved the evaluation of several factors including buffer type, ionic strength, pH, organic composition, and column type.

Prakash K. et. al. \(^{(4)}\), has developed the combination method for the simultaneous determination of Aspirin and Dipyridamole in pharmaceutical formulations. Separation of both Aspirin and Dipyridamole was achieved within 5 min with required resolution, accuracy and precision thus enabling the utility of the method for routine analysis. Chromatographic separation was achieved on a waters symmetry C18 3.5 µm, 50 x 4.6 mm using a mobile phase consisting of 0.1% ortho phosphoric acid and acetonitrile in the ratio of 75:25 at a flow rate of 1.0 ml per minute. The detection was made at 227 nm. The method was found linear over the range of 4 to 80 µg/ml for Dipyridamole and 0.5 to 10 µg/ml for Aspirin.

Rajput A.P. et. al. \(^{(5)}\), has developed a novel stability indicating Ultra high performance liquid chromatography (UPLC) method for the simultaneous estimation of Aspirin and Dipyridamole in the capsule dosage form. Chromatographic separations were carried using Hypersil Gold C
Columns (1.9 μm, 100 mm X 2.1 mm) with a mobile phase composition of triethylam
e phosphate buffer (pH 2.5) and methanol in the ratio 50:50% (V/V) have been deliver
ed at a flow rate of 0.5 mL/min and the detection was carried out using 230 nm.

**Hassan H. Hammud et. al.**\(^{(6)}\), has developed Spectrofluorimetric and HPLC methods for the
Aspirin in mixture with Dipyridamole and in presence of its degradation product (Salicylic acid).
The spectrofluorimetric method was based on the use of the first and second derivatives of the
ratio of the emission spectra with a zero-crossing technique. The proposed RP-HPLC method
utilized an Adsorbosil C\(_8\), 10 μm, 250mmx4.6mm i.d. column, at ambient temperature, optimum
mobile phase consisted of water-acetonitrile-ortho-phosphoric acid (65:35:2 v/v/v), with flow
rate monitored at 1.5 ml/min, and UV detection at 250 nm. The total chromatographic time per
sample was about 6 min with dipyridamole, aspirin and salicylic acid eluting at retention times
2.2, 3.8 and 4.6 min, respectively. Evaluation of linearity, accuracy, precision, selectivity and
sensitivity of the methods produced satisfactory results.

**Davood Beigi et. al.**\(^{(7)}\), has reported a simple, rapid and specific high-performance liquid
chromatographic procedure for quantitative determination of dipyridamole in human plasma.
The assay uses a reversed-phase high-performance liquid chromatographic (HPLC) and UV
detection at 280nm and has a limit of detection of approximately 5ng/mL. The mobile phase
consists of MeOH-H2O (60:40) adjusted to pH 3.3. Dipyridamole was extracted from plasma by
back-extraction procedure, with propranolol as the internal standard.

**Jerry Brisson et. al.**\(^{(8)}\), was extracted dipyridamole using an automated protein precipitation
method. The automated method used a Tomtec Quadra96 to perform the protein precipitation.
Dipyridamole was separated on a Phenomenex Luna C18(2) HPLC column (2.1 x 50 mm, 5 μm)
using a gradient mobile phase. A Sciex API 3000 was operated in selected reaction monitoring
(SRM) mode under optimized conditions for the detection of dipyridamole and ketoconazole
(internal standard) positive ions formed by TurboIonSpray\(^{\text{TM}}\) ionization. The cycle time between
injections was approximately 3 minutes for both compounds.

**Ting Qin et. al.**\(^{(9)}\), has developed a method using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) for determination of dipyridamole in human plasma.
After protein precipitation of 200 microL plasma with methanol, dipyridamole and diazepam (internal standard) were chromatographed on an Ultimate XB-C(18) (50 x 2.1 mm i.d, 3 microm) column with the mobile phase consisting of methanol-ammonium acetate (5 mM; 80 : 20, v/v) at a flow rate of 0.25 mL/min. The detection was performed on a triple quadrupole tandem mass spectrometer by multiple reaction monitoring mode via positive electro spray ionization source (ESI(+)). The method was validated, which meets the requirements of the FDA guidance.

**Simpson K. et. al.**(10), has concluded that fexofenadine is clinically effective in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria for which it is a suitable option for first-line therapy. Comparative data suggest that fexofenadine is as effective as loratadine or cetirizine in the treatment of seasonal allergic rhinitis. In those with excessive nasal congestion the combination of fexofenadine plus pseudoephedrine may be useful. In clinical trials fexofenadine is not associated with adverse cardiac or cognitive/psychomotor effects.

**Oliveira, D. C. et. al.**(11), has developed and validated RP-HPLC method using a PDA detector for the analysis and dissolution studies of fexofenadine hydrochloride in dosage forms. Mobile phase: triethylamine phosphate 1%, pH 3.2: acetonitrile (ACN): methanol (50:30:20), 210 nm detection, C18 Phenomenex& column. The method was validated regarding accuracy/precision (RSD < 1%), linearity (r2 = 0.9999), and robustness.

**Breier, A. R. et. al.**(12), perform study which describes the development and validation of dissolution tests for fexofenadine hydrochloride capsules and coated tablets using an HPLC method. the appropriate conditions were determinate after testing sink conditions, dissolution medium, and agitation intensity. The apparatus, paddle and basket, were applied to tablets and capsules, respectively. Fexofenadine hydrochloride capsules, products A and B, and coated tablets, products A, B and C were evaluated. The best dissolution conditions tested, for the products in each respective pharmaceutical dosage form were applied to evaluate the dissolution profiles. The parameters of difference factor, similar factor, and dissolution efficacy were employed.

**Karakus, S. et. al.**(13), was develop a reversed-phase HPLC method and subsequent validation using ICH suggested approach for the determination of antihistaminic-decongestant
pharmaceutical dosage forms containing binary mixtures of pseudoephedrine hydrochloride with fexofenadine hydrochloride or cetirizine dihydrochloride. The chromatographic separation was achieved on a Zorbax C8 (150 mm x 4.6mm; 5 microm particle size) column. The optimized mobile phase was consisted of TEA solution (0.5%, pH 4.5)-methanol-acetonitrile (50:20:30, v/v/v). According to the validation results, the proposed method was found to be specific, accurate, and precise.

Zafar, F. et. al.\textsuperscript{(14)}, has presented research work in development of a liquid chromatographic method for the determination of Fexofenadine in tablets and the dissolution method by UV/VIS spectrophotometer was also developed. Method was developed by using Lichrospher 10µm (C18) column. The mobile phase is composed of acetonitrile-5mM ammonium acetate buffer (50:50, v/v) pumped at a flow rate of 1ml/min. The UV detector was operated at 254nm.

Hofmann, U. et. al.\textsuperscript{(15)}, has developed a sensitive method to determine fexofenadine in human plasma and urine by HPLC-electrospray mass spectrometry with internal standard. Extraction was carried out on C18 solid-phase extraction cartridges. The mobile phases used for HPLC were: (A) 12 mM ammonium acetate in water and (B) acetonitrile. Chromatographic separation was achieved on a LUNA CN column (10 cm x 2.0 mm I.D., particle size 3 microm) using a linear gradient from 40% B to 60% B in 10 min. The mass spectrometer was operated in the selected ion monitoring mode using the respective MH+ ions, m/z 502.3 for fexofenadine and m/z 530.3 for the internal standard. The limit of quantification achieved with this method was 0.5 ng/ml in plasma and 1.0 ng in 50 microl of urine.

Flynn, C et. al.\textsuperscript{(16)}, has studied on investigations of specific transporter functions and screening for potential drug-drug interactions, both in vitro and especially in vivo, will require validated experimental probes. Author has developed analytical method for quantitation of fexofenadine to support this work. Analytes were analyzed by tandem mass spectrometry using the m/z 502.17/466.2 transition for fexofenadine and m/z 389.02/201.1 for cetirizine.

Nirogi, R et. al.\textsuperscript{(17)}, has develop a HPLC/ESI-MS/MS method to support the pharmacokinetic and bioavailability study of a once-daily fexofenadine/pseudoephedrine combination, for the simultaneous quantification of fexofenadine and pseudoephedrine and validated with 500 microL
human plasma using mosapride as an internal standard (IS). The analytes were separated using an isocratic mobile phase on a reversed-phase column and analyzed by MS/MS in the multiple reaction monitoring mode using the respective [M+H]+ ions, m/z 502/466 for fexofenadine, m/z 166/148 for pseudoephedrine and m/z 422/198 for the IS. The method is precise and sensitive enough for its intended purpose.

Miura, M. et al.\(^{(18)}\), has developed HPLC method for an assay for fexofenadine enantiomers in human plasma. Fexofenadine enantiomers were separated using a mobile phase of 0.5% KH\(_2\)PO\(_4\)-acetonitrile (65:35, v/v) on a Chiral CD-Ph column at a flow rate of 0.5 ml/min and measurement at 220 nm. This method can be applied effectively to measure fexofenadine enantiomer concentrations in clinical samples.

Arayen, M. S. et al.\(^{(19)}\), worked on development of isocratic reverse-phase HPLC method for the determination of fexofenadine hydrochloride in bulk drug, pharmaceutical dosage forms and in human serum. The isocratic mobile phase was phosphate buffer pH 7.4 and methanol (methanol–phosphate buffer, 35:65, v/v), detection was made at 218 nm and the mobile phase flow rate at 1 ml min\(^{-1}\). Validation parameters included linearity, accuracy, precision, specificity, limit of detection (LOD), limit of quantification (LOQ), and robustness according to the ICH guidelines.

Pathak, S. M et. al.\(^{(20)}\), has developed a sensitive high performance liquid chromatographic (HPLC) method involving fluorescence detection for the determination of fexofenadine. The chromatographic separation was achieved using a Supelco C(18)-DB (250 mm x 4.6mm I.D./5 microm particle size) column with mobile phase comprising of ammonium acetate buffer and acetonitrile (63:37, v/v), delivered isocratically at a flow rate of 1.0 mL min\(^{-1}\). Diphenhydramine was used as an internal standard (I.S.). The established method provides a reliable bioanalytical methodology to carry out FEX pharmacokinetics in rat plasma.

Breier, A. R et. al.\(^{(21)}\), has described the photostability of the fexofenadine hydrochloride. The stress studies revealed the photostability of the drug as the most adverse stability factor. The main photodegradation products were isolated and its structures were elucidated by 1H, 13C, COSY, HSQC, HMBC NMR and mass spectrometry techniques. The drug was exposed to UVC
light at 254 nm in methanolic solutions and the degradation was followed by HPLC and TLC. The photostability of fexofenadine tablets was studied and the same degradation products were observed. The two photodegradation products isolated were characterized as the isopropyl derivative, obtained by decarboxilation of fexofenadine, and a benzophenone compound, which was obtained by rearrangement of aromatic rings and oxidation reactions. The results show the importance of appropriate light protection during the drug development process, storage and handling.

Breier, A. R et. al.\(^{(22)}\), has demonstrated the kinetics of photodegradation of the antihistamine fexofenadine hydrochloride using a stability-indicating high performance liquid chromatography (HPLC) method. The degradation was carried out in methanol and in water solutions, prepared from coated tablets. The kinetics parameters of order of reaction and the rate constants of the degradation were determined for both solvents. The degradation process of fexofenadine hydrochloride in solutions can be described by second-order kinetics under the experimental conditions used in this study. The obtained results show that the HPLC method is satisfactory in the determination of the kinetics of degradation of fexofenadine hydrochloride in the presence of its photolytic degradation products.

Radhakrishna, T et. al.\(^{(23)}\), has developed a RPLC method for the determination of fexofenadine hydrochloride and its related compounds A and B. The method utilizes a C8 column for the separation and determination of meta-isomer (related compound B). The separation was achieved using an Eclipse XDB C8, 5 microm, 4.6 x 150 mm column and a mobile phase comprising 1% triethylamine phosphate (pH 3.7), acetonitrile and methanol in the ratio 60:20:20 (v/v/v). 5-Methyl 2-nitrophenol has been used as internal standard for the purpose of quantitation of fexofenadine. The described method was linear over a range of 0.7-18.7 microg/ml for related compounds A and B and 60-750 microg/ml for assay of fexofenadine.

Sharaf El-Din M. K et. al.\(^{(24)}\), has developed a simple, stability - indicating, reversed phase liquid chromatographic method for the determination of fexofenadine hydrochloride in the presence of its forced alkaline, acidic and oxidative degradation products. Reversed phase chromatography was conducted using an ODS C18 (150 x 4.6 mm id) column at ambient temperature with UV-detection at 225 nm. A mobile phase consisting of potassium dihydrogen
phosphate buffer: acetonitrile (35:65, v/v) adjusted to pH 5.5 with phosphoric acid, has been used for the separation of the studied drug and its degradation products at a flow rate of 1 ml/min. The proposed method was successfully applied for the analysis of fexofenadine hydrochloride in its dosage forms.

S.M. Chen et al.\(^{(25)}\), studied sample of 0.104 M nicardipine in methanol & photo irradiated with a Philips 400 W UV lamp for 3 h in a photochemical chamber. A total of four major photoproducts were found from the HPLC chromatogram. The same sample was used for taking LC-MS, while eight major photoproducts were observed and the structures elucidated by analyzing the CID patterns of their respective mass spectra. A reaction scheme of nicardipine is proposed that the photochemical reactions occur mainly via oxidation of 1,4-dihydropyridine moiety, following the stepwise photo-reduction of the m-nitro group and demethylation of the ester group at 5-position of the pyridine ring.

M.C. Bonferoni et al.\(^{(26)}\), has developed a stability indicating high-performance liquid chromatographic (HPLC) method which is suitable to assess the photo degradation of nicardipine·HCl solutions. The method was validated with particular regard to selectivity. The application of such a procedure to the study of the degradation rate of nicardipine·HCl under both UV and daylight conditions is illustrated. Further structural studies were performed, by means of mass spectrometry, on the main degradation product collected from HPLC: this allowed its identification as the pyridine analogue of nicardipine.

S.K. Owusu-Ware et al.\(^{(27)}\), has conducted forced acid degradation of nicardipine by heating 12 ml of 1 mg/ml nicardipine with 3 ml of 2.5 M HCl for two hours. A gradient HPLC method was developed using Agilent Technologies 1200 series quaternary system. Separation was achieved with a Hichrome (250 x 4.6 mm) 5 µm C18 reversed phase column and mobile phase composition of 70% A(100%v/v water) and 30% B(99%v/v acetonitrile + 1%v/v formic acid) at time zero, composition of A and B was then charged to 60%v/v A; 40%v/v B at 10minutes, 50%v/v A; 50%v/v B at 30minutes and 70%v/v A; 30%v/v B at 35minutes. 20µl of 0.8mg/ml of nicardipine degradation was injected at room temperature (25°C). The gradient method was transferred onto a HPLC-ESI-MS system (HP 1050 series - AQUAMAX mass detector) and
analysis conducted with an acid degradation concentration of 0.25mg/ml and 20µl injection volume. ESI spectra were acquired in positive ionisation mode with MRM 0-600 m/z.

K.E. Ibrahim et. al.\textsuperscript{(28)}, has developed and validated a stability indicating reverse phase high performance liquid chromatographic method for determination of nicardipine hydrochloride (NC) in the presence of its degradation products. The chromatographic separation was performed on Hypersil, BDS-C18, 30 cm × 3.9 mm id, at ambient temperature with UV-detection at 254 nm. A mixture of 20% (v/v) aqueous 0.01 M sodium acetate/acetic acid buffer (pH 4.5) and 80% acetonitrile was used as the mobile phase at a flow rate of 1.5 mL min\textsuperscript{-1}.

C. V. Fernandez et. al.\textsuperscript{(29)}, has developed and validated a stability indicating reverse phase high performance liquid chromatographic method for determination of nicardipine hydrochloride and impurities. The chromatographic separation was performed on Lichrocart 12.5 cm × 4 mm id, at ambient temperature with UV-detection at 254 nm. Mobile phase was phosphate buffer(0.05M,pH 4.8), methanol and acetonitrile in the ratio of 600:65:370  with flow rate of 1.5 mL min\textsuperscript{-1} and column temperature 40°C.

T.Gadkari et. al.\textsuperscript{(30)}, has studied  a forced degradation study of nicardipine in bulk and in its tablet form under the conditions of hydrolysis, oxidation and photolysis in order to develop a stability indicating LC-UV method for quantification of nicardipine. Nicardipine was found stable in acidic buffer upto 48 hrs while in alkaline buffer found degraded. The drug and its degradation products were optimally resolved on C18 column with mobile phase composed of acetonitrile acetate (100mM) (70:30 v/v).A 150 mm ,5 µ ODS column was used for rapid separation with UV detection at 237 nm.

S.L. Kharad et. al.\textsuperscript{(31)}, has developed a reverse phase high-performance liquid chromatographic method for nicardipine hydrochloride. Method was developed using Kromacil C-18 column on an isocratic mode. Mobile phase containing methanol and potassium dihydrogen phosphate (70:30 v/v) and pH of buffer adjusted to 3.0 with ortho phosphoric acid. The flow rate and detection wavelength were 1 ml/min and 236 nm, respectively. The method was validated with respect to the parameters viz., linearity, precision, accuracy, limit of detection and limit of
quantitation. The proposed LC method was found to be rapid, precise and accurate and it can be used for the routine sample analysis of nicardipine HCl in quality control laboratories.

**S.M. AL-Ghannam et. al.** (32), has developed a sensitive spectrophotometric method for the determination of some 1,4-dihydropyridine compounds namely, nicardipine and isradipine either in pure form or in pharmaceutical preparations. The method is based on the reduction of nicardipine and isradipine with zinc powder and calcium chloride followed by further reduction with sodium pentacyanoaminoferrate (II) to give violet and red products having the absorbance maximum at 546 and 539 nm with nicardipine and isradipine, respectively. The proposed method was applied successfully for the determination of nicardipine and isradipine in their dosage forms.

**S.M. AL-Ghannam et. al.** (33), has developed a simple and highly sensitive spectrofluorometric method for the determination for nicardipine, nifedipine and isradipine in pharmaceutical preparations and biological fluids. The method is based on the reduction of nicardipine, nifedipine and isradipine with Zn/HCl and measuring the fluorescence intensity obtained ($\lambda_{\text{em}}/\lambda_{\text{ex}}$) at 460/364, 450/393 and 446/360 nm, respectively. The proposed method was successfully applied to commercial tablets containing the compounds. The method was further extended to the in vitro determination of the compounds in spiked human plasma and urine samples.

**S.M. AL-Ghannam et. al.** (34), has developed and validated a reversed-phase liquid chromatographic method for the determination of nicardipine hydrochloride (NC) in pure, pharmaceutical preparations, human plasma and the study of the pharmacokinetics of the drug in human body. Nicardipine in plasma were extracted and then measured by HPLC-UV using a Waters Symmetry C18 column as stationary phase and methanol– triethylamine buffer (0.01M) pH 4 with acetic acid (70:30) as mobile phase. Nicardipine was quantified by ultraviolet absorbance at 353 nm.

**C.M. Fernandes et. al.** (35), has developed and validated a simple and sensitive reversed-phase liquid chromatography for the determination of nicardipine hydrochloride (NC) in rabbit plasma. After extraction, nicardipine hydrochloride was separated by HPLC on a C18 column
and quantified by ultraviolet detection at 254 nm. A mixture of acetonitrile-0.02 M sodium phosphate buffer-methanol (45:40:15) with 0.2% of triethylamine of pH of 6.1 was used as mobile phase. The analytical technique was used to determine NC plasma concentration after drug oral administration to rabbits.