Literature review:

The literature reviews regarding Olmesartan Medoximil and Hydrochlorothiazide suggest that various analytical methods were reported for its determination as drug in presence of its degradation products, in pharmaceutical formulation. The literature reviews for analysis of Olmesartan Medoximil and Hydrochlorothiazide titles are as under:

Raj N.D.et.al reported validated stability indicating gradient RP-HPLC method for the estimation of antihypertensive drugs in bulk and pharmaceutical dosage by using INERTSIL ODS 3V (150 x 4.6, 5µ) column. Mobile phase-A consists of 1ml triethanolamine in one liter water and the pH was adjusted to 2.5 with orthophosphoric acid and mobile phase-B acetonitrile. The flow rate of 1ml/min, throughout the gradient program and detection wavelength of 225nm for both the compounds with injection volume of 10µl. [6]

Hamrapurkar P.D.et.al reported optimization and validation of RP - HPLC stability indicating method for determination of OlmesartanMedoximil and its degraded product. Successful separation of a drug from degradation product formed understress condition was achieved on C18 column using methanol: water (60:40, v/v) mobile phase, pH 3.75 adjusted with 10mM orthophosphoric acid. Flow rate was 1 ml min and the detector was set at wavelength of 270 nm [7]

Saminathan J.et.al reported method development and validation for the estimation of Olmesartan, Amlodipine and Hydrochlorothiazide in combined tablet dosage form. The proposed method has estimated Olmesartan 99.45±0.94%, amlodipine 98.95±0.32% and hydrochlorothiazide 100.46±0.68% in marketed tablets [8]

Zaveri M.et.al reported simultaneous estimation of Olmesartan Medoximil and Hydrochlorothiazide by validated reversed phase high performance liquid chromatography. The separation of these two components done by isocratic mode using Inertsil-phenyl column (25cm X 4.6mm, 5µm) and a mobile phase composition of Buffer: Acetonitrile (480:520) pH adjusted to 3.0 with dilute orthophosphoric acid. The flow rate was 1.0 mL/min and the analytes monitored at 257nm.[9]
RajaB. et al. reported development and validation of a reversed phase HPLC method for simultaneous estimation of Olmesartan and Hydrochlorothiazide in combined tablet dosage form. The method was based on reversed phase liquid chromatography using a X-Terra symmetry C18 column (150 × 4.6 mm, 5µ) with UV detection at 230 nm. The mobile phase consisting of acetonitrile and potassium dihydrogen phosphate buffer in a ratio of (45:55, v/v) adjusted to pH 2.5 and flow rate of 0.7 ml/min. [10]

Godse V.P. et al. reported the ICH guidance in practice: Validated stability-indicating HPLC method for simultaneous determination of OlmesartanMedoximil and Hydrochlorothiazide in combination drug products. The drugs were well separated from degradation products using a reversed-phase (C-18) column and a mobile phase comprising of acetonitrile: phosphate buffer (pH 3.0), which was delivered initially in the ratio of 15:85 (v/v) for 6 min, then changed to 30:70 (v/v) for next 20 min, and finally equilibrated back to 15:85 (v/v) from 20 to 25 min. Other HPLC parameters were: flow rate, 1 mL/min; detection wavelengths, 258 nm for Olmesartan and 224 nm for hydrochlorothiazide and injection volume, 20 µL. [11]

Sharma R.N. et al. reported RP-HPLC-DAD method for determination of Olmesartan Medoximil in bulk and tablets exposed to forced conditions. Olmesartan Medoximil and all the degradation products were resolved on a (C18) column with the mobile phase composed of methanol, acetonitrile and water (60:15:25, V/V/V, pH 3.5 by orthophosphoric acid) at wavelength 260 nm using a photodiode array detector. [12]

Doshi N. et al. reported validated revered phase high performance liquid chromatographic method for simultaneous estimation of Olmesartan Medoximil and Hydrochlorothiazide and Amlodipine besylate in newly designed pharmaceutical dosage form. The determination was carried out on Zorbax SB phenyl, 250x4.6, 5µ column using mobile phase of sodium perchlorate buffer (pH 3.0):10% THF containing Acetonitrile (60:40 v/v). The flow rate was 1 ml/min and detection at 250 nm. [13]
Ashok kumarJ. et.al reported the simultaneous Estimation of Olmesartan Medoximil and Hydrochlorothiazide by RP-HPLC Method from Combined Dosage Forms. The chromatography was performed on 250x4.6 5µ C8 Qualisil BDS column with 50:50 v/v mixture of buffer and Acetonitrile as mobile phase and pH was adjusted to 4.7 using diluted o-phosphoric acid. [14]

ParikhP. et.al reported derivative spectrophotometric method for simultaneous estimation of Chlorthalidone and Olmesartan Medoximil in their tablet dosage form. The quantification of Chlorthalidone (CHT) and Olmesartan Medoximil (OLM) was achieved by the first-order derivative spectroscopic method at 239.40 nm and 275.60 nm [15]

PanchumarthyR. et.al reported improved rapid HPLC method for the separation of five Anti-Hypertensive agents Using C18 Column: Application to Hydrochlorothiazide determination in bulk and tablet dosage. RP-HPLC method was developed by using WelchromC Column (4.6 mm X 250 mm, 5 µm). The mobile phase constituted of 10 mM Phosphate buffer (pH3.0, adjusted with triethylamine): acetonitrile in the ratio (50:50, v/v). The flow rate was set to 1.0 mL/min with the responses measured at 235nm [16]

SivasakthiR. et.al reported the development and validation of RP-HPLC and UV-Spectrophotometric method for Olmesartan Medoximil and Hydrochlorothiazide in combined dosageform. A reverse phase high performance liquid chromatography method has been developed for the simultaneous estimation of Olmesartan Medoximil and Hydrochlorothiazide in tablet dosage form using C18 column in Isocratic mode. The mobile phase consists of Acetonitrile, methanol and phosphate buffer adjusted to pH 3.5 in ratio of 60:20:20 v/v with ultraviolet visible detection at 230 nm and injection volume of 20 µl. [17]

PandyaG.P. et.al reported development and validation of stability indicating HPLC assay method for simultaneous determination of Amlodipine besylate, Olmesartan Medoximiland Hydrochlorothiazide in tablet formulation. Isocratic RP-HPLC method was developed on Phenomenex Gemini C18 250 × 4.6mm, 5µm column using mobile phase as 0.02M ammonium acetate buffer pH 4.5 and Acetonitrile (60:40, v/v) at a flow rate of 1.0 ml/min and the detection was carried out at 241 nm using photo-diode array detector.[18]
Ashutosh Kumar S. et.al reported development & validation of RP-HPLC method for simultaneous estimation of Hydrochlorothiazide, Amlodipine & Olmesartan in tablet dosage form. The separation was achieved on column (4.6 X 150mm, 5µm, Make: X-Terra) or equivalent in an Isocratic mode. The mobile phase was composed of TEA Buffer (40%) whose pH was adjusted to 3.5 by using Ortho Phosphoric Acid & Acetonitrile (60%). The flow rate was 0.8 ml per min and the detection was at 230 nm. [19]

The literature reviews regarding Emtricitabine and Tenofovir Disoproxil Fumarate suggest that various analytical methods were reported for its determination as drug, in pharmaceutical formulation and in various biological fluids. The literature reviews for analysis of Emtricitabine and Tenofovir Disoproxil Fumarate titles are as under:

**Bojja S.** et.al reported simultaneous determination of Tenofovir Disoproxil Fumarate and Lamivudine by UV Spectrophotometric method. A simple and rapid UV spectrophotometric method has been developed for simultaneous estimation of Tenofovir Disoproxil Fumarate and Lamivudine [20]

**Murugan S.** et.al reported the development and validation of first order derivative uv spectrophotometric method for the estimation of Tenofovir Disoproxil Fumarate, Lamivudine and Efavirenz in bulk and tablet dosage form. A simple, sensitive, rapid, economic and accurate first order derivative spectrophotometric method has been developed for estimation of Tenofovir Disoproxil Fumarate (TDF), Lamivudine (LAM) and Efavirenz (EFV) and in bulk and in tablet dosage form [21]

**Appala Raju N.** et.al reported the Simultaneous RP-HPLC method for the estimation of the Emtricitabine, Tenofovir Disoproxil Fumarate and Efavirenz in Tablet Dosage Forms. Chromatography was carried on an Inertsil ODS 3V column using gradient composition of 0.02M sodium dihydrogen orthophosphate as mobile phase A and mixture of Methanol and water in ratio of 85:15 as mobile phase B at a flow rate of 1.5 ml/min with detection at 265 nm [22]
**Devanaboyina N.**et.al reported HPLC method development and validation for simultaneous estimation of Tenofovir and Emtricitabine in combined pharmaceutical dosage form. Chromatography was carried out by using Chromosil C-18, column having 250 x 4.6mm internal diameter with a mixture of methanol, Acetonitrile and TEA in the ratio of 46:50:04 (v/v/v) as mobile phase [23]

**Dhaneshwar S. R.**et.al reported development and validation of a stability-indicating LC method for the determination of Tenofovir Disoproxil Fumarate in pharmaceutical formulation. Separation of drug and degradation products was successfully achieved on C18 analytical column using methanol: water (60:40, v/v) at a flow rate of 1.0 ml/min and detection at 260 nm [24]

**Kavita K.Y.**et.al reported development and validation of RP-HPLC analytical method for simultaneous estimation of Emtricitabine, Rilpivirine, Tenofovir Disoproxil Fumarate and its pharmaceutical dosage forms. Chromatography was carried out on aquity BEH C18 column using Acetonitrile and phosphate buffer pH 3.0 in the ratio of 55:45 v/v at flow rate of 0.35 ml/min and detection at 261 nm. [25]

**Hussen.S.S** et.al reported development validation of stability indicating RP-HPLC method for Tenofovir nanoparticle formulation. A Lichrocart (C18) (250mm4.6mm, 5µ) column and a mobile phase composed of acetonitrile and 0.025M potassium dihydrogen phosphate buffer (pH 3.0 adjusted by using 10% v/v Orthophosphoric acid) in the ratio 35:65 (v/v) was used, and the detection wavelength of 260 nm. [26]

**Abdelhay M. H.**et.al reported simple spectrophotometric methods for determination of Tenofovir Fumarate and Emtricitabine in Bulk Powder and in Tablets. The first method involves the application of first derivative spectrophotometry where the first derivative amplitudes were measured at 298.5 nm for determination of EMT in presence of TEN. The second method involves first derivative of ratio spectra spectrophotometry where the amplitudes at 251.5 nm have been used for quantitation of TEN in the presence of EMT. [27]
Komaroju D. et.al reported method development and validation for simultaneous estimation of Emtricitabine and Tenofovir Disoproxil Fumarate in tablet Dosage Form by using RP-HPLC was developed. The estimation was carried out on a Phenomenax Luna C18 (250mm x 4.6mm, 5μm) column with mixture of methanol: phosphate buffer pH-3 (70:30 v/v) as mobile phase. The flow rate was 1ml/min. UV detection was performed at 258 nm. [28]

Kumar Pradeep et.al reported validated HPTLC method for the determination of Tenofovir as Bulk Drug and in Pharmaceutical Dosage Form. The method employed TLC aluminium plates precoated with silica gel 60 F 254 as the stationary phase. The mobile phase used was a mixture of (Chloroform: Methanol 8.5: 1.5v/v). The detection of spot was carried out at 270nm. [29]

Hussena S.S et.al reported development and validation of HPLC method for Tenofovir in small volumes of rat plasma using SPE and application to pharmacokinetic studies. Chromatographic separation was achieved using a Lichrocart C18 (250 × 4.6 mm inner diameter 5-μm) column with mobile phase comprising of Acetonitrile and potassium dihydrogen buffer containing tert butyl-amine as an ion pair reagent (53:47 %v/v), delivered isocratically at a flow rate of 1.0 mL/min. [30]

Venkateswara raoJ. et.al reported simultaneous estimation of Tenofovir Disoproxil, Emtricitabine and Efavirenz in tablet dosage form by RP-HPLC method. Chromatographic separation was achieved using Hypersil BDS C18, 250x4.6 mm, 5 μm particular size column, with mobile phase consisting of acetonitrile and 0.03 M KH2PO4 in water (pH adjusted to 3.2 with orthophosphoric acid) in the ratio of 60:40 v/v. The flow rate was 0.8 ml/min and the effluents were monitored at 260 nm. [31]

Soni A. et.al reported simultaneous estimation of Tenofovir and Emtricitabine in Human Plasma Using HPLC after Protein Precipitation Extraction was also reported. A reverse phase high performance liquid chromatographic method was developed and validated for the simultaneous estimation of TNF and FTC in human plasma using stavudine as the internal standard. Protein precipitation extraction procedure utilizing perchloric acid was employed to extract the drugs from human plasma. Estimation of the drug contents was done by using a mixture of sodium
dihydrogen orthophosphate buffer (pH 6.9) and methanol as the mobile phase and absorbance was read at 259 nm for TNF and 280 nm for FTC. [32]

**NevaseP.A.et.al** reported UV spectrophotometric method for estimation of Tenofovir Disoproxil Fumarate tablet dosage form. A simple, rapid and accurate spectrophotometric method has been developed for quantitative estimation of Tenofovir Disoproxil Fumarate in bulk and tablet. In methanol Tenofovir Disoproxil Fumarate exhibits absorption at 260.0 nm and method obeys Beer’s law at the concentration range of 10-100 µg/mL. [33]