LITERATURE REVIEW:

1. Yanli Deng, Armina Madatian., et.al (2011) carried out studies on Metabolism and Disposition of Eltrombopag, an Oral, Nonpeptide Thrombopoietin Receptor Agonist, in Healthy Human Subjects the studies were conducted on six healthy men after a single oral administration of a solution dose of eltrombopag 75 mg. Drug Metabolism And Disposition, by The American Society for Pharmacology and Experimental Therapeutics - Vol. 39, No. 9, pg: 1734–1746.

2. Rambabu Maddela., et.al (2014) studied the Liquid chromatography–tandem mass spectrometric assay for eltrombopag in 50 µL of human plasma: A pharmacokinetic study using eltrombopag 13C4 as internal standard. Analyte and the IS were extracted from 50 µL of human plasma using protein precipitation technique with no drying, evaporation and reconstitution steps. The chromatographic separation was achieved on a C18 column by using a mixture of 10 mM ammonium formate (pH 3) and acetonitrile (10:90, v/v) as the mobile phase at a flow rate of 1.0 mL/min. The linearity of the method was established in the concentration range 50.0–10007 ng/mL. Journal of Pharmaceutical and Biomedical Analysis Vol. 98, pg: 68–73.

3. Wei Zeng., et.al (2010) Determined the sitagliptin in human plasma using protein precipitation and tandem mass spectrometry and the separation achieved on HILIC Silica c18 column using a mobile phase of ACN/H2O (80/20, v/v) containing 10mM NH4Ac (pH 4.7) and the calibration range achieved 1-1000ng/mL. Journal of Chromatography B Vol. 878, pg: 1817–1823.

4. Wei Zeng., et.al (2008) used HTLC for the Determination of sitagliptin in human urine and hemodialysate using turbulent flow online extraction and tandem mass spectrometry method, A narrow bore large particle size reversed-phase column and a BDS Hypersil C18 column were used as extraction and analytical columns and the linearity dynamic range was found at 0.01-5ng/mL. Journal of Pharmaceutical and Biomedical Analysis 46, pg: 534–542.

5. R. Nageswara Rao., et.al (2011) Developed the molecularly imprinted polymer for selective extraction followed by liquid chromatographic determination of sitagliptin in rat plasma and urine which is water-compatible molecularly imprinted solid-phase extraction (MISPE) combined with zwitterionic hydrophilic interaction liquid chromatography
(ZIC-HILIC) method for selective extraction and determination of sitagliptin. Talanta 85, pg: 950–957.

6. **Ramakrishna Nirogi, et.al** (2008) did the Sensitive liquid chromatography tandem mass spectrometry method for the quantification of sitagliptin, a DPP-4 inhibitor, in human plasma using liquid–liquid extraction and the the analytes were separated using an isocratic mobile phase on a reverse-phase column and analyzed by MS/MS in the MRM mode. The assay exhibited a linear dynamic range of 0.1–250 ng/mL. Biomedical Chromatography 22, pg: 214-222.

7. **Laura Else, et.al** (2010) Validated a rapid and sensitive high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) assay for the simultaneous determination of existing and new antiretroviral compounds eluted in reverse phase on c18 column with the run time of 5min and the detection is carried out in SRM mode. Journal of Chromatography B, 878, pg: 1455–1465.

8. **Lieven Baert, et.al** (2009) has conducted the analysis on anti- retrovirals on HIV subjects and Developed the long-acting injectable formulation with nanoparticles of rilpivirine (TMC278) for HIV treatment. European Journal of Pharmaceutics and Biopharmaceutics 72, pg: 502–508.

9. **Dinesh S.Patel, et.al** (2011) done the LC–MS/MS assay for olanzapine in human plasma and stated the application to a bioequivalence study, the analyte and the IS was extracted by SPE technique on Waters Oasis HLB cartridges, Chromatographic separation was achieved on an ACE5C18-300 column under isocratic conditions in a run time of 3.5 min.Mass spectrometric detection involved ESI in the positive ion mode. Acta Pharmaceutica Sinica B, 2211, pg: 1-14.

10. **V.Sreedevi, et.al** (2011) performed the LC-MS Method Development and validated for the estimation of Felodipine in human plasma and Stability studies of freeze thaw analyte, the separation was carried out on Princeton SPHER C18 column using Mobile Phase Acetonitrile : Ammonium acetate in the ratio of 80:20% v/v on Isocratic Elution mode with the Flow rate: 0.8 ml/min and detected by using PDA detector at 38.10 nm. International Journal of Pharma Sciences and Research, Vol.2 (2), pg: 65-73.

11. **Gayatri Gullipalli, et.al** (2001) Developed and Validated a Method for the simultaneous estimation of Flupirtine Maleate and Paracetamol in Bulk and Dosage Form by RP-
HPLC, The components were separated on Inertsil ODS, C18 column by isocratic elution with the mobile phase of potassium dihydrogen phosphate: methanol (70: 30), pH 3.0 was adjusted with orthophosphoric acid at a Flow rate of 1ml/min and detected at 217nm. International Journal of Pharmaceutical Science Invention, Vol 3(5), pg: 49-59.

12. Singaram Kathirvel., et.al (2013) investigated the Stress Degradation Studies on Flupirtine Maleate by Stability-Indicating isocratic RP-HPLC Method which is coupled with PDA detector, the resolution between the peaks for degradation products and the analyte was achieved on a Waters Agilent XDB C18 column by utilising mobile phase mixture of phosphate buffer pH 3.36 and acetonitrile in the ratio of 65 : 35 and eluted the compounds at 344 nm with a flow rate of 1 mL/min. Chromatography Research International, vol 1, pg: 1-6.

13. N. V. S. Ramakrishna., et.al (2004) investigated for the development of Simple, sensitive and rapid liquid chromatographic / electrospray ionization tandem mass spectrometric method for the quantification of lacidipine in human plasma with a The method involves a simple single-step liquid–liquid extraction with tert-butyl methyl ether, the analyte was chromatographed on an Xterra MS C18 reversed-phase chromatographic column by isocratic elution with 20 mM ammonium acetate buffer–acetonitrile 10 : 90 v/v at pH 6 and analyzed by MS in the MRM mode. 39, pg: 824–832.

14. A.B. Baranda., et.al (2005) Developed a liquid–liquid extraction procedure for five 1,4-dihydropyridines calcium channel antagonists from human plasma using experimental design, amlodipine, nitrendipine, felodipine, lacidipine and lercanidipine belonging to the group of calcium channel blockers, experimental tools such as a full factorial design, a central composite design and the Multisimplex program was used to optimise the concentration of NaOH, volume of organic solvent and shaking time as main factors that influence the liquid–liquid extraction procedure. The quantitation of the 1,4-dihydropyridines concentrations were performed by HPLC-DAD compiled with Supelcosil ABZ+Plus column and the mobile phase mixture of acetonitrile–water 70:30 v/v containing 10mM acetate buffer pH 5 and deteted at 360nm and concluded that the main factors that influence in the extraction process were the volume of organic solvent and the shaking time. The Multisimplex program suggested as optimal conditions an average of 6ml of organic solvent and 23 min of shaking time. Talanta, 67, pg: 933–941.
15. **J.A. Lo´pez., et.al** (2000) did the High-performance liquid chromatography with amperometric detection applied to the screening of 1,4-dihydropyridines like nifedipine, nimodipine, nisoldipine, nicardipine, felodipine and lacidipine in human plasma. The chromatographic separation was performed on a Supelcosil LC-ABZ1Plus C column using mobile phase of methanol-water 70:30, containing 2 mM CH COOH–CH COONa to adjust the pH 5.0 at a flow-rate of 1 ml/min. Journal of Chromatography A, 870, pg: 105–114.

16. **Jing Tang., et.al** (2008) studied the Ultra-performance liquid chromatography–tandem mass spectrometry for the determination of lacidipine in human plasma and its application in a pharmacokinetic study, developed and validated for the quantification of lacidipine in human plasma using nifedipine as an IS, sample pre treatment did with a simple liquid–liquid extraction with tert-butylmethyl ether of 1ml plasma and the analysis was carried out on an BEH C18 column with flow rate of 0.28 ml/min using the mobile phase of 30mM ammonium acetate buffer– ACN 18:82, v/v, pH 5.5 and detected on a triple quadrupole tandem mass spectrometer by MRM mode via ESI. At a Linear calibration curves were obtained in the concentration range of 0.025–10.000 ng/ml. Journal of Pharmaceutical and Biomedical Analysis, 47, pg: 923–928.

17. **M. Pellegatti., et.al** (1992) performed the Validation of a high-performance liquid chromatographic-radioimmunoassay method for the determination of lacidipine in plasma which is sensitive and reproducible, a new potent antihypertensive dihydropyridine, is reported. This method involves SPE, HPLC, RIA of the collected fraction. This assay provides a LOD of 20 pg/ml of plasma, allowing the determination of trough 24 hrs plasma concentrations. This method is suitable for pharmacokinetic studies in man. Journal of Chromatography, Biomedical Applications – 573, pg: 105-111.

18. **Ana B. Baranda., et.al** (2006) reported the Instability of calcium channel antagonists during sample preparation for LC–MS–MS analysis of serum samples, 1,4-Dihydropyridines calcium channel antagonists (1,4-DHP CCAs) are photolabile and the products of their photodecomposition have no pharmaceutical activity. Lercanidipine and Nicardipine were also degraded by esterhydrolysis. Several additional minor degradation products were found for the other tested 1,4-DHPs, however, some of them could not be identified. Preconditions for storage and handling of plasma samples prior to
and during analysis for 1,4-DHP CCAs are suggested in order to avoid photodecomposition of the analytes. Forensic Science International, 156, pg: 23–34.

19. Paolo Rossato., et.al (1993) Investigation into lacidipine and related metabolites by high-performance liquid chromatography-mass spectrometry methods were developed in order to characterize the main biotransformation products of lacidipine. Thermospray and particle beam interfaces were used because of their complementary information. In fact, the former provided molecular mass indication, while PB allowed the acquisition of typical electron impact and chemical ionization spectra. Chemical ionization was performed with methane and isobutane as reagent gases. Journal of Chromatography, 647, pg: 155-166.

20. Rihana Parveen Shaik et.al (2013) validated LC–MS/MS method for the determination of tolterodine and its metabolite in rat plasma and application to pharmacokinetic study LC–MS/MS method was used for simultaneous quantification of tolterodine and its metabolite 5-hydroxy methyl tolterodine in rat plasma. Tolterodine-d6 and 5-hydroxy methyl tolterodine-d14 was used as IS. Chromatographic separation was achieved on A scentsi Express RPamide column with isocratic mode, mobile phase composed of 10mM ammonium acetate and acetonitrile in the ratio of 20:80 v/v, at a flow-rate of 0.5mL/min. Journal of Pharmaceutical Analysis, 3 vol-6, pg:489–499.

21. Manish Yadav et.al (2010) performed LC-MS/MS separation and estimated simultaneously for the determination of tolterodine and its active, 5-hydroxymethyl tolterodine in human plasma using symmetrical c18 column and a mobile phase of acetonitrile : formic acid in the ratio of 65:35, pH 5 was adjusted with ammonium formate. Chromatographia, 72, pg: 255-264.

22. S. Ashutosh Kumar et.al (2013) was developed & validated Tolterodine Tartrate in Bulk as well as in Pharmaceutical Formulation by RP-HPLC equipped with Auto Sampler and DAD or UV detector, the Column used is Symmetry C18. The mobile phase was consists of Phosphate Buffer pH 3.0 and ACN. The flow rate at 0.8 ml/min, at a wavelength of 282 nm for detection. Linearity range is 20-100 µg. International Journal of Pharmacy and Pharmaceutical Sciences, Vol 5 - 3, pg: 665-671.

Human Plasma and Urine Samples the assay of Tolterodine Tartrate in pharmaceutical dosage form. Chromatographic run time was 6 min in RP mode and UV detection was carried out at 220 nm for quantification. Efficient separation was achieved for all the degradants of Tolterodine Tartrate on BEH C18 column using Tri fluoro acetic acid and acetonitrile as organic solvent in a linear gradient program and the test solution was found to be stable for 40 days when stored in the refrigerator between 2 and 8 °C. Sci Pharm. 80 pg: 101–114.

24. S. Radha Krishna et.al (2009) Validated Stability-Indicating HPLC Method for the Determination of Related Substances and Assay of Tolterodine Tartarate and also for the separation of related substances, degradants obtained from samples generated after stress degradation. The separation was achieved on Water X-terra MS C18 column and the mobile phase contains 0.05% TFA in water as mobile phase A and 0.05% TFA in Acetonitrile as mobile phase B using a binary gradient mode with flow rate at 1.0 ml/min. The sample concentration was 0.5 mg/ml and detection carried out at a wavelength of 220 nm. Rasaya. J. Chem, Vol 2 - 1, pg: 144-150.

25. A S. Reddy et.al (2012) performed the identification, isolation and quantification of unknown impurity in tolterodine tartrate tablets by stability indicating HPLC method. The identification of new unknown impurity of Tolterodine tartrate formed in stability samples of the drug product at a level up to 0.5% by used. This impurity molecular weight was identified by LC-MS and characterized by various spectroscopic techniques such as 1H NMR, 13C NMR, LC/MS/MS, elemental analysis and FT-IR. Based on the data obtained from spectroscopic tools, the impurity was named as, 6-methyl-4-phenylchroman-2-ol. The structure of this impurity was also established unambiguously, prepared by isolation and co-injected into HPLC to confirm the retention time. Journal of Chemical and Pharmaceutical Research, 4 -7, pg: 3659-3664.

26. A. Lakshmana Rao et.al (2013) did the Analytical Method Development and Validation for the Simultaneous Estimation of Febuxostat and Ketorolac In Tablet Dosage Forms by RP-HPLC, the separation of the two drugs in RP mode using C18 column using mobile phase consisted of phosphate buffer: acetonitrile in the ratio of 50:50 v/v at a flow rate of 0.7 mL/min and UV detection was set at 299 nm. International Journal of Pharmaceutical, Chemical and Biological Sciences, vol 3 - 3, pg: 571-576.
27. B. Prathap et al. (2014) performed the Analytical Method Development and Validation for Simultaneous Estimation of Febuxostat and Ketorolac In Bulk And Pharmaceutical Dosage Form In Rat Plasma by RP-HPLC, The separation was achieved on symmetry C18 column using tri ethyl amine buffer and ACN 60:40 %v/v as mobile phase, pH is 6.0 by ortho phosphoric acid in isocratic mode, flow rate is 1.0 ml at 255nm detection range. Indo American Journal of Pharm Research. Vol 4 - 4, pg: 1717-1729.

28. Babu Rao Chandu et al. (2013) investigated for the Bioequivalence and pharmacokinetic study of febuxostat in human plasma by using LC-MS/MS with liquid liquid extraction method. Febuxostat (FB) in human plasma using Febuxostat D7 (FBD7) as an IS was used. Separation was performed on Ascentis Express C18 Column using mobile phase composed of 10 mM Ammonium formate: ACN 20:80 v/v, with 0.8 mL/min flowrate. MS Detection in MRM positive mode. SpringerPlus, vol 2 - 194, pg: 1-10.

29. Monita Gide et al. (2014) did the Method Development and Validation for Determination of Febuxostat from Spiked Human Plasma Using RP-HPLC with UV Detection. The analyte and IS diclofenac were extracted using LLE with diethyl ether. The chromatographic separation was performed on Shodex c18 with a mobile phase comprised of methanol: acetate buffer pH 4, 20mM at a ratio of 90 : 10 v/v, at a flow rate of 1 mL/min. The calibration curve was linear in the range of 250–8000 ng/mL. Chromatography Research International vol 4, pg: 1-5.

30. Vaka VR et al. (2013) investigated for a sensitive LC-MS/MS method for the quantification of febuxostat in human plasma and its pharmacokinetic application with 100 L human plasma using febuxostat-d7 IS. The analyte and IS were extracted from human plasma via liquid-liquid extraction using diethyl ether and chromatographed on a Zorbax C18 column using a mixture of acetonitrile and 5 mm ammonium formate 60:40, v/v as the mobile phase at a flow rate of 0.5 mL/min in a mean run time of 5.0 min and the elution of febuxostat and IS occurred at 1.0 and 1.5 min. A linearity was established for the range of concentrations 1-6000 ng/mL. Biomed Chromatogr. Vol 27 -11, pg: 1406-1412.

31. Shi Z et al. (2013) investigated for the Development of a simple LC-MS/MS method for the determination of febuxostat in human plasma and its application to a bioequivalence study in healthy Chinese male volunteers febuxostat and etodolac as IS were isolated
from plasma samples by protein precipitation with acetonitrile. The supernatant was chromatographed on a Zorbax SB-C18 column with a SecurityGuard Inertsil Symmetry C18 column. The linearity was achieved over a concentration range from 13.40 to 21440 ng / mL. Pharmazie, vol 68 – 6, pg: 396-400.