2.1 **Review of Literature:** I have chosen three drugs and in this chapter include the all my three drugs related review of literature. A Study on reference tells that several spectrophotometric and chromatographic procedures have be located testified for the determine of carbamazepine in pharmaceutical.

2.1.1 **Review of Literature for Carbamazepine CR Tablets:**

**Bhatti M.M. et al, 1998** was defining the Instantaneous purpose of phanlytoin, carbamazepine, and 10, 11-carbamazepine epoxide in anthropological plasma through high-pressure liquid chromatography through ultraviolet exposure, and perform the method Acetonitrile was added to plasma protein. After centrifugation, the acetonitrile supernatants were removed to an uncontaminated cylinder and disappear beneath nitrogen. The become dry sample abstract were re-formed in 0.4 ml of mobile phase and inserted for analysis by high pressure liquid chromatography. Columns were use Sphereis orb ODS2 methodical column and mobile phase ratio acetonitrile: methanol: potassium phosphate buffer respectively 18: 18: 70. And using ultraviolet detector at 210 nm. In Chromatogram obtained retention time was Carbamazepine E, phenytoin and carbamazepine respectively 5.9, 9.8 and 11.9 min^{10}.

**Mowafy H.A. et al; 2012** was define, progress and confirmation of an HPLC-UV technique meant for the quantefication of carbamazepine in rabbit plasma, and procedure technique has stayed develop and authenticated for the resolve of carbamazepine in in two solution method and rabbit plasma use as a propylparaben as an internal standard. And mobile phase ratio methanol: water respectively 50: 50 and movement rate was 1.0 ml per min and UV finder at 285 Nano meter. Perform this analysis consuming a column μ-Bondapak C_{18} length (15 cm x 0.46 cm i.d). The method was established to be particular for carbamazepine, no. meddling peaks remained detected with a generally analytical run time of 15 min^{11}.
Demirkaya Fatma et al; 2005 developed the method was Resolve of Carbamazepine usages Reverse phase-High pressure liquid chromatography technique in Medical Measures, CBZ was established as an anticonvulsant drug, this is similarly used as an antiepileptic, antidepraessive, antianealgesic and antimenic drug. A RP- technique for the quantifiable resolve in Carbamazepine untainted forms and medicinal determination remained established and confirmed in the current study, in this method using the column C18 (15 cm x 0.39 cm. 5µm).and ratio of mobile phase, Acetonitrile: Water are respectively 3: 7 v/v, and pump flow rate 1 mL per min. and the volume of injection of sample 10 microliter and using Ultra Violate-detector at 220 nanometer. And linaerity were obtained in the renge 0.25 to 25 µg per ml 12.

Ambrsio A.F et al; 2002 are derived Mechanism of Achievement of Carbamezepine and his byproducts, Oxcarbezezine, BIA 2-093, in addition BIA 2-024, this method derived the mechanism of carbamazepine and related derivatives, the mechanism of achievement of this drug is not totally clarified and are silent material of discussion. In hence Carbamazepine is not actual operational in specific epileptic petients and might basis more than a few antiepileptic drugs have been established by structure difference of CBZ, such as ox carbamazepine (OXC), which is hand-me-down in handling of epilaepsy subsequently 199 0. (S)-(−)-10-acetoxy-10,11-bihydro-5H-bibenz [b, f ]azepine-5-carboxamide (BIA 2-093) and 10,11-bihydro-10-hydroxyimino-5H-bibenz[b,f]azepine-5-carboxamide (BIA 2-024), which remained freshly industrialized by BIAL, are novel reputed antiepilaeptic medicines, using certain upgraded possessions 13.
Mathieu Olivier et al; 2011 are defined properties of carbamazepine and metaboltes on IL-2, I L-5, I L-6, I L-10 and IFN-γ excretion in epilaecpt patients: the inspiration of co-medication, and metabolic way indications not individual to the main energetic metabolites, carbamazepine-10,11-epoxide, but then again to slight irrepressible metabolites such as iminostilbene acridine. Carbamazepine is frequently well-tolerated, but then again it might principal to intermittent, but severe, oversensitive responses concomitant with hyper eosinophilia. The appliances of hyper senstivity reaction to carbamazepine are unmoving basically unidentified and consequences of the cell-interceded protected reply (Th1 pathway) or the humorel protected reply (Th2 pathway) are silent not assumed in these responses. Mathieu Olivier et al are study done ex vivo experiment to estimate the encouragement of cytokine emission through carbamazepine, carbamazepine-10,11-epoxide, iminostilbene acridine. I L-5, I L-6 and I L-10 was measured as indications of the Th2 way, and IL-2 and IFN-γ was uses as the indicators of Th1 path 14.

Patil S.R et al; 2011 were defined Validation HPLC technique for simultaneous strength of mind of antipyrene, carbamazepine, furosemide and phenytoin and its presentation in Valuation of drug absorbency done caco-two cell monolayars all are simultaneous determination. And use the reverse phase chromatography technique an C18 column, by means of (H2O pH 3.0 and methanol 50: 50 in ratio) and mobile phase ratio 58: 42 v/v respectively combination of methanol and water and (ACN) acetonitrile. And movement rate of pump 1.0 m L per min. and a use colume temperature of 40.0°C. And different different wavelength uses at UV-detection was supported at 205 nanometer for carbamazepine and phenytoin and at 230 nanometer for Antipyrene and Furosemide. Elution of drugs Antipyrene, Furosemide, Phenytoin, and carbamazepine were observed at 4.12, 5.13, 12.34 and 13.51 minutes, correspondingly. These procedures were consumed for determenation of std. combinations in Caco-two absorbency experimnts 15.
Barakat N.S. et al; 2005 were define carbamazepine acceptance addicted to rat brain subsequent intra-olfactory transportation; A appropriate gel preparation was premeditated to afford the preoccupation of a extremely lipophilic drug concluded nasal mucosa. Hypromellose and carbopol was hand-me-down as mucoadhesive polymers in the preparation to intensification the habitation time of the gel on the mucosa. The independent of this study was to follow the actuality of a conveyance corridor for a carbamazepine to the brain unswervingly from the nasal cavity, by linking the awareness of medicine in the mind subsequently intranasal, intravenous, and oral administration 16.

Patel Rashmin B. et al; 2011 are define estimation of carbamazepine by HPTLC method, title with progress and justification of High pressure thin layer chromatography technique intended for valuation of carbamazepeine in preparations and it’s in vetro publication learning. This method does by TLC method. Carbamazepine(CBZ) were chromatograph on sileca gel 60 F254 Thin layer chromatography plate uses. And mobile phase use in ratio ethyl acetate: toluene: methanol, respectively 5: 4: 1 v/v/v. carbamazepine were counted by densitometry chemist at 285 nanometer. This methods were establish to give compressed acnes for the drugs (Rf = 0.470± 0.01). The undeviating recession examination records for the standardization plots presented good linear correlation by r² = 0.9995 and absorption range 100 to 600 ng per spot. That was minimum detectable volumes were establish to be 16.7 ng per spot, but the perimeter of quantitation were establish to be 50.44 ng per spot 17.

Breton H. et al; 2005 were develop the LC-electrospray spectrometre purpose of carbamazepine, oxcarbazepine and eight of their metabolites in human plasma. Which are mentions as principal line drugs for the action of incomplete and comprehensive tonic-colonic epileptice seizures. This method uses electrospray ionization mass spectrometry. And this method through instantaneous resolve of carbamazepine, oxcarbamazepine, and eight of their metabolites [CBZ-10,11-epoxide (CBZ-EP),10,11-bihydro-10,11-trans-
bihydroxy-carbamazepine (DiOH-CBZ), 10-hydroxy-10,11-bihydro CBZ (10-OH-CBZ),
2-hydroxycarbamazepine (2-OH-CBZ), 3-hydroxycarbamazepine (3-OH-CBZ),
iminostilbene (IM), acridone (AO) and acridine (AI) in human plasma. Separation of this
analyte were found within 50 min uses Zorbox eclipse XD8C8 analytical colmn. And
use moveable phase a combination of CNCH₃ and format buffer (2mM, pH 3.0 ).
Detections were done consuming a quadruple mass spectrometer tailored with an
electrospray ion basis. Mass spectrometric records was attained in only ion record
method at m/z 337 for carbamazepine, m/z 180 for Carbamazepine-EP and AI, m/z 236
for OXCBZ, m/z 237 for 10-OH-CBZ, m/z 253 for 2-OH-CBZ, 3-OH-CBZ and DiOH-
CBZ, m/z 196 for AO and m/z 194 for IM. Used for all analytes, the inside standard peak
height ratio was connected via a quadratic bond to plasma concentration ¹⁸.

Rao K. S et al; 2010 distinct improvement and validate of a particular immovability
representative liquefied chromatographic technique for carbamazepine in bulk and
pharmaceutical quantity forms. In this method use HPLC was isocratic and reverse phase.
And main focus in forced degradation studied was achieved on carbamazepine
consuming oxidation, acid, base, heat and photolytic situations. These perform used in
different condition Zorbax Ecliple XDB-C18,(25 cm x 0.46 cm1, 5µ ) column uses and
moveable phase ratio methanol: water respectively 57: 43 v/v, and pump flow rate of 1
ml per min with photo diaode Array detector at 280 nanometer. And inject the sample
was 5 µl. The retention time of the drug was initiate to be 7.2 minute ¹⁹.

Manoj Babu M.K; 2004 was study Instantaneous parting and quantitation of 4
antiepilaptic drugs- a study with prospective for practice in patient drug level observing,
this learning was to elucidate the applicability of high pressure liquid chromatography
attached with evaporative light scattering detector(ELSD) in instantaneously extrication
and quantitating four generally used antiepeleptic drugs, (AEDs). In this method was
used for separation C8 column and unstable moveable phases and was detector
Chapter-2

consuming ELSD. Ideal contributory situations was attained through evaluating the influence of several precarious investigational limitations just like a evaporator cylinder temperature, transporter gas movement rate, photomultiplier achievement on separation competence, accuracy, reproducibility and sensitivity of quantity on all four AEDs 20.

Chen K, et al; 1991 were describe the Proportional examination of antiepileptic drugs by GC consuming vessel or crowded columns and through fluorescence separation immuno assay, the gas chromatography quantification of underivatized antiepileptic drugs just like a carbamazepine, phenobarbital, phenytoin and primidone in fused-silica vessel columns were associated with that in crowded columns 21.

Miller R.B et al; 1993 were validate a method of determination of carbamazepine 10, 11 epoxide in human plasma, and in this validation and analysis usages a RP- high pressure liquid chromatography and detector were using UV for examination of carbamazepine and its biggest metabolite, carbamazepine 10,11-epoxide (CBZ-E), in human plasma remained described. The retention time of carbamazepine epoxide and carbamazepine and internal standard are found at 3.31, 7.01 and 10.81 minutes correspondingly, and run time of chromatogram were found 12.01 minutes. In this method find the peak heigh percentage vs plasma concentrretion in linear over the rang of 0.10 to 10.0 μg per m L fore every analyt and displays correletion coefficiants of 0.9975, and other results are average complete recaptures of carbamazepine and carbamazepine epoxide by means of the defined assapurity are 89.81 and 86.82 % correspondingly found. The intra- and inter- day accuracy and precission is inside 11.61 % of the authentic valu for totally concentration considered22.
**Mennickent et al; 2003** was validate and develop a technique using involved planar chromatography for measureable examination of Carbamazepine in slobber, epilepsy is a chronic syndrome of the essential nervous method described by recurring, variable and self-limited seizures. In this methods show the carbamazepine is non-ionized at the pH series of saliva, a significant factor in the examination. Carbamazepine solution was prepared in ethanol. Saliva of helper contributors was hand-me-down for the recapture study. Chromatography were conceded on silica gel F254 HPTLC plates, firstly chromatography washed in methanol and activated at 130°C during heat at 20 minutes. And for the chromatographic development use the mobile phase ethyl acetate: toluene: methanol (5: 4: 1 ) v/v/v and length of progress were 5cm occurring in a period of 10 minutes. After improvement of method, carbamazepine fluorescence initiation was achieved by involvement of the plates in 60% HClO₄ in ethanol: Water (1: 1.) respectively, and then insertion the plates on a radiator at 120°C for 7 minutes. Densitometry reading was supported by means of a Scanner camag III spectrodensitometer helped by a computer prepared with CATS type 4.05, and a mercury lamp remained used as the contamination source. Determination were completed at a W/L of 366 nanometer.

**Owen A et al; 2001** was determine the Liquid chromatography resolve of Carbamazepine in Murene intelligence as a use of RP High pressure liquid chromatography technique use, carbamazepine were recovered from murene intelligence by solvent extrection wthetyle acetate and determined from imipremine (use as a internal Std. ) and braine endogenous measurable expending a colum type a Lichrospher Reverse phase selecte B through a linear gradieant of acetonitrile in ratio(400-800 v/v, 25.0 minutes) in ammonium acetate buffer 25mm and buffer pH was 4.0 and use UV wavelength at 285 nm.
Sevgi 2006 determine the carbamazepine using High pressure Liquide Chromatography and derivative spectrophotometry. In High pressure Liquide Chromatography technique, for separation of carbamazepine use the phenomenex C18 column and moveable phase was acetonitrile: water in 75:25 ratio respectively, and movement rate were 1.0 ml per min. and the UV detector use at 285nm. Enalapril were using as an internal std. For the subsequent derived spectrophotomaetric technique, carbamazepines were resolute by smearing the procedure of the “peak to peak generosities”. The assay remained linear concluded the concentration choice of 0.20 to 2.00µg per ml for high performance liquid chromatography and 4.0 to 10.0µg per ml for second unoriginal spectrophotomaetric technique. The finding limits of carbamazaepine was 0.055 and 1.25µg per ml for High pressure Liquide Chromatography and derived spectrophotomaetric approaches, correspondingly 25.

Rajadhyaksha NS et al; 2007 was performed the carbamazepine determine the assay by HPLC stability indicating method. In this method developed by HPLC method and use the mobile phase ratio CNCH3, MeOH and H2O 10, 60, 40 in v/v/v correspondingly. The calibration curvature of the drug were the linear in the series of 1.0 – 20.0 µg per ml. in this method use the limit of finding and quantitaetion was 85.51 and 285.0 ng, correspondingly. The mean out of a hundred recovery were establish to be 100.21 % 26.

Yuan X et al; 2003 were describe the purpose of carbamazaepine in uncoatede and film-coated drugs by High pressure Liquide Chromatography and for finding use UV detection and use ibuprofene as an internal std. The tablets was weigh and pulverized independently, and was removed in MeOH by consuming sonification process. These extracte were dilute and filter with 0.45 µm filter paper. Separation were done on Econosphere C18 and 5µ systematic column and uses a moveable phase 28: 72 CH3CN: sodeium phosphate buffere respectively. And finding was carried out as a UV at 230
nanometer consuming a photodiode array sensor. The malicious retention time of carbamazepine and ibuprofen was found 4.21 and 12.31 min., correspondingly. The linear calibration range was 5.00 to 25.00 µg per ml through the minor limit of detection of 18 ng per ml and lower limit of quantitation of 60 ng per ml\(^\text{27}\).

**Oh EK et al; 2006** were define the analysise of carbamazepine and inactive metabolit, carbamazepin 10,11-epoxid, in humen plasm consuming HPLC and detector are UV. Use the column for separation Reversee Phase C18 column with a moveable phase of CH\(_3\)CN, MeOH, H\(_2\)O, 18: 19: 63, v/v/v correspondingly, and use UV detector at 210 nanometer. The calibration curve remained linear terminated the concentration series of 0.01-10.0 µg per ml used for carbamazepine and 0.005-5.0 µg per ml for carbamazepine 10, 11-epoxiede in human plasma respectively\(^\text{28}\).

**Huang C et al; 2002** was developed the photochecmicale reactions carbamazepine can be changed to a robust fluorescente composite which takes a resolute discharge wavelength of 478 nanometer and maximume occurses wavelength of 254 nanometer. Acidity of the reactiione intermediate and the acid category remained initiate to be dangerous for the photochemical influenced fluorescence, weak hydroecloric acid existence the most appropriate. A movement injecte photochemical spectrofluorimetricce method for purpose of the drug were established\(^\text{29}\).

**Bhoite D S et al; 2013** was progress and validetion of stebility representing HPTLC method for determine of oxcarbamazepine in bulk and pharmaceuticcal formulation. This method use the LC chromatographi for analyses of oxcarbamazepine were develope to resolve drug response from degradetion productes. In this process applied Thin Leyer Chromat. Alu. plats pre-coated with seleca gel 60 F\(_{254}\) use as a stationery phase and as a mobile phase uses ethyl acetate: methanol (6:4 v/v).
This system were founds to give compact form for oxcarbamazepine and Rf value 0.64 ±0.01. In this method also validate in stress condition this drugs stress condition like acid, alkeli, neutra hydrolyses and oxidetive degradetion. The spot for degradation product of was well resolved beginning the druge, densitomitrice analyses of drug were the fluroscence mode at 366.0 nm. The linear regrassion statistics for for the calibretion plotle showing goodlinear association with $R^2=0.999$ found and concentration sort of 101-351 ng/band.30

Laroudie et al; 2000 were investigated by correlated of the carbamazepine and Nafazodone interaction in healthy subjects, in this paper shows the pharmacokinetic interaction between nefazodone and carbamazepine was investigated in 12 healthy male volunteers. And this is received nefazodone 200 mg twice daily rutein for five days and blood sample collected perform on the day five for 0 to 48 hours pharmacokinetics analysis. A four days washout the phase then followed from days 6 to 9. Carbamazepine 200 mg was administered once daily from 10 to 12, and then 200 mg ws given twice daily from days 13 to 44. An 0 to 48 hours pharmacokinetic analysis was performed on day 38. Coadministration of nefazodone increased the steady –state plasma area under the concentration time curve (AUC) of carbamazepine from 60.77 (±8.44) to 74.98 (±12.88) µg.hr/ml (p<0.001) and decresed the active carbamazepine -10,11-epoxide metabolite AUC concentration from 7.10 (±1.16) to 5.71 (±0.52) µg.hr/ml(p<0.005). in during the combination of both , the steady state AUC of nefedazodone decreased from 7326(±3768) to 542(±191) ng.hr/ml, and AUC of its metabolism of decreased significantly as well (P<0.001).31
Mandrioli R, et al; 2001 were determine the simultaneous HPLC method for determination of carbamazepine and five of its metabolites in plasma of epileptic patients, in this method determine to high performance liquid chromatography method and use the UV detector for the simultaneous analysis of the antiepileptic drug carbamazepine and 5 of its metabolites in human plasma has been developed. These analysis was conceded on a RP column use and column properties C8, 150x 4.6 and 5 μm and using mobile phase was acetonitrile and methanol and a pH 1.9 phosphate buffer. And under these chromatography conditions carbamazepine and its metabolites 10, 11-dihydro-10, 11-epoxycarbamazepine, 10, 11-dihydro-10, 11-dihydroxycarbamazepine, 2-hydroxycarbamazepine, 3-hydroxycarbamazepine and 10,11-dihydro-10-hydroxycarbamazepine are baseline separated in less than 18 min. in this method extraction of the analytes from plasma sample were performed by means of an original solid-phase extraction procedure using oasis HLB cartridge. The method only suitable for reliable therapeutic drug monitoring of patients undergoing chronic treatment with carbamazepine and for kinetic-metabolic studies of this drugs. 32

Mennickent S et al, 2009 determine the planar chromatographic method for determine of carbamazepine in human serum, HPTLC method for quantification of carbamazepine in human serum were developed using liquid – liquid extraction with dichloromethane, fluorescence activation with perchloric acid 60%, ethanol, and water (1:1:1, v/v) and fluorescence detection. Planar chromatographic separation was performed on precoated silica gel F254 HPTLC plates using a mixture of ethyl acetate, toluene, methanol, glacial acetic acid (5:4:0.5:0.5, v/v) used as a mobile phase. Detection was a densitometric at 366 nm. This method was validated for linearity, precision and accuracy. The intra-assay and inter-assay precision, expressed as the RSD, was in a range of 0.41 – 1.24 % (n= 3) and 2.17 – 3.17 % (n=9), respectively. Instrumental planar chromatography method add the LOD were 0.19 ng and the LOQ was 0.57 ng. Accuracy calculated as percentage recovery. Were under the limit 98.98 and 101.96 % with RSD not the higher than 1.52%. This method selective for the active principle tested. 33
2.1.2 Review of Literature for Memantine HCl Tablets:

A Study on literature expresses that several spectrophotometric and chromatographic procedures must been described for the purpose of memantine hydrochloride in pharmaceutical.

Narola B et al, 2010 was determine and authenticated stabilite-indicating reverse phase High pressure liquequid chromatography assay process for the purpose of Mementine hydrochlorid drug constituent with UV-Detaction by means of Pre column Derivatization method. Memantinie hydrochloride were derivatized through 0.015M 9-fluorenelmethyl chloroformat (FMOC) & 0.50 M borat buffer sol’t and store at rum (25°C) temperature for 20 mintes and use water HPLC photodiod arrey detector using kromosil C18 column (15 cm x 0.46 cm x 5μ) length and injection volume use 10 μL of derivatized mixture, and mobile phase use in ratio Acetonitrile and phosphate buffer solution respectively 80:20 v/v and movement rate of pump 2 ml per minute. Memantinie were eluted at 7.5 minutes.

Jagathi V et al, 2010 were find spectrophotometric determination of memantin in bulk and in pharmaceautical formulation, and that process based on the two types. Process A created on reduction of Foline-Ciocalteau (F.C) reagente through the drug and the condensed species possess a characterestic extreme blu colour (λ max 760 nm), process B founded on the abbreviation of memantin with 1,2-Napthequinone-4-sulphonate(NQS) in an alkalin intermediete to form an orenge stained producte (λ max 460 nm). Bears low is followed in the concentretion range of 4.0-12.0 microgram per mL (technique A) and 7.50-17.50 μg per mL (method B) with respectable correlation coefficients of 0.9970 and 0.9990 correspondingly for Method A and Method B separately.
Jadhav SA et al, 2012 determine the change and authentication of stabilite-indicaeting Gas Chromatographe-FID procedure for the quantitition of memantin hydrochlorid and it non chromphoeric scums in bulk and pharmaceutacal dosage, in this method by means of gas chromatographe attached with conflagration ionization detectar (Gas Chromatographe-FID). The constancy representative environment of the process has ben verified through starting peck purite and approving the mas stability of all examples by exposing them to pressure environments like hydrolyses, photolysis, oxedation, and thermale degredation readings. The efficiency of the procedure was established by examination of changed bulk example of memantine hydrochlorid 36.

Michail K et al, 2011 develop spectrophotometrec and spectrofluorimetric resolve of memantene hydrochlorid in substance and pharmaceutecal measures, 1st process is created on the response of the druge through 4-chlor-7-nitro-2,1,3-benzoxadiazole in alkaline buffeer. The producte molded is unhurried considers the response of the analytic with o-phthaldehyde/N-acetyl-L-cysteine and the absorbence of the producde unoriginal is measure at 340 nanometer 37.

Siddappa K et al, 2011 were determination of a gas chromatographic proceess for the assey of memantin hydrochlorid in unalloyed and tablet dosage form, in this method has been used gas chromatography and recognition was supported using flame ionization detector. And separation was completed on a use though DB-624 fused silica bursting capillary column and length (30.00 x 0.320 x 1.8 micrometer), and nitrogen remained use the same as a mover gas at a movement rat of 40 m l per minutes. use & column temparature maintain at 300°C though the temperature of injection seaport and detector were preserved temperature at 270°C and 300°C, correspondingly. Gabapentin (GPN) was used as an internal standard 38.
Teixeira MG et al, 2006 were definite immovability of memantine in an impromptu equipped oral liquid. Glutamete has been described to subsidize to the pathogenesis of Alzheimer’s syndrome by over inspiring the N-methyl-D-aspartate receptors, subsequent in brain cell mutilation. The aqueous fluid formulations were prepared by reconstructing memantine powder commencing triturated tablets with beionized water. The memantine liquid transferred in to 2 Glass treatment thermoses, one were stockpiled at rom temperature (25°C), and extra in freezer (2°C). Aliquot from each thermos was examined in quadruplicate on days 0, 1, 2, 3, 4, 7, 14 and 28 by by means of a gas chrometograph-mass spectrometer 39.

Shafaati A et al, 2010 studies profound and quick HPLC technique for resolve of memantine in human plasm by means of OPA derivatization and fluorecence detaction: Submission to pharmacokinitic revisions, and were use method was maintained out on a monoelthic silica colon Chromolith presentation Reverse phase-18e,10 cm x 0.46 cm. and amantedine were used as inner stad.. And moveable phase were combination of CH$_3$CN and 0.025 M phosphate buffer (p H=4.6), respectively 50:50 v/v by means of a movement rate of 2.5 ml/min. the excitetion and production wavelenghts was see at 335.0 nanometer and 440 nanometer correspondingly. The examine permits the quantity of mementine for beneficial drug observing with a subordinate quantifecation bound of 2 ng per ml 40.

Freudenthaler S. et al, 1998 develop Encouragement of urin p H and urenary movements on the renale secretion of memantin, memantin in plama and urin sample was resolute with valideted assay methods which active gas chromatography with mass choosy detection and were accompanied permitting good research laboratory practice. That's method 0.5 ml plasma or urine were treatd at 70° C for 30 min later adding of 0.5 ml HCL (2 N), after freezing the combination was made alkeline by adding of 0.25 ml sodium hydroxid(NaOH) solution (32% w/v). consequently the analysis was removed
into 1 ml n-hexane for 30 min. the carbon-based layer were then moved into a reaction vial covering 15 μl N-methyl-dis-trifluoro acetamid 41.

Koeberle MJ et al, (2003) determine the of a liquid chromatography-mass spectrometrical technique for calculating the compulsory of mementine to changed melanin, for this studies and source of melanin studies was sepia, synthetic and slow melanin. Memantine remained chromatographed on a reversed phase system and use column Prodigly ODS (3) 10 cm x 0.46 cm x 5μ. 100 A, by means of gradient pump using moveable phases of 0.1 % formic acid in bionized H2O and 0.1 % foarmic acid in methanol and adjust the movement rate of pump 0.8 ml per min. the mode of ionization was achieved atmospheric pressure-electrospray and recognition by single ion observing of ion m/z 180 42.

Almeida AA et al, 2007 developed the determine of memantine in humane plasma by liquid chromatography-electraospray pushbike mass spectromatry: submission to a bioequivalence studi. in method sample planning contained of the calculation of amantadine as a use inner standard, liqueide-liqueide abstraction in basec condition usinge a combination of biethyl ether-chloroforms (70: 30, v/v) as removing solvents, and further centrifuged the sample than solvenent disappearance and sample re-formation in MeOH. Sample and standard was examined by means of a C18 colun and moveable phase ratio methanol, water and formice aced (80: 80: 0.1, v/v/v). Analyze was particular reaction observing consuming the father to spawn Combination of m/z, 180>163 memantin and m/z, 152>135 amantadin 43.
Liu MY et al, 2008 were studies Pharmacokinaetics of one-dose and multiple-dose memantine in fit Chinese undertakes consuming an analytic technique of liquefied chromatography-tandem mass spectrometry, and use liq. Chromate. mass spectrometry process for resolve of memantin in man plasm. Subject were randomized to accept a only dose of 5, 10, or 20 mg of memantine to learning the linear features of pharmacokinetics, or a manifold dose of 5 mg once every day for 14 days to study the drug increase. The pharmecokinetic constraints intended involved C(max.), T(max.), AUC t(0.5), mean residence time (MRT), maximum steady-state plasma concentration (C(ssmax)), minimum steady-state plasma concentration, mean steady-state plasma concentration, and instability calculation. Consecutive blood sample were collected from 0 to 360 hours for single-dose pharmacokinetic resolves after the dose on 1 day, in the multiple-dose pharmacokinetic arm, the sequential blood sample was also found from 0 to 360 hours on 14 days after accumulating the Predose sample at 0 hrs on 11, 12, 13 days.

Konda RK et al, 2012 define as a new technic by Bio investigative technique progress and authentication of memantine in man plasma by high pressure liquid chromatography with tendem mass spectrometry: claim to bioequivalence study, method were established and corroborated for measurable approximation of memantine in human plasma. Chromatography was succeeded use the zorbaxe SB-C18 column and column length 4.6 x 75mm, 3.5μm. extraction of memantine and internal standard memantine-d6 spending liquid-liquid abstraction and examined by LC-ESI-MS/MS and consuming the several reaction observing approaches. The assay displayed a linear enthusiastic range of 50-50000 pg per ml for memantine in humane plasma.
Pan RN et al, 2009 are explain purpose of memantine in human plasma by LC-MS-MS: request to a pharmaecokinetic study, these method develop and validatede completed the linearity range 0.1 -25 ng per ml with 0.5 ml of plasma spending procaenamide use as an internal standard. This analysis were approved on a Cromosil 5C18-MS colmn use and moveable phase, mixture of MeOH and 0.5 % formic acid in ratio 50: 50 v/v, respectively. Detector were use a tripale-quadruple tandem mass spectroameter consuming +tive ion mode electroaspray ionizaetion and quantification were accomplished by many reaction observing modes. The MS-MS ion transitions observed was m/z 180→107 memantine and 236→163 for procaineamide.

Raichová NA et al, 2002 explain the Electrophoretic performance of adamantane derivetives having antivirale action and their resolve by vessel zone electrophorasis with subsidiary detection, separation and determineation of adamantane derivative with antieviral activity, after optimization, using as an unintended uncovering method 5 mm 4- methylbenzylamine in etheanol and H₂O solution in proportion (1:4) as instantaneously engrossing and protecting backgrund electrolyte with detaction at 210 nanometer were originate appropriate for resolve of the separable compoundes.

Shuangin C et al, 2007 was define new method for HPLC resolve of amantadine and its equivalents in rate plasma, use derivative method and achieved at room temperature by means of anthrequinone-2-sulfonyle chloride (ASC) as substance for single 10 min and deprived of postderivationtization conduct to inactivate additional reagent. The derivative was analyzing by isocreatic HPLC and uses a UV detactor at 256 nanometer, and column Lichroesper C18. For linearity purpose of three drugs pointed in plasma (0.2 ml) was 0.05-5.0 µg per ml for amantadine and nimantadine, 0.05-2.0 microgram per m L for memantin, correspondingly.
Suckow RF et al, 1999 were find complex and discerning liquide chrometographic assay of memantin in plasm through fluorescance detaction subsequently pre.-colum derivetization, in this method use extraction method liquide- liquide from 1 mililiter of plasma encompassing the inside std. amantadine, abstract were reprivatized at rom temperature through dansyl chloraride, and the extremely fluoreascent derivative was chromatogreaphed through a reversed-phase C18 colum use and a moveable phase composition use of phosphate buffer and CNCH₃. Dansylated amantadine and memantine was elutd in not more than 13 min with no interfering from endogaenous substantial 49.

Xie MF et al, 2011 was estimate high-pressure liquide chromatographic resolve of memantine HCL in rat plasma by means of profound fluorometric derivatization, which were groaunded on derivetization with 9-fluorenyl methil chloro format. FMOC-CI use as a derivatization for memantin hydrochlorid in rat plasm. The amino group of memantin hydrcelrde and amantadine hydrcelrde (intarnal standard) was surrounded through FMOC-Chloride to form mementine hydochloride-FMOC-Chloride and amantadine hydrochloride –FMOC-Chloride arrangements, precipiteten of plasma proteineis by CNCH₃ were monitored by vortex socializing and then centrefaugation. Chromatography separation were perforemede on a C18 Diamonsil 15 cm x 0.46 cm x 5μm, column uses, and mobile phase use the combination of acetonitrile and water at a movement rate of pump 1.0 mL per minutes. the retention time of amantadine hydrochloriede-FMOC-CI was a 40.27 min and memantine hydrochloride-FMOC-CI was 23.69 min 50.

Higashi Y et al, 2005 was use a derivative method Immediate purpose of the compulsory of amantadene and its similarities to imitation melanine by liquid chrometography after pre-column derivetization with danesyl chloride, and determinetion of amantadine (1-ADA), 2-adamentanamine (2-ADA), memantin (MEM), and rimantedine (RIM) in melanine compulsory studieas, and the instantaneous determinetion
of 1-A D A , 2-A D A, M E M, and R I M is examined by H-pressure liquide chromatographic assay through dansyl chloride as a fluorascent derivetive componant. Dansyl derivetives with fluorascent intenste are identified at an excitetion wavelenght of 370.0 nanometer and release wavelength of 506.0 nanometer.

Askal HF et al; 2008 was established the quantitetive TL chromatography process for resolve of Amantadin hydrochloride. By Askal HF et al was use the thin later chromatography aluminum plates pre-coatede with sileca gele 60F-254 as a stationery phage. And mobile phage for improvement involved of n-hexan: MeoH: di ethyl amine (8.00: 4.00: 0.5, v/v/v). The alienated spots was envisaged as brown spots after drenching with modifiead dragendorff’s substance solutione. Amantadines HCL were subjectaed to enhanced pressure situations, blistering, acide and alkeline OH, oxidation and irrediation with ultra-violet lighte. The drugs were establish toward be constant under all the considered stress situation. The process was validated for linearity, limit of deteaction (LOD) and quantetation (LOQ), precison, robustnss, selectiviti and accureci. The optical denseties of the seperated spots were found to be lineiar with the quantity of Amantadine in the range of 5-40 µg per spot with good correlaetion coefficient (r=0.9994). the LOD and LOQ value was 0.72 and 2.38 µg per spot, correspondingly. Statisticale analysis provaed that the process is accurate and repeateble for the determinetion of amantadine. The process, in termes of its senstivity, accuracy, precision and robustness use the internationale conferance of Harmonizetion ICH/FDA requirments. In this method amantadine labeled claime percentages was 99.0 ± 1.0 %.

In addition, process relies on the usage of inexpensive apparatus, a scanrar and software, and not critecal derivetizing reagent, thus maxemizing the ability of laboratories word wide to analyzze sample of amantadine.
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Achim M et al; 2011 was define the LC/MS analytical method meant for memantine hydrochloride measure remained conventional and validate the process. It was define memantine hydrochloride is a water solubility at 20°C of 47.035mg/ml. The studies concerning a physico-chemical estimation of memantine, and a non-competitve N-mathyl-D-aspartate (NMDA) receptor adversary, presented in that work. This cataloging of memantine hydrochloride is pre essential for the formulation of a paternal solution. The thermal performance and the chemical dependability in aqueous solution, depending on the pH, temperature, UV light and the occurrence of oxidizing or isotonising mediators was determined. Thermal analysis exposed that it is an anhydrous substance, offering a crystalline form, and that sparkling form melting point at 297.16°C. In aqueous elucidation memantine hydrochloride is unchanging at room temperature (20°C), thoughtlessly the pH of medium, UV light, isotonising mediator or oxidizing agent and at 80°C, at acidic pH vale. These consequences designate that memantine hydrochloride has suitable physico-chemical possessions used for a parenteral solution formulation

El Nashar RM et al; 2012 was defined and analysis the potentiometric membrane sensors for the choosy determination of memantine HCL in pharmaceutical preparations in this method use the 3 potentiometric sensaors responsive to memantine hydrochloride drug are describead, charcterized, related and used for drug valuation. The devices are based on the use of the ion-association compound of memantine cation with Flavianate, 5-nitro-barbiturate and phosphomolybdete anion as electro active material in plasticized poly (vinyl chloride) membranes. The sensors demonstrate fast near- Nernstian response for memantine with lower limits of quantificaetion of: 4.76 x10⁻⁶, 5.25x10⁻⁵ and 9.18x10⁻⁶ M with detection limits of 1.78x10⁻⁶, 9.19x10⁻⁶ and 2.95x10⁻⁶ M, with slopes of 55.49, 45.86 and 54.68 mV/concentration decede over a pH range of 2.65-9.55, 4.66-8.56 and 4.62-9.12 for flavianate, 5-Nitro-barbiturate and phosphomolybdete, correspondingly. The 3 sensors showed good selectivity for memantine drug over several inorganic cations, nitrogeneous excipients and diluents normally used in drug formulations


Salama NN et al; 2012 were validate the time of flighte mass spectrometry for quantitative determination of amantadine hydrochloride and memantine hydrochloride, instantaneous determination of amantadine and memantine in drug material and products without chromatography separation. Time-of-flight mass spectrometer (Tof MS) analytical technique has several advantages over the aforementioned methods, where direct HPLC and GC are unsuitable, because structure of the studies drugs lack suitable UV chromophore. There is no requirement for procedure development, a little analytical time. Calibration curves for amantadine and memantine hydrochloride displayed good linearite over the concentretion range studied (23.8-2380.0 ng per ml) for amantadine and up to 1190.0 ng/ml for memantine in drug substances as stated\textsuperscript{55}.

Literature review shown that only visible spectrophotometrieic technique and derivatized technique, and use for extraction different types of plasma, have been informed for its measureable determination in its pure form and pharmaceutical formulation. This stimulated the author to develop accurate and reasonable visible spectrophotometric methods that can be considered for predictable determination of memantine hydrochloride in pure and market formulations.

Dubey SK et al, 2009 were quantititative analysis of memantin in a humen plasma using the ultre performance liquide chromatographi and tendem mass spectometri, purpose of this study according to author comparing of single dose of memantin hydrochlorid 10 mg tablet of Ranbaxi with NAMENDA tablets and fed conditions. This study were carried out as a two means intersect designe on eight subjact in fast and fad condition. The plasm sample was obtaine over a 70 hourse post dos in every period. Plasm memantin sample was analysed by L C coupled to tendem mass spectometri (LC-MS/MS) with +tive ion electro sprai ionizetion using many reaction monitering (MRM). This method were sensitiv, reproduceble, accurat and validated LC-MS/MS technique through limit of quantifecation (LOQ) 0.200 na.gr/m L were use to analysed mementine. This methods 90.0% confidence intervals for mixture of test and refrence (proportion of
least-squares mean) for in-transforms $AUC_{0-72}$ & $C_{\text{max}}$ was inside the regulator acceptance criteria of 81.0-126.0%.\textsuperscript{56}

**Chladek J et al; 2008** was study of two memantine tab and oral solution in helathy volunteers and found the bioavailability of memantine was comparing consider the two tab one is a Memantin LACHEM 10 tab and Akatino Memantin 10 as a name this studi A, and second 2 oral sol’s formulation done memantin LACHEM gtt and Akatinol Memantine gtt, and this name Studi B both containing 10 mg mementine hydrochlorid in 2 rendomized, 2 period, 2-sequenc, crossove studis with 24 healthi volunteer. In this studi both period memantin concentration was determine by gas chromate, and use electrone capture detector for plasme sample teken at the steadi stata after 22.0 days of 1 –daili dosing. The arithmect mean (Standard Deviation) in pharmacokinetic parameter in the studes A and B was: $AUC_{769.00}$ (141.0) vs. 728.0 (99.0) & 808.0 (154.0) vs. 837.0 (156.0) nan.gr/m L h, $C_{\text{max}}$ 37.30 (6.10) vs. 36.20 (4.50) and 40.20 (8.30) vs. 40.60 (6.70) ng/ml medium value of Tmax was in the renge of 4.0 to 5.0 hrs. bothe tablets and orle sol's formulation was establish bioequivalence 90.0% -confidance interval for $AUC$ $C_{\text{max}}$88 with in 101.0-114.0 % as a study A & 93.0 and 105.0 % studi B. and peckrought fluctuotion the bioequivelence interval was 86.0-107.0 % and 87.0-04.0%, respectivaly found. By mutual analysi of both studi, the geometri mean (91.0 % CI) relativ bioavailebility of memantin from tablats compar to orle solution were 92.0 % (85-98).\textsuperscript{57}
Baumann P et al; 2004 were a one type of monitoring in psychiatry of therapeutic drug, in enavle the clinicen to adjust the dosge of drug according to the charectorstics of the individual patients. In the sence of psychiatrics lithium is a stabilized procedure for TDMs, some antidepresants and antipsycotics. In spite of its obvious advantages, however, the make use of TDM in evreyday clinicale practice is for starting most advantageous. The interdisciplinery TDMs groups of the arbeitsge meinchaft fur neurosychipharmakologie under pharmacopsychiatric (AGNP) has therfor workd out consensuse guidelins to asiste psychiatrist and laboratory involvd in psychtropec drug analyses to optimize the uses of TDMs of psychotropics drugs. 5 research base lvel of recomandation was define with regard to routene monetoring of plasm concentretion for dos titretion of 65 psychoactiv drugs:

1. Strongli recomanded

2. Recommended

3. Usefully

4. Probablie usefully

5. No recomandation

A sec. approach defined indecations to uses TDMs. Example controle of complianc, leck of clinecal respons or adver effect at recomanded dose, drug interetion, pharmacovigilence programes, presence of a genatic particularly concerning the drug metbolism, childrene, adolescente and elderli petients. Indication for TDMs are relavant for all druge eithar through or not including validated therapeutic renges. When study are therapeutic range are lecking targete range, when study on therapeutic range are lacking, therapeutic range of plasma concentration that are considerd to be optimale for treatmente for those druge, from which evalulation demonstrate strong evidence.
2.1.3 Review of Literature for Clopidogrel Bisulphate Tablets:

A Study on literature that several spectrophotometric and chromatographic procedures must been described for the purpose of clopidogrel bisulphate in pharmaceutical.

Shrivastava PK et al; (2008) was distinct Simultaneous Estimation of Clopidogrele Bisulphet and Aspirine in Tab. by authenticated Revers phase-HPLC Technique, this process uses the moveable phase ratio were ACN, 50 mM potassium dihydrogan phosphate buffar, CH3OH respectively 50,30, and 20 v/v and solution pH adjusted to 3. And movement rat of 1.5 m L per minutes and wavelength detectione at 240.0 nanometer. In thes situations Clopidogrele bisulphate and aspirine were eluted at the 7.49 and 2.32 minutes.

Chaudhari PB et al; (2010) were defined the Stabilite representing spectrophotometric technique for determenation and validation of Clopidogreel bisulphate in tablet dosage form, this is normal spectrophotometer method and all value measured at 220.0 nm.

Londhe SV et al; (2011) were Developmaent and Validetion of a Reserved-phage liqued chromatographi technique for Instantaneous Resolve of Aspirine, Atorvastatine Calcium and Clopidogrel Bisulphate in Capsules. And use in method movable phage as a combination of ACN and phosphete buffar (p H 3.0 adjust with (OPA) o-phosphoric acid respectively 5:5 v/v and flow rete of system 1.2 m L per minutes, UV detaction was achieved at 235 nanometer. For separation usese column Inertsil ODS analytical column 150 x4.6 mm x 5μm. The retention time was found 1.91, 6.72 and 19.91 min. for aspirine, atorvastatin calcium and Clopidogrel bisulphate, correspondingly.
Renapurkar SD et al; (2010) was developed A LCMS Like-minded Stabilite-Indicating liquide chromatography Assay Technique for Clopidogrel bisulphate, in this technique use for departure was accomplished on a Inertsile C8 HPLC column by means of a mobile phas ratio mixture of 0.1 % trifluoroacetic acid is a (solvent A) and CNCH₃ is a (solvent B). degradation was detected under acidics, basic and unbiased hydrolysis condition to contribute Clopidogrel carboxylic acid, and uses mas spectrum for uniqueness of humiliation products designed and substantiates the specificity of the technique unambiguously⁶².

Sinha PK et al; (2009) was defined and validates, A Validated immovability representative HPTLC technique for purpose of Aspirine and Clopidogrele Bisulphat in collective Dosege form, thin layer chromatography technique of examination for Aspirin and Clopidogrel bisulphate were established, the process engaged TL Chromat. aluminume plats pre. coated use selica gel 60 F₂₅₄ as a stationery phage. The solvant method consisting of carbon tetrachlorid (CCL₄)-acetone ( 6: 2.4 v/v ). The system were establish to give compressed spots for both Aspirin and Clopidogrel bisulphate (RₑValue 0.15±0.02, 0.79±0.02 correspondingly)⁶³.

DERM § S et al; (2009) define Express and Exact determination of Clopidogrel in Tablats by exhausting Spectrophotometric and chromatographie techniques. Measureable determination of Clopidogrel was approved by using zero-ordr and derivetive UV-spectroscopy. For calibretion curve calculate of Clopidogrel in 0.1N hydrochloric acid between 0.1-0.8mM (42-336 μg per ml) concentration range and measurement at 267.6, 271.4 and 279.9 nanometer for first derivative, at 269.6, 273.5, 277.4 nanometer for another derivative and at 268.2, 271.4, 275.7 nanometer for third derivative UV spectrophotometry, and use another HPLC method an in isocratic system consisted of analytical column NOVA-Pak C18 and mobil phas consisted of pH 8 phosphete buffer: acetonitrile (30: 70, respectively ) use and flow rate of pump is 0.8 m L per minute & using U V detaction at 210 nanometer⁶⁴.
Reddy et al; (2011), were development and validation of stabilite indecating relative substance technique for Clopidogrel bisulphate drug ingredient by normale phase liquide chromatography, as a normal phase use HPLC method and validation of determination of related substances of clopidogrel bisulphate. Separation of all known impurities from each other and also from Clopidogrel was achieved with in shorter run time, chromatography separation was achieved on a chiral Cel OD-H Colum (250 x 4.6, x 5μ) & use mobil phas ratio 920 ml n-Hexane, 50 ml Ethanol and 30ml of Isopropyl alcohol and 0.3 ml of Diethyl amine and flow rate of pump 0.9 ml per min. and detaction were use at 240 nanometer. The retantion time of Clopidogrel is 20.8 minutes 65.

Rajput S J et al; (2008), developed the Chemo metric Immediate Approximation of Clopidogrel Bisulphate and Aspirin from Collective Dosage Form, in this method twelve mixed solution was equipped for the chemomatrical calibration as exercise usual and 10 mixede solution was prepered as validation sat. The abosbance data matrex were achieved by determining the absorbence at sextenw wavelengths ponts, from 220.0 to 250.0 nanometer with the intermission of two nanometer (Δλ = 2 nanometer). The established calibration was positively tested for laboratory 66.

Game M D et al; (2010), was develop and define the measurable analysisis of Clopidogrel Bisulphate and aspirin through Principal Derivative Spectrophotomaitric Technique in Tablats, the first instruction derivative preoccupation at 232.5 nanometer (ziro cros points of aspirine) were usede for Clopedogrel bisulphat and 211.3 nanometer (zero cros pointe of Clopedogrel bisulphete) for aspirine. Together the drug submited linaerity in the concantration rang of 5.0 μg per m L to 25.0 μg per m L (correletion coeeficient r² <1) 67.
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Patel R B et al; (2008), develop the HPLC and HPTLC method for simultaneous estimation of acetyl salicylic acid and Clopedogrel bisulphat in pur powder and formulation. The liquid chromatography separation was completed on a Neucleosil C8 column (15 cm x 0.46 cm, 5µ) using mobile phase in ratio acetonitrile and phosphete buffer, pH 3.0, 55: 45 v/v, respectively. And movement rate of 1.0 m L per minutes at 25°C temp.. The High pressurethin layer chromatate. separations were done on an aluminum-backd layar of selica gel 60F254 useng ethyle acetete: meoH: toluen: gla. acetic acid (5: 1: 4: 0.1, v/v/v/v) as a mobil phag. Use UV detaction at 235 nanometer over the concentration range 424 g per ml for both drugs 68.

Mitakos A et al; (2002), were developed and validate for the resolve of clopidogrel and achieved on a semi-micro colmn, BDS octaselyl (250 x 2.1 ,5.0 µm) and mobil phas ratio of the mixtre of 0.01 M sodium dihydrogen phosphate adjust the p H is 3.0 and ACN ,3:5: 6.5 v/v, respectively, and pump movement rate 0.3 ml per minutes. detector UV at 235 nanometer. The retention time of clopidogrel and naproxen, which were usd as inner std, was 3.12 and 6.32 minutes, correspondingly 69.

Shin BS et al; 2007 was develop and validate the resolve of Clopidogrl by LC/MS/MS in hnum plasma. Clopedogrel were removed by singl liqued-liqued abstraction with pentane, and meant for separation uses the chromatographic condition column C18. The use of several reaction distinguishing was established on m/z conversion of 322.2→211.9 for Clopedogrel & 264.1→125.1 for ticlopedine as an intrenal std. In this method use the totals analytical run time were comparatively small (3min), and the LLOQ was 10pg/ml by means of 0.5ml of human plasma. The intra.- & intar- day exactitudes was 101.6-108.9 and 98.6-103.6%, correspondingly, and the intra- and inter- period assay precessions was 1.8-5.6 and 4.5-8.2%, correspondingly. These established assay techniques were used for pharmecokinetic studi in humen volunteears behind orale adminestration of Clopedogrel at a quantite of 150.0 miligram 70.
Rao DD et al; 2010 was define and validate approximation stability indecating normal phase liquid chromatography technique for Clopedogrel bisulphete & its contaminations in bulke drug & pharmaceutcal dosage forms. That’s method was indicated the accomplished of separating all the linked substance of Clopedogrel alonge among the chirel imp.. And that process similarly use in determination of assay. For develop method using chiralcael OJ-H 25 cm x 4.6 x5μm colun, and mobil phage ratio was n-Hexane, eth anol, and diethyl amine in ratio 95: 5: 0.05 v/v/v, in that order. The eluted compound was observed at 240 nanometer. Clopidogrel bisulphate were subject to the stresh condition of oxidetive, acid, base, hydrolitec, thermale and photolitic degradetion. The humiliation produc remained wel determined as of main peck & its imp., showing the stabilety representative powar of technique 71.

Sheth A et al; 2012 was developed instantaneous estimate of rosavastetin calcium and Clopedogrel bisulphete since balk and prıtable product useng a validated RP high pressure liquide chromatography method. The seperation of both the drug were acheaved on Nova pak octadesylselane colun (100 mm x 0.39 cm, 4μm) and using movable phage of sodium perchlorete buffer sol’s p H 2.5 and ACN, 650:350 v/v, respectively. And movement rete were 1.0 m L per minute and recognition were prepared at 242.0 nanometer. The retantion time for Rosavastatin ca. was 4.5 minute & Clopedogrel bisulphete were 7.8 minutes. Rosavastatin cal. & Clopedogrel bisulphete indicated a lineare respons in the concentrretion renge of 10-60 microgram per mililiter & 18.75-112.5μg/m L respectevely. The correletion co-efficients for rosavastatin cal. & Clopedogrel bisulphete was 0.9992 and 0.9998 in that order. The percentas recovery obtain for Rosvastatin calc. and Clopedogrel bisulphete range from 99.10 to 100.50 % and 99.1 to 99.6 % respectively72.
Panda SS; 2010 was estimated the Clopidogrele bisulphte and Aspirine through ion-pairing Reverse phage high presre liquid chromatography process, the proposed method using column for separation is a LiChroCart-LiChrospher 100; C18 column 250 x4 x 5.0 micrometer & using movable phas ACN: 0.01M TBAHSs in 50: 50 v/v ratio respectively and movement rate of pump was 1.0 ml per minutes, Quantitition was accomplished withs U V detaction at 240 nanometer. The retention time was 3.16 min. & 5.75 min. for Aspirine and Clopedogrel correspondingly. The linearety range was 1-250µg per m L for aspirine & 0.5-125µg per m L for Clopidogril. The process were validate for accuracy, precesion, lineariti, LOD, LOQ & system suitabilitu 73.

Yarkala S et al; 2012 was analysis the physeco-chemicale studyes on stabilety of Clopidogrele tablet preparations, Clopidogrele is enantio-selective chiral drug and need to be watched for the active form in tablet preparation. Stable tablets preparation was developed for Clopidogrele using two dissimilar disintegrents of LHPC and PVPP XL. Tablet was estimated for constancy analysis using authenticated analyticale methods. The significances displayed similar drug released profil and assay on stabiliti. Clopidogrele R-isomer were detected in both LHPC and PVPP XL contaening tablet preparations and it were establish to be not more than 2.5% after six months stability studies undere acclerarated condition which is imitation of three year storege period 74.

Ramya SSK et al; 2012 was developed and validate the RP-Liquide chromatography process for estimate of amlodepine and Clopedogrele simultaneous balk and dosag form, the seperation and quanfication were achiev by thermo hypersil BDS C18 25 cm x 0.46 cm x 5 µm colmn use and system is isocretic mode, with movable phage containing of buffer-methanol (30: 70 v/v). the pump run rate were use the 1.5 m L per minute. and the detaction were supported available 238 nanometer. The retaining time of amlodipine and Clopidogrele was initiate to be 1.86 and 3.79 minutes, correspondingly. In this process were linearity detected in the conacntration renge of 20-
60 microgram per mL & 300-600 microgram per mL. Calibration curve was linear over study range with correlation co-efficient originate to be 1.00 \(^7\).

**Vanitha M; 2012** was simultaneous determined the aspirin, Clopidogrel and Atorvastatin calcium in capsule dosage form by RP-HPLC, HPLC chromatogram was carried out at 10°C on a 50 x 2.5mm x5 μm equisil ODS column use with isocratic mode and movable phage consiting 0.1 % OPA & ACN (5: 5% v/v) and flowing rate was 1.0 ml per minute. The detection with UV visible detector at 245 nanometer. The retention time were about 1.09, 1.24 and 2.99 min for aspirin, Clopidogrel and atorvastatin, correspondingly. The whole run time were 4 minutes. the technique was lined in the renge of 12-48 μg per ml for aspirin, 12-48 μg per ml Clopidogrel and 3-12 μg per ml for atorvastatin. Limit of detection obtained was 0.03 micro grm./m L for aspirin, 0.06 microgram. per mL for Clopidogrel and 0.07 μg per ml for atorvastatin. The percentage recovery were initiate to be 98.0% for aspirin, 96 % for Clopidogrel and 93.3 % for atorvastatin\(^7\).

**Varun raj V et al; 2010** was estimate the residual solvent in Clopidogrel bisulphate by using chromatography techniques like a gas chromatography, residual solvent in pharmaceutical ‘normally known as organice volatile impurity’ are organic volatile chemicals thet are either used or produced for the duration of the manufacture of active pharmaceutical ingredients, excipieants, and drug productes. Organic solvents such as aceton, ethylacetate, isopropylo alcohol, MeOH, tetrahydrofurane & toluene normally use in pharmaceutcal industri for the developed of dynamic pharmaceutacal ingredients. GMP condition commends to be in charge of adequately the qualities of Active pharmaceutical ingredients. This was the selective gas chromatography process has been established and valideted as per ICHs guidelin for enduring solvent examination in sextine dissimilar APIs. Residual solvent in Active pharma ingradients was observed using gas chromatotography withs flam ionisation detector. The separation were supported obtainable on VB-624 column 300 x 5.3 x 3μm coating thiackness and system GC 17A.
Yamreudeewong W et al; 2011 was developed stability of Clopidogrel in three impromptu compounded Oral liquid provisions, the determination of this study was to estimate Clopidogrel stability in three extemporaneously compounded oral liquid provisions after storage of up to 28 days at room temperature and in the freezer, three groups of Clopidogrel tablets (75-mg/tablets, 4 tablets/set) was triturated independently in a filling to a fine powder. The ended powder was miscellaneous with water, apple juice, and sugar-free syrup, correspondingly, to a last volum of 50 ml for every conventional. The Clopidogrel concentration of the three combinations was 6 mg per ml. the contented of each combination was transferred to four separate 100 ml instruction bottles. Two bottle of each mix were kept at room temperature around 23°C to 25°C. the other two bottle of each combination were deposited in the freezer at a temperature of 4°C to 8°C. after storage periods of 7, 14, 21, and 28 days, sample from all 12 bottles four bottle from each combination were examined in duplicate for Clopidogrel concentration by using stability-indicating high pressure liquide chromatography. Over the time dated of up to 28 days at room temperature and in the freezer, there was no significant reduction of Clopidogrel concentration in all three combinations, except for some test samples of Clopidogrel varied in apple juice that had been deposited in the freezer. The concentration of Clopidogrel was found to be within ±10% of the early concentration in all test examples of the combinations of Clopidogrel in water 78.
Raut DS et al; 2011 was simultaneous estimate the atorvastatin calcium and Clopidogrel bisulphate development by reverse phase high pressure liquide chromatography in pharmaceutical preparation, and separetion was achieve on a C 18 colum 250 x 4.6 x 5μ & consuming mobil phage ratio was ACN: potassium dihydrogen phosphate 0.01 M (7.5: 2.5) and p H 6.1. The flowing rate of pump at 1.0 milliliter per minute, and pump pressure observed 2630 psi. And using detector is UV detector at 240 nanometer. The retantion time obtained of atorvastatin calcium and Clopidogrel bisulphate was just about 3.7 and 10.07 min correspondingly. Atorvastatin and Clopidogrel was recovery values are 100.10+0.31 and 99.92+0.30 correspondingly, and RSD of not more than 2% for the assay and linaerity coefficients of 0.9989.

Agrawal H et al; 2003 was determine the Clopidogrel bisulphate as a balk drugs & method stability indiceting high parform. liquide chromatographi thin layer chometography, use for seperation employe TL chromatographi alumenium plates precoeted with selica gel 60F-254 as the use as a stationery phage. The solvant coordination consist of CCl4-chloroform-aceton in ratio (6: 4: 0.15, v/v/v).that systems was initiate to compacted spots for Clopidogrel bisulphate Rf valu of 0.30+/− 0.01. Clopidogrel bisulphates were subject to acid and alkeli hydrolyses, oxidetion, photo degradation & dry heat treatment. Also the degreded product were separeted from untainted drugs. Densetometric analysise of Clopidogrel bisulphate were accepted out in the absorbence mod at 230 nanometer. The liniar regresseion records for the calibretion plot indicated good liniar relationship with r² is 0.999+/- 0.001 in the concentretn renge of 200-1000 nanogrm. The mean valu of correlation coefficent, slop and intercaptic was 0.999+/- 0.001, 0.093+/-0.022 & 8.83+/-0.99, correspondingly. The limit of detection and quantitition was 41 and 121 nanogrm per spot, correspondingly. The drug undergoe degredation under acidec and basic condetions, oxedation and dri heat treatment.

Vocilkova et al; 2009 was determine the clopidogrel by chromatography method, clopidogrel individual a potent platelete aggregagion inhibetor, are usd broadly
approximately the word to decrease cardiovascular risk in patients with stroke, myocardial infarction, & atherosclerosis. The plan of the review firstli focal point on a comprehensive update of chromatography determination of clopedogrel and its metabolites as well as in human plasma, wister ret plasma, & in pharmaceutical preparations, it have been described using TLCs, HPLCs/MSs, Rev.Phase-HPLC, and GC/MS procedure, secondary to localize the chromatography condition for separation & quantification, thes reviw provides detail information on separation condition for clopidogill & its metabolites. In laboratory condition adjust the new high perf. Liq. Chromat. Procedure was residential for evaulation of assay and puresy of clopedogrel in coated tab.81

Mohan A et al; 2008 were identify the principle of oxid's imp. in cloedogrel drug substance & drugs products, this study focus on the identification and isolation of principle impuriti of clopedogrel whih range starting 0.050 to 0.12 % using highs pressure liquide chromatography technique, this imp. is considerd as principle oxid. impurity as it is observd in oxidation degredation it means stressed studi. Prepartive HPL Chromatographi through xtera M S C 18 ODB colun were used to isolete the imp. The isolatd impueity were co-injected with the sampl containg impurity and establish the relation time competition of the speiked impurity. A through studi were undertoken to characeterize this impuriti & base on ther spectral records U V, M S, M S H 13C, DEPT and 2D NMR) structur were characeterized as 5-[1-(2-chlorophnyl)-2-methoxy-2-oxoethyl]-6,7-dihydrothieno[3,2-c]pyridine-5-iume with a molcular weght 320 amu.82
Belay F et al; 2009 were defined stabiliti-indecating miceller liquide chromatographic procedure for detarmination of clopedogrel, this method show applecation to apply to tab. and cont. unif. test this method applie and prove the simpl stabiliti-indecating, R P micellar liquide chromatographec procedure were devaloped for the analyses of the antiplatelets drugs and were determine the in this method presence of carboxilic acid degredation producte it means stressed condition, namely SR26334, this analysis using column were 15 cm x 0.46 cm and 5 micrometer particle size and column will take C18 column. In this method mobile phase containing used 0.15 M sodium dodicyl sulphete & 10 % n-propenol & 0.3 % triethylamin in 002 M OPA at p H=3.0, and flowing rete of pumpe was 1.0 milliliter/min.,and detector was used U V detector and wavelength 235 nanometer. This method identify the good linearety in the renge of 1 to 20 microgrm./m L with LOD (S/N=3)0.06 microgm. / m L (1.86 x 10⁻⁷M). this author sujest this method fully applieed for the analyses of clopedogrel in balk and comercenal tab. with recovery of 99.62 % ±0.94 %, and 100.27±0.89%. respectively. The pupose procedure were also applieed the determination of clopidogril in the presence of its co-admenestered drug, acetylle salecylace, with with applecation to synthititc mixture & prepered tab.⁸³

Froimovic MM et al; 1997 were defined surfac – secretion won wilebrand factoer medates aggregetion of Adinosine diphasphate-activeted pletelets at modarate, this is previously showed that ADP activation of washed human platelets in plasma-free suspensions support aggregetion at modarate shar stress in poisuiile flood Although most activated platelets expressed maximum fibrinosen –occupied GPII b-IIIa recaptors aggregetion appered to be independent of bounde fibrinogen but blocke by the hexpeptide G R G D S P. In these flow cytometric measurements with monoclonal antibody (mAb) 2.2.9 reporting on surface bound vWF, and withinAb S12reporting on alfa0granule secreted P-selectin, showed that 65% and 80%, respectively, of all plateletswere maximally activated with respect to show maximum secretion and surface expression of these protein.⁸⁴
Mega JL et al; 2009 was determine the cytochrome p-450 polymorphisms and response to clopidogrel requires transformation in to an active metabolite by cytochrom p-450 enzymes for its antiplatelets effect. The genes encoding CYP enzymes is poly-morphic, with the common alleles conferring reduced functions. In these methods show the testing of associate method between functional genetic variants in CY P genes, plasma concentration of active drugs metabolites, and response the platelet inhibition in response to clopedogrel in 162 healthy subjects. We examine the association between the genetic variants & cardiovascular outcomes in a separate cohort of 1475.0 subjects with acute coronary syndrome were treated with clopidogrel in the trial to access improvement in therapeutic outcome by optimising platelet inhibition with prasugrel-thrombolysis in myocardial infarction. 85