ejpmr, 2021,8(12), 160-165

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

AN OVERVIEW –ANALYTICAL METHODS FOR THE ESTIMATION OF FELODIPINE BULK AND IN PHARMACEUTICAL DOSAGE FORM

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Article Received on 11/10/2021 **Article Revised on 01/11/2021** **Article Accepted on 22/11/2021**

ABSTRACT

Felodipine is a medication used in the treatment of hypertension. It belongs to the dihydropyridine (DHP) class of calcium channel blockers. It is widely analysed by HPLC method. Felodipine can be analysed not only in neat solution but also in pharmaceutical products alone and in combination with other products. Felodipine is also used to prevent future heart diseases, heart attacks, angina and strokes. This review discusses the different analytical methods for the estimation of Felodipine. In this review the instruments used are HPLC methods, UV spectrophotometry, HPLC-UV, HPLC-MS, GC-MS, LC-MS, Chiral normal phase liquid chromatography and Electrospray ionization mass spectrometry, Chiral stationary phase chromatography and gas chromatography/mass spectrometry and Ultra sound assisted dispersive liquid-liquid micro extraction coupled with high performance liquid chromatography. A simple and sensitive stability indicating HPLC method was developed and validated for the quantitative determination of Felodipine in the presence of its degradation products, using atenolol as an internal standard. Moreover this review will be useful for further research and studies on felodipine.

KEYWORDS: Felodipine, Calcium channel blocker, Hypertension, Spectroscopy.

INTRODUCTION

Felodipine (Figure -1) is a long acting diester of 4-(2,3-dihydrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid. It is a calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, Felodipine prevents calcium dependent myocyte contraction and vasocontraction. Felodipine is the most potent CCD in use and is unique in that exhibit fluorescent activity. In addition to binding to L- type calcium channel, Felodipine binds to a number of calcium binding proteins, exhibits competitive antagonism of the mineralocorticoid receptor, inhibits the activity of calmodulin- dependent cyclic nucleotide phosphodiesterase, and blocks calcium influx through voltage gated T- type calcium channel. Felodipine is insoluble in water and is freely soluble in dichloromethane and ethanol. Felodipine is a racemic mixture. They are available as tablet formulation containing 2.5 mg, 5 mg or 10 mg of felodipine for oral administration. The brand name of the felodipine is Plendil. The Colour of Felodipine is slightly yellowish crystalline powder. Its molecular weight is 384.26 gm/mol and Chemical formula of Felodipine is $C_{18}H_{19}Cl_2NO_4$.

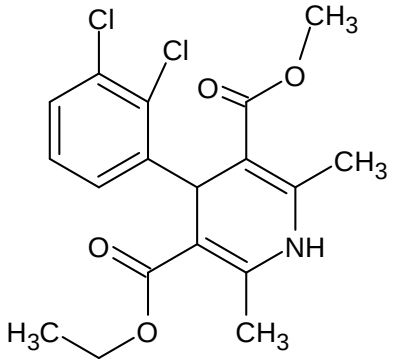

Figure 1: Structure for Felodipine.

Methods of Analysis

Various methods are used for the determination of Felodipine in neat solution and pharmaceutical products. Some of these methods are discussed below which are more rapid and robust. These methods help for the novel approach of Felodipine in future research works.

Spectrometric Methods

Hemalatha M. Nimje *et al.*, reported spectrophotometric analysis for estimation of Felodipine tablet dosage form by calibration curve method. A simple, rapid and accurate spectrophotometric method has been developed for quantitative estimation of Felodipine in bulk and tablet. In methanol Felodipine exhibits absorption at

362.4 nm and method obeys Beer's law at the concentration range of 10-100 µg/ml. The percentage label claim was found in the range of 98-103%. The proposed method was validated statistically and recovery studies.[1]

HPLC

Santhosh Kumar Pasupuleti *et al.,* reported validation, quantitative and qualitative analysis of Felodipine drug using HPLC method. A rapid and reproducible HPLC method has been developed for the estimation of Felodipine in its pure form as well as pharmaceutical dosage forms. Chromatography was carried out on a symmetry C_{18} column (25cm×4.5mm, 5µ), Isocratic elution was carried with the mobile phase Acetonitrile and water (80:20%v/v) at flow rate of 1ml/min. detection was done at 234 nm. The retention time of drug was 3.617 min. Initially a method was developed and partially validated with parameter such as LOD and LOQ, linearity, accuracy and precision etc. Results obtained from the study indicates that the method is showing perfect linearity in the range of 25-200 µg/ml. LOD and LOQ were found to be 0.125 and 1.25 ng/ml respectively.[2]

Salunkhe NH *et al.,* reported validated RP-HPLC method for quantification of Felodipine in Rabbit plasma. An Isocratic elution of samples was performed on capsell pack C_8 DD S5 column (4.6mm × 250mm particle size 5µm) column with mobile phase consisting 5mM phosphate buffer (pH 4.8 adjusted with dilute ortho-phosphoric acid solution): acetonitrile (25:75%v/v) at flow rate of 1.0 ml/min. The detector wavelength was 360nm. A linear response was achieved over the range of 0.25-20.00 µg/ml. LODs and LOQs for Felodipine were found to be 0.055 and 0.201µg/ml respectively.[3]

Bhavana G *et al.,* reported Method development and validation of stability indicating RP-HPLC for the estimation of Felodipine PR tablets RP-HPLC estimation of Felodipine in pharmaceutical tablet dosage form was done with Inertsil ODS C_{18} (100×4.6mm,3µ) using HPLC Shimadzu (2010CHT) instrument with LC solutions software. The suitable wavelength for determination of Felodipine is 238nm. The mobile phase was optimized to buffer: Acetonitrile: Methanol in proportion (2:2:1v/v) respectively. Flow rate 1ml/min. temperature was maintained at ambient. Standard deviation and % RST were calculated and obtained as 0.3% respectively. LOD and LOQ were found to be 0.56 µg/ml, 1.71µg/ml respectively. The percentages Recovery for 50,100,150 % levels are obtained as 98.13%, 99.56%, 98.52% respectively. The percentage degradation results were within the limits and the method was validated.[4]

Sai Chaitanya *et al.,* reported simultaneous HPLC determination of Enalapril and Felodipine in pharmaceutical dosage form. The method is based on HPLC on a reversed -phase column, shim -pack CLC, ODS(C_{18}), 4.6 mm into 25cm and 0.5µm using a mobile phase of ammonium acetate buffer (pH was adjusted to 4.5 ± 0.05 with glacial acetic acid) Acetonitrile and methanol (35:30:35v/v). The buffer used in the mobile phase contains ammonium acetate in double distilled water. The chromatographic conditions are flow rate of 1.5 ml/min, column temperature at 40 and wavelength of 237 nm. The retention times were around 1.5 min for Enalapril and 3.4 min for Felodipine. The method was validated as shown to be linear for Enalapril and Felodipine. The correlation coefficients for Enalapril and Felodipine are 0.999 and 0.999 respectively. The relative standard deviations for six replicate measurements in two sets of each drug in the tablets is always less than 2 % and mean percentage error of active recovery not more than ± 1.5 %. This method was validated for precision and accuracy.[5]

Liandong Hu *et al.,* reported a validated stability indicating HPLC method for the determination of Felodipine and its related substance. A C_{18} column (5µm, 250 × 4.6 mm) was used for the separation at room temperature with Methanol: Acetonitrile: Water (50:15:35 %v/v) as the mobile phase at the flow rate of 1.0 ml/min. the detector wavelength was 238 nm. The method showed good linearity for Felodipine and its related substances with correlation coefficients in the range of 5.05-40.4 µg/ml and 0.312-15.50 µg/ml. method accuracy was assessed for this substance at three levels. The recovery ranged from 98.86 to 101.03%. The intermediate precision was 0.42 % for Felodipine and 1.01 % for the related substances.[6]

Nataraj KS *et al.,* reported method validation and estimation of Felodipine in pure and capsule dosage form by RP-HPLC. A rapid and precise reverse phase HPLC method has been developed for the estimation of Felodipine in its pure form as well as capsule dosage form was carried out on a Inertsil C_{18}, 250×4.6 mm, 5µ using a mixture of phosphate buffer, Acetonitrile and Methanol (40:40:20v/v/v) as the mobile phase at a flow rate of 1.0 ml/min, detection wavelength at 362 nm. Retention time of the drug was 3.34 min. the method produced linear responses in the concentration range of 10-100 µg/ml of Felodipine.[7]

Basaviah K *et al.,* reported determination of Felodipine in bulk drug and in tablets by HPLC. The HPLC determination was carried out on a reversed phase C_{18} (250×4.6 mm) column using a mobile phase consisting of Acetonitrile- 20 Mm aqueous ammonium acetate buffer of pH4.5 (80:20) at a flow rate of 1.0 ml/min. Detection range was 236 nm. Calibration graph was linear from 2.49 to 99.60 µg/ml. Recoveries ranged from 97.80 to 102.10 %. The excipient presents in the tablets did not interfere in the method.[8]

S.NO	Compounds	Methods	Wavelength	Mobile phase	Flow rate	Retention time	Author name
1.	FLD	HPLC	234nm	Acetonitrile: water (80:20v/v)	1ml/min	3.617min	Santosh Kumar Pasupuleti[2]
2.	FLD	RP-HPLC	360nm	Phosphate buffer: Acetonitrile (25:75v/v)	1ml/min	_____	N H Salunkhe et al[3]
3.	FLD	RP-HPLC	238nm	Buffer: Acetonitrile: Methanol (2:2:1v/v)	1ml/min	_____	Bhavana G[4]
4.	FLD+ Enalapril	HPLC	237nm	Buffer: Acetonitrile: Methanol (35:30:35v/v)	1.5ml/min	1.5 min for enalapril and 3.4 min for FLD	Sai Chaitanya[5]
5.	FLD	HPLC	238nm	Methanol: Acetonitrile: Water (50:15:35%v/v)	1ml/min	_____	Liandong Hu[6]
6.	FLD	RP-HPLC	362nm	Phosphate buffer: Acetonitrile: Methanol (40:40:20v/v/v)	1ml/min	3.34±25mins	Nataraj K S[7].
7.	FLD	HPLC	236nm	Acetonitrile: Aqueous ammonium acetate buffer (80:20v/v)	1ml/min	_____	K Basaviah[8].
8.	FLD	HPLC	240 nm and 440nm	Sodium dodecyl sulphate: Phosphate buffer: Pentanol	_____	_____	Sahar Zayed[9]
9.	FLD	Protein Binding study using HPLC	230nm	Methanol: Acetonitrile(50:50v/v)	1ml/min	10mins	Swarna Vijitha[10]

Sahar Zayed et al., reported Micellar liquid chromatographic determination of Felodipine in tablets and human plasma with fluorescence detection: application to stability studies and content uniformity testing. The separation was performed on a C_{18} column using a Micellar mobile phase consisting of 85 Mm sodium dodecyl sulphate, 25 Mm phosphate buffer and 6.5% pentanol at pH7. Fluorescence detection set at 240 nm (excitation) and 440 nm (emission) was used. A good linear response was achieved in the range of 0.05-15 µg/ml, with a lower detection limit (LOD) of 0.011µg/ml and a quantification limit (LOQ) of 0.032µg/ml. This method was successfully applied for the analysis of FLP in its commercial tablets, with a mean percentage recovery value of 100.69± 0.24%. This method was extended to the in-vitro determination FLP in spiked human plasma samples with mean percentage recovery of 99.62 ± 0.51 %[9]

Swarna Vijitha *et al.*, described protein binding study of Felodipine using validated chromatographic method. The separation was carried on HPLC system consisting C_{18} column (150 mm X 4.6nm, 5 µm) at room temperature coupled with a phenomenix column silica with flow rate 1 ml/min. The mobile phase used was Methanol: Acetonitrile in the ratio of 50:50. The drug was detected using the wavelength of 230 nm and run time was 10 mins.[10]

UV

Santhosh S Chhajed *et al.*, reported development and validation of UV spectrometric method for estimation of Felodipine using green solvent in tablet formulation. This method is developed at wavelength of maximum absorbance 363.5nm. The relative absorbance of the drug found to be proportional to the drug concentration in the linear ranges of 5-50 µg/ml for Felodipine. The performance of the developed method was evaluated in terms of standard deviation and relative standard deviation to find out the significance of proposed methods over the reference spectrophotometric method.[11]

Pandey MM *et al.*, reported determination of pKa of Felodipine using UV- visible spectroscopy. For the first time, experimental pKa value of Felodipine was reported. Dissociation constant, pKa is one of the very important physiochemical properties of drug. The method used for the pKa determination of Felodipine was essentially a UV- Visible spectrophotometric method. The pKa of Felodipine was found to be 5.07. Ruggedness of the determined value is also validated in this study in order to produce exact value pKa of Felodipine.[12]

Rajesh K *et al.*, reported simultaneous estimation of Atorvastatin calcium and Felodipine by UV-Spectrophotometric method in formulation. The estimation of Atorvastatin calcium was carried out at wavelength of 241 nm, while Felodipine was estimated

as single component at 366.5 nm. The linearity range was 2-10 µg/ml for each Atorvastatin calcium and Felodipine.[13]

HPLC AND UV

Fusun Gedil *et al.,* reported Quantitative determination of Felodipine in pharmaceuticals by HPLC and UV spectroscopy. Felodipine was determined by isocratic system using methanol-0.55M phosphate buffer (83:17v/v pH is 3±0.1) as mobile phase. Disulfiram was chosen as an internal standard. Detection was carried out with UV detection at 275 nm.[14]

HPLC- MS

Luis H Miglioranca *et al.,* reported felodipine quantification in human plasma by High performance liquid chromatography coupled with tandem mass spectrometry using Nemodipine as internal standard Felodipine was extracted from 0.5 ml human plasma by use of a liquid/liquid procedure using diethyl ether/hexane (80:20v/v) as eluent. The chromatographic run of 5 min using a C18 column (100 mm × 4.6 mm), linearity over the range from 0.02 to 10 ng/ml. the between –run precision determined as relative standard deviation of replicate quality control was 5.7% (0.06ng/ml), 7.1%(0.6ng/ml) and 6.8% (7.5ng/ml) the between run accuracy was ± 0.0, 2.1 and 3.1% for the above mentioned concentrations respectively.[15]

CHIRAL NORMAL PHASE LIQUID CHROMATOGRAPY AND ELECTROSPRY IONISATION MASS SPECTROMETRY

Bo Lindmark et al., reported enantioselective determination of felodipine in human plasma by chiral normal-phased liquid chromatography and electrospray ionisation mass spectrometry. Felodipine was extracted from plasma using toluene as extraction solvent. The enantiomers were separated on a cellulose tris (4-methyl benzoate) stationary phase (chiracel OJ-R) using 2-propanol-iso-hexane (11:89) as a mobile phase. Post-column addition of ammonium adducts by electrospray ionisation and selected reaction monitoring. Deuterated felodipine racemate was used as internal standard. Within-run repeatability was determined and coefficient of variation below 10% was achieved at 22 nmol/l and below 10% at 0.27nmol/l. between-day precision was evaluated and coefficient of variation of 3.6% at 4 nmol/l plasma was obtained. Limit of LOQ was set at 0.25nmol/l (0.10µg/l).[16]

GC-MS

Dru JD *et al.*, reported determination of felodipine, its enantiomers, and a pyridine metabolite in human plasma by capillary gas chromatography with mass spectrometric detection. Sensitive methods based on capillary gas chromatography with mass spectrometric detection in a selected-ion monitoring mode (SIM) for the determination of racemic felodipine, its enantiomers and a pyridine metabolite in human plasma are described. Liquid- liquid extraction from plasma, enantiomers of felodipine was separated on a chiral HPLC column (chiralcel OJ) and fractions containing each isomer were collected on a continuous basis using a fraction collector. These fractions were later analysed by GC-MS-SIM. The limits of quantitation in plasma were 0.1ng/ml for both the R (+) and S (−) enantiomers of felodipine and 0.5ng/ml for both racemic felodipine and its pyridine metabolite.[17]

CHIRAL STATIONARY PHASE CHROMATOGRAPHY AND GAS CHROMATOGRAPHY/MASS SPECTROMETRY

Sakamoto T *et al.,* reported determination of felodipine enantiomers using chiral stationary phase chromatography and gas chromatography/mass spectrometry. The study of their pharmacokinetic profiles was done in human and dog. This method has been developed and the pharmacokinetic profiles of the enantiomers comparatively studied after oral administration to dogs and humans. D6-Felodipine, the internal standard, was added to the plasma, extracted with a solvent. Each enantiomer in the effluent was analysed by capillary column gas chromatography/positive ion electron mass spectrometry. After oral administration of the felodipine racemate, the Tmax and $t_{1/2}$ values hardly differed between the two enantiomers in dogs and humans. The Cmax and AUC0-24 h values pf the S (−) enantiomer were slightly higher than those of the R (+) enantiomer in humans but the difference between the enantiomers was not significant. These results suggested that there is no large difference in the absorption, distribution and elimination of felodipine enantiomers after oral administration of the racemate in either dog or human.[18]

LC - MS

Sreedevi V *et al.,* LC-MS Method development and validation for the determination of felodipine in human plasma and stability studies of freeze thaw analyte. The separation was carried out on Princeton SPHER C_{18} (150×4.6mm) as stationary phase, mobile phase was acetonitrile: 2 mM ammonium acetate elution mode: isocratic A: B - 80:20%v/v. flow rate: 0.8ml/min using SPD M-10AVP photo diode array detector at 38.10nm. Linearity concentration range of 0.8-13.0 ng/ml. Pantoprazole was used as internal standard. The felodipine and pantoprazole showed retention factor of 2.97 respectively. The LOD and LOQ of felodipine was 0.10ng/ml,0.50ng/ml and for pantoprazole 0.06,0.21ng/ml respectively. The stability of the drug spiked human plasma samples during three freeze thaw cycles were stable in plasma for about one month when stored at frozen state.[19]

HPTLC AND RP- HPTLC

Jain PS *et al.,* HPTLC and RP-HPTLC method development and validation for the estimation of felodipine in bulk and pharmaceutical formulation. Chromatographic separation was performed on pre-coated aluminium plates with 250 µm layer of silica gel

60 F_{254} and silica gel 60RP-18 TLC $F_{254}S$ using toluene: methanol (8:2%v/v) and acetonitrile: water: glacial acetic acid (8:2:1% v/v/v) as a mobile phase, respectively. Scanning was carried out densitometrically at 237nm. The Rf value of felodipine in HPTLC and RP-HPTLC were 0.40 and 0.53 and the reliability of the method was assessed by the evaluation of linearity which was found to be 300-1800 and 500-3000ng/band with the r^2=0.998 correlation coefficient along with the accuracy of the method in terms of % recovery was found to be from 98-101± 1.04% and 99-100± 0.47% and the limit of detection and quantification were 11.51, 34.90 and 29.90, 90.61 respectively.[20]

ULTRA SOUND ASSISTED DISPERSIVE LIQUID-LIQUID MICRO EXTRACTION COUPLED WITH HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Sameh Ahmed *et al.,* Ultra sound assisted dispersive liquid-liquid micro extraction coupled with high performance liquid chromatography designated for bioavailability studies of Felodipine combination in rat plasma. In this method photodiode array detector was developed and validated for the simultaneous determination of FLD, MET and RAM in rat plasma after oral administration of these combinations. The factors affecting UA-DLLME were carefully optimized. In this study, UA-DLLME method could provide simple and efficient plasma extraction procedures with superior recovery results. Under optimum condition, all target drugs were separated within 13mins. Linear calibration ranges were obtained in the range 0.05-2.0 µg/ml for FLD and MET and 0.1-2.0 µg/ml for RAM with detection limits of 0.013-0.031µg/ml for all the studied drug combinations. The percentage RSD for inter-day and intra-day precisions was in the range of 0.63-3.85 % and accuracy results were in the range of 92.13-100.5 %.[21]

CONCLUSION

The different analytical methods available for the estimation of the felodipine have been summed up in the article providing the knowledge of the analysis which can be utilized for the determination of Felodipine. This review article has provided evidence which supports the role of Felodipine as an agent which can reduce the risk of hypertension and heart diseases. From this review, it is concluded that the different analytical methods are used for determination, validation and estimation of felodipine, to determine its bioavailability. Felodipine has been determined using different instruments like HPLC, HPTLC, LC-MS, Spectrometers, Capillary gas chromatography-MS, Ultra sound assisted dispersive liquid-liquid micro extraction with HPLC. Development and validation of UV Spectrometric method are for estimation of felodipine using green solvent in tablet formulation, while hyphenated LC-MS, HPTLC-MS methods are used for determination of felodipine in human plasma and estimation of felodipine in bulk and pharmaceutical formulation. Further methods were reported for its pharmacokinetic studies. Few chromatography methodologies like HPTLC, HPLC and stability studies carried out using LC-MS are also reported in the review. The above mentioned methods are useful in the development and novel approach of Felodipine in further research activities.

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