International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 6, 2023

Review Article

FELODIPINE-REVIEW OF ANALYTICAL METHODS DEVELOPED FOR PHARMACEUTICAL DOSAGE FORMS AND BIOLOGICAL FLUIDS

KIRAN MALLI[1], LALIT KUMAR[2], RUCHI VERMA[1*]

[1]Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal-576104, Udupi, Karnataka, India. [2]Department of Pharmaceutics, National Institute of Pharmaceutical Education, Hajipur-844102, Vaishali, Bihar, India

[*]Email: ruchiverma.pharma@gmail.com

Received: 23 Aug 2023, Revised and Accepted: 09 Oct 2023

ABSTRACT

Felodipine (FDP) is a vascular selective L-type calcium channel blocker, in hypertension patients FDP significantly lowers systolic and diastolic blood pressure (BP). It is a lipophilic drug molecule that contains a dihydropyridine ring responsible to show pharmacological activity, it is mainly used to control and prevent essential hypertension. This review article provides a summary of various analytical techniques for determining felodipine in pure form, pharmaceutical formulations, and biological fluids. Various analytical techniques are developed and validated, such as ultraviolet/visible spectrophotometry, high-performance liquid chromatography (HPLC), high-performance thin layer chromatography (HPTLC), and bioanalytical techniques. Estimated validation parameters such as linearity, LOD (Limit of Detection), and LOQ (Limit of Quantification) are discussed for each method. The wavelength of detection (λmax), mobile phase, columns, flow rate, retention time (Rt) and sample preparation techniques are all important quality elements for calculating Felodipine via analytical procedures.

Keywords: Felodipine, Analytical methods, Pharmaceutical dosage forms, Biological fluids

DOI: https://dx.doi.org/10.22159/ijap.2023v15i6.49211. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Hypertension is one of the main risk factors for atherosclerosis and other life-threatening cardiovascular diseases. Calcium channel blockers are categorised chemically into three groups: benzothiazepines, dihydropyridines, and phenylalkylamines [1]. Chemically FDP is ethyl methyl (4RS)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5 dicarboxylate produces antihypertensive activity due to the presence of dihydropyridine ring [2]. Belongs to the class of dihydropyridine and is chemically similar to nifedipine, nimodipine, nisoldipine, nicardipine and nitrendipine. FDP suppresses contractile responses to calcium in potassium-depolarized tissue in cardiac and smooth muscle at therapeutic doses. Contraction of cardiac muscles takes place by binding of calcium to calmodulin protein, which results in the activation of myosin light-chain kinase (MLCK), which causes heart muscle contraction. Myosin light chain is phosphorylated by activated MLCK, causing myosin head attachment to act in, which causes smooth muscle contraction and vasoconstriction. FDP acts by binding to calmodulin protein, hence prevents calcium-calmodulin interaction [3]. Dilation of peripheral arterioles is the primary effect of FDP. *In vitro* researches revealed that selectivity is more for vascular smooth muscle than myocardial muscle when compared to nifedipine or verapamil [4]. Felodipine does not cause orthostatic hypotension because it has no effect on venous smooth muscle in clinical doses [5]. FDP also have natriuretic and diuretic property as it has direct action on tubular reabsorption and thus prevents retention of salt and water and hence lowers blood pressure and increased cardiac output [6]. FDP does not appear to have a significant effect on glomerular filtration rate (GFR), creatinine clearance, glucose tolerance, or plasma lipoprotein concentrations in hypertensive patients [3].

Felodipine (FDP) belongs to the class of dihydropyridine calcium antagonist and it is lipophilic in nature. According to research, once-daily use of an extended-release (ER) formulation is equivalent to twice-daily administration of conventional tablets in terms of antihypertensive efficacy. At the therapeutic dose, in patients with congestive heart failure (CHF), FDP seemed to have no negative inotropic effect but it might slightly increase myocardial contractility [3, 4]. FDP gets absorbed in GI tract rapidly and completely when given as an oral solution and reaches peak plasma concentration after 15-90 min (tmax) of administration. It Takes 1h to 2h when administered as plain tablet. It takes 3h to 5h to attain peak plasma concentration when administered as an extended-release tablet. Only about 15% of the drug reaches systemic circulation due to first-pass metabolism. FDP is highly distributed to extravascular tissue. FDP has a volume of distribution of about 10.3L/Kg, which signifies that less than 1% of the drug is concentrated in the blood. Plasma protein binding was found to be 99.64% [7]. FDP gets metabolized in the liver by Cytochrome P-450-dependent oxidation to its pyridine analogue [8]. Small amount of the drug gets excreted in the urine in its unchanged form. The elimination phase of FDP plasma drug concentration-time curve, which begins 8 to 10 h after administration, reflects the drug's elimination [9]. FDP is an orally administered drug, available as extended-release tablets with the strength 2.5 mg 5 mg and 10 mg in the market. FDP can be estimated using a wide range of analytical techniques in formulations and biological samples.

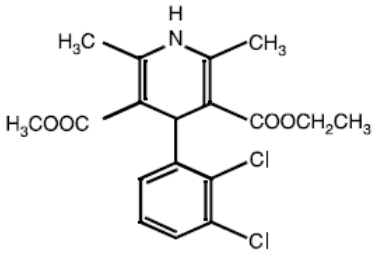

Fig. 1: Structure of felodipine

Molecular formula C18H19Cl2 NO4 and molecular weight t 384.254 g/mol [2]. Felodipine USP is a crystalline powder that is light yellow to yellow in colour. It is insoluble in water but freely soluble in dichloromethane and ethanol. FDP is a highly lipophilic neutral molecule within normal pH range. The partition coefficient of FDP is about 30000 between toluene and water.

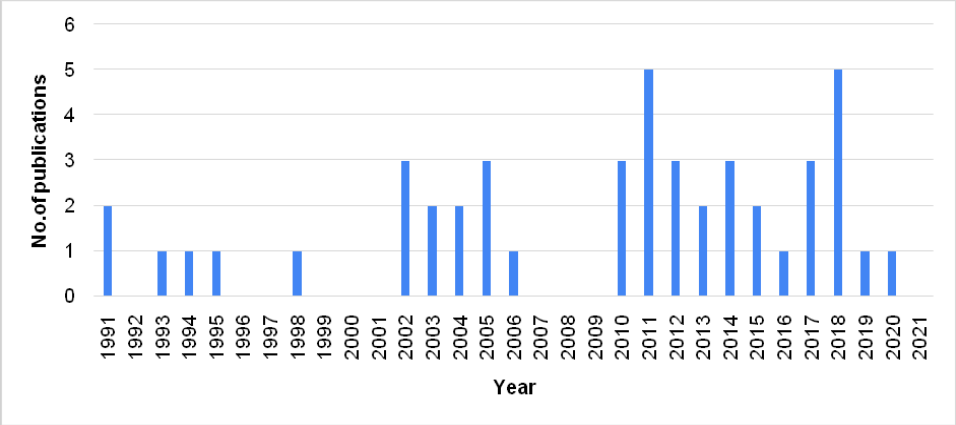

Fig. 2: Number of publications from 1991 to 2021 for quantification of FDP
Database sources: Scopus, Springer, Web of Science

Fig. 2 shows the number of papers published from the year 1991 to 2020. The literature was obtained from various databases i.e. science direct, scopus, taylorand francis, web of sciences, Elsevier, springer, pubmed. The data collected was from 1991-2021. Among all these, year's highest number of papers were published in the year 2010 and 2018.

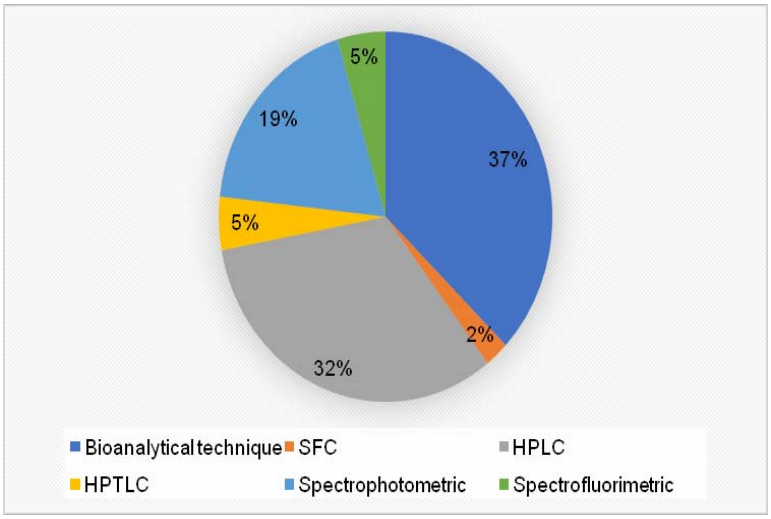

Fig. 3: An outlook of various analytical methods proposed for estimation of FDP

Fig. 3 is the statistical pie diagram representing various analytical techniques proposed for the estimation of LAC. It shows that HPLC and LC/MS/MS, GC/MS are the most widely used chromatographic technique for the estimation of FDP in API, formulations and in biological fluids, respectively.

Spectroscopic techniques

Ultra-violet visible spectrophotometric technique

UV/vis spectrophotometry is a quick, easy, and sensitive approach for detecting and quantifying FDP based on UV absorption and chemical interactions. This method is cost-saving, accurate and precise for the routine analysis of the FDP in tablet dosage form. Table 1 represents the various spectrophotometric methods for determining and estimating FDP in pharmaceuticals, formulations, bulk pharmaceuticals as a whole and in combination with other drugs.

Spectrofluorimetric methods

The spectrofluorimetric methods are also used to estimate FDP in tablet dosage forms, in addition to the UV-visible spectrophotometric techniques. The spectrofluorimetric techniques are used because they are highly selective, sensitive, simple to operate, and cost-effective. Mohamed AM and his colleagues developed micelle-enhanced spectrofluorimetric techniques to determine FDP and Nimodipine in formulations and human plasma, and the sample was treated with 2% Tween-80 solution. Using tween-80, fluorescence intensity was measured at 423 nm after getting excited at 385 nm. In the range of 0.05-4.0 g/ml, the standard fluorescence–concentration curve was found to be linear. For the reported linearity range LOD and LOQ were found to be 2-0.02µg/ml and 2-0.05µg/ml respectively [10]. Table 1 represents the spectrofluorimetric methods for determining and estimating FDP in pharmaceuticals, formulations and in biological matrix.

Chromatographic methods

HPTLC

For the quantitative determination of felodipine in solid dosage form and in bulk, simple, precise, and sensitive HPTLC and RP-HPTLC methods have been developed and were validated as per ICH. These techniques can be used to analyse Felodipine in bulk and pharmaceutical preparations on a regular basis [21, 22]. Table 2 represents the HPTLC methods for determining and estimating FDP in pharmaceuticals, formulations.

Table 1: Spectrofluorimetric and spectrofluorometric methods for determining and estimating FDP in pharmaceuticals, formulations and in biological matrix

Method	Drug	Matrix	Diluent	Wavelength (nm)	Linearity (µg/ml)	LOD	LOQ	Ref.
Spectrophotometric	FDP	Tablet	Ethanol	363.5	5-50	NA	NA	[11]
Spectrofluorometric	FDP	Tablet/Plasma	Method 1-Methanol (MeOH), Method 2-2% Tween-80 and distilled water	λem Method 1-426 nm, Method 2-423 nm λex Method 1and2-385 nm	Method 1-0.2–3.0µg/ml, Method 2-0.05-4.0 µg/ml	Method 1-0.04µg/ml, Method 2-0.02µg/ml	Method 1-0.12µg/ml, Method 2-0.05µg/ml	[10]
Spectrofluorometric	FDP	Tablet	Methanol	375 nm	0.2-2 µg/ml	0.02 µg/ml	0.06 µg/ml	[12]
Spectrophotometric	FDP	Tablet	Water	760 nm	1.5-5.0 µg/ml	NA	NA	[13]
Spectrophotometric	FDP	Tablet	Solvent A-acetonitrile (ACN)-distilled water (70: 30), Solvent B-0.1 N HCl, phosphate buffer pH 6.8 and water-ACN (70: 30 v/v)	268 nm, 245 nm	2 to 12 µg/ml	NA	NA	[14]
Spectrophotometric	FDP	Tablet	Methanol and 0.1N HCl in 1:9 ratio	366.5 nm	3 to 10 µg/ml	NA	NA	[15]
Spectrophotometric	FDP	API and Formulation	MeOH	237 nm	2-18 µg/ml	0.265	0.8835	[16]
Spectrophotometric	FDP	Tablet	MeOH	BTB-420 nm, BCP-415 nm	BTB: 5.0-25.0µg/ml, BCP: 4.0-20.0µg/ml	NA	NA	[17]
Spectrophotometric	FDP	Tablet	MeOH	234 nm and 360 nm	4-24µg/ml and 8-60µg/ml	2µg/ml and 2.5µg/ml	1µg/ml and 5µg/ml	[18]
Spectrophotometric	FDP	API and tablet	MeOH	326.4 nm	10-100 µg/ml	NA	NA	[19]
Spectrophotometric	FDP	API and tablet	Method B (Methyl Orange)-Water, Method C (Indigo Carmine)-Water	Method B-520 nm, Method C-610 nm	Method B: 0.12–0.87µg/ml, Method C: 0.5–6.0µg/ml	Method B: 0.013µg/ml, Method C: 0.09µg/ml	Method B: 0.044µg/ml, Method C: 0.32µg/ml	[20]

FDP: Felodipine, NA: Not available, MeOH: Methanol, ACN: Acetonitrile, HCl: Hydrochloric acid

Table 2: HPTLC methods for determining and estimating FDP in API and tablets

Method	Drug	Matrix	Stationary phase	Mobile phase	Rf	Wavelength	Linearity	LOD and LOQ	Ref.
HPTLC	FDP	Tablet	Precoated aluminium plates with silica gel 60 F254	n-hexane: ethyl acetate 6: 4 (v/v)	0.53±0.027	366 nm	NA	23.54ng/spot and 71.33 ng/spot	[21]
HPTLC	FDP	API and formulation	Pre-coated aluminium plates with 250 µm layer of Silica gel 60 F254(NP), Silica gel 60 RP-18 TLC F254S(RP)	Toluene: Methanol (8:2 v/v) (NP), acetonitrile: water: glacial acetic acid (8:2:1 v/v/v)(RP)	0.40(RP), 0.53(RP)	237 nm	300-1800 and 500-3000 ng/band	11.51(NP), 34.90(RP) and 29.90(NP), 90.61(RP)	[22]

FDP: Felodipine, NA: Not available, RP: Reverse phase, NP: Normal phase

High-performance liquid chromatography

HPLC is a simple and sensitive method for estimating and measuring FDP in the presence of impurities, employing a simple mobile phase and minimal amounts of samples, and it has been validated in terms of accuracy, precision, stability, sensitivity, specificity, and robustness.

Ultra-performance liquid chromatography

Ultra-high-performance liquid chromatography (UPLC) is a more efficient and effective method for determining FDP. To identify and quantify FDP, its impurities, and degradation products, simple and accurate RP-UPLC methods are developed. Table 3 represents the HPLC/UPLC methods for the determination and estimation FDP in pharmaceutical, formulations.

Biological matrices

For the determination and quantification of FDP in biological matrices, various bioanalytical methods have been developed. Bioanalytical methods are useful for identifying and quantifying drugs and their metabolites in biological matrices, which helps in drug evaluation of bioequivalence, pharmacokinetics, and pharmacodynamic studies [23]. Various analytical approaches have been developed, including hyphenated techniques for estimating FDP as a single entity and in combination, which requires less time. Table 4 represents various analytical methods for determining and estimating FDP in biological matrix (serum and plasma).

Table 3: HPLC methods for determining and estimating FDP in API and pharmaceutical formulations

Method	Drug	Matrix	Sample preparation	Mobile phase	Flow rate	Column	Detection	Linearity	LOD and LOQ	Rt (min)	Ref.
SFC/UV, LC/UV	FDP	Tablet	NA	6% (v/v) MeOH-modified CO2, CAN-MeOH0.05 M Potassium phosphate buffer (40:20:40, v/v/v)	2 ml/min	Hypersil Silica (25 cm * 4.6 mm * 5 µm)	254 nm	NA	NA	<6 min	[24]
HPLC-fluorescence detection	FDP	Tablet	Pulverisation	25 mmol of sodium dihydrogen phosphate and 85 mmol of sodium dodecylsulfate with 6.5% v/v pentanol	1.5 ml/min	CLC-C18 (250 mm * 4.6 mm * 5 µm)	240 nm (excitation) 440 nm (emission)	0.05–15 mg/ml	0.011 mg/ml and 0.032 mg/ml	NA	[25]

Method	Drug	Matrix	Sample preparation	Mobile phase	Flow rate	Column	Detection	Linearity	LOD and LOQ	Rt (min)	Ref.
HPLC	FDP	Tablet	Trituration	Methanol–potassium dihydrogen orthophosphate (75:25, v/v).	1.5 ml/min	LiChroCART (250 mm * 4 mm * 5.0 µm)	238 nm	1–7 µg/ml	150ng/ml and 500ng/ml	NA	[26]
HPLC	FDP	Tablet	Trituration	Potassium di-hydrogen phosphate: MeOH: ACN 15:15:70 (v/v/v)	1.5 ml/min	Hyperchom C18 (250 × 4.6 mm, 5.0 µm)	210 nm	5-80 µg/ml	1.21 µg/ml	NA	[27]
HPLC	FDP	Tablet	NA	Buffer: ACN: MeOH (2:2:1 v/v)	1 ml/min	Inertsil ODS _2 C_18 (100 × 4.6 mm, 3.0 µm)	238 nm	NA	1.71µg/ml	NA	[28]
HPLC	FDP	Tablet	NA	ACN: water (70:30 v/v)	1 ml/min	KYA TECH HiQ Sil C18HS (250 mm x 4.6 mm, 5.0 µm)	238 nm	5-30 µg/ml	0.12µg/ml and 0.36µg/ml	11.46 min	[29]
HPLC	FDP	API and tablet	NA	ACN: water(70:3v/v)	1 ml/min	Phenomenex C-18 (150 mm x 4.6 mm, 5.0 µm)	238 nm	2-10 µg/ml	0.000665µg/ml and 0.002014µg/ml	8.29 min	[30]
HPLC	FDP	Tablet	Dilution	ACN–0.01 M KH2 PO4	1.5 ml/min	JASCO-metaphase ODS (25034.0 mm) 5.0 µm column	250 nm	25–3200 ng/ml	NA	12.20 min	[31]
HPLC	FDP	API	NA	Acetonitrile: Methanol: Phosphate buffer (40:20:30v/v)	1.0 ml/min	Lichrocart C18 (150 ×4.6 mm, 5.0 µm)	326 nm	NA	4.5ng/ml	NA	[32]
HPLC	FDP	Tablet	NA	ACN: Water (80:20 V/V)	1.0 ml/min	ODS C18 (4.6 x 150 mm, 5.0 µm)	305 nm	15-75 µg/ml	0.19µg/ml and 0.6µg/ml	NA	[33]
HPLC	FDP	Tablet	NA	ACN: water (80:20 v/v)	1.0 ml/min	Symmetry C18 (25 cm × 4.5 mm, 5.0 µm)	234 nm	25 to 200 µg/ml	0.125 ng/ml and 1.25 ng/ml	NA	[34]
HPLC	FDP	API	NA	Methanol: acetonitrile: water (50:15:35%, v/v/v)	1.0 ml/min	C18 (5µm, 250 ×4.6 mm)	238 nm	5.05-40.4µg/ml	1ng and 4ng	6.5 min	[35]
HPLC	FDP	Tablet	Trituration	Phosphate buffer: acetonitrile (20:80v/v)	1.2 ml/min	C18 Zorbax (250 mm × 4.6 mm, 5.0 µm)	234 nm	0.1–150 µg/ml	0.0279µg/ml and 0.0852 µg/ml	2.51 min	[36]
HPLC	FDP	Tablet	Trituration	Acetonitrile-20 mmol aqueous ammonium acetate (80:20v/v)	1.0 ml/min	RP C18 (250x4.6 mm i. d)	236 nm	2.49 to 99.60 µg/ml	0.6µg/ml and 1.60µg/ml	NA	[37]
HPLC	FDP	Tablet	Trituration	MeOH-0.055M phosphate buffer (83:17 v/v)	0.7 ml/min	Luna C18 (250x4.6 mm, 5µ)	275 nm	2-20µg/ml	0.4µg/ml and 1µg/ml	12.52 min	[18]
HPLC	FDP	Agglomerates	NA	MeOH 0.055 M phosphate buffer (83:17v/v)	0.8 ml/min	HIQ Sil C 18 HS 4.6 mm×250 mm	232 nm	10-60µg/ml	0.8891µg/ml and 1.42758µg/ml	NA	[38]
HPLC	FDP	Tablet	NA	0.02 mmol Ammonium acetate and acetonitrile (55:45, v/v)	0.7 ml/min	Phenomenex Gemini C18 (150 × 2.0 mm, 5.0 µm)	240 nm	0.2-8.0 µg/ml	0.05µg/ml and 0.15 µg/ml	NA	[2]

Table 4: Various methods for determining and estimating FDP in biological matrix (serum and plasma)

Method	Drug	Matrix	Sample preparation	Mobile phase	Flow rate	Column	Detection	Linearity	LOD and LOQ	Rt (min)	Ref.
HPLC	FDP	Plasma	Ultrasound assisted dispersive liquid-liquid micro extraction	10 mmol phosphate buffer pH= 3.0, ACN (50:50; v/v)	1.0 ml/min	Thermo BDS Hypersil C18 column (4.6 mm × 150 mm, 5.0 µm)	NA	0.05–2µg/ml	0.013-0.031 µg/ml and 0.043-0.103 µg/ml	13 min	[39]
HPLC, GC/MS	FDP	Plasma	Frozen	n-hexane: isopropanol (5:l v/v), Helium	NA	Chiralcel OJ column (4.6 mm x 250 mm), JEOL JMS-Dx-300, Hewlett Packard 0.20 mm x 12.5 m, UI	240 nm, mlz 238	0.05-10.00 ng/ml	0.05ng/ml	NA	[40]
GC/MS	FDP	Plasma	Liquid-liquid extraction	Helium, n-hexane-isopropanol (88:12 v/v)	0.365 ml/min	GC column (30 m* 0.2 mm0.5 µm) Chiralcel OJ (250 x 4.6 mm 10 µm)	240 nm	NA	0.1 ng/ml	13 min	[41]
LC–ESI–MS–MS	FDP	Plasma	Liquid–Liquid Extraction	1 mmol ammonium acetate–ACN, 20:80 (v/v)	200 µl/min	C8 Capcell Pak (2.0 mm150 mm5.0 µm)	NA	NA	0.05 ng/ml	NA	[42]
LC/MS	FDP	Plasma	Solid phase extraction	Solvent A (0.1% Formic acid with 1 mmol Ammonium formate) solvent B (ACN/0.1% formic acid with 1 mmol ammonium formate, (95:5v/v)		Luna RP-C18 (15 mm * 3.2 mm, 3.0 µm)	NA	NA	<1 ng/ml	NA	[43]
HPLC/MS	FDP	Plasma	Liquid liquid extraction	ACN: water (80:20v/v, 10 mmol of formic acid)	0.80 ml/min	C8 (100 mm × 4.6 mm, 3 µm)	NA	0.02 to 10 ng/ml	20pg/ml	NA	[1]

Method	Drug	Matrix	Sample preparation	Mobile phase	Flow rate	Column	Detection	Linearity	LOD and LOQ	Rt (min)	Ref.
HPLC-MS/MS	FDP	Plasma	Frozen	ACN and 0.1 % formic acid (75:25, v/v)	0.25 ml/min	C18 (3.0 mm, 150 mm; 3.5 µm)	NA	0.1 to 20 ng/ml	0.1ng/ml	NA	[44]
LC-ESI-MS	FDP	Plasma	Toluene	2-propanol–iso-hexane (11:89, v/v)	1 ml/min	Chiralcel OJ-R (150 mm×4.5 mm, 5.0 µm)	NA	NA	0.10ng/ml	NA	[45]
HPLC-MS/MS	FDP	Plasma	Solid phase extraction	0.1% formic acid-methanol	1 ml/min	Zorbax Eclipse XDB-C18 (150 mm 4.6 mm3.5 µm)	NA	0.1 to 5 ng/ml	0.1ng/ml	NA	[46]
LC-ESI-MS/MS	FDP	Plasma	Liquid–liquid extraction	0.2% formic acid in water–acetonitrile (25:75, v/v)		Atlantis C18 (50* 4.6 mm 3 µm)	NA	0.59–1148ng/ml	NA	1.05 min	[47]
HPLC-MS/MS	FDP	Plasma	Liquid–liquid extraction	MeOH-10 mmol/l ammonium acetate (80: 20v/v)	0.70 ml/min	Nucleosil C (50 mm x 4.6 mm5 µm)	NA	0.05-10.00 ng/ml	0.05ng/ml	NA	[48]
GC-ECD/GCMS	FDP	Plasma	Solid phase extraction	Helium	40 ml/min	GC-ECD ULBON HR-52 (25 m x 0.32 mm.) GCMS-Hewlett-Packard HP-1 (12 m x 0.20 mm.)	NA	0.2-20ng/ml (M-1, M-2), 2-150 ng/ml (M-3,M-4,M-5)	0.02ng/ml (M-1, M-2) 2ng/ml(M-3,M-4,M-5)	NA	[49]
HPLC	FDP	Plasma	Liquid–liquid extraction and Solid phase extraction	Methanol in phosphate buffer (0.05 M)	1.15 ml/min	LiChrospher 60 RP-select B (250 mm x 4 mm 5.0 µm)	220 nm	NA	20 nmol/l	NA	[50]
HPLC	FDP	Plasma	Protein precipitation	5 mmol Phosphate Buffer: acetonitrile (25:75: v/v)	1.0 ml/min	C8 DD S5 (4.6 mm × 250 mm, 5 µm)	360 nm	0.25-20.00 µg/ml	0.055µg/ml and 0.210µg/ml	<3 min	[51]
LC/MS	FDP	Plasma	Protein precipitation	ACN: 2 mmol ammonium acetate 80:20%	0.8 ml/min	Princeton SPHER C18 (150 x 4.6 mm, 5 µm)	NA	0.8-13.0ng/ml.	0.10 ng/ml and 0.50 ng/ml	NA	[52]
HPLC	FDP	Serum	Evaporation	ACN and 50 mmol ammonium acetate buffer pH-5 at a ratio of 67:33 v/v	1 ml/min	C18 (25 cm, 4.6 mm, 5 µm)	240 nm	1-4000 ng/ml	0.75 ng/ml and 1ng/ml	10.53 min	[53]

DISCUSSION

FDP is calcium channel antagonist [54, 55] which belongs to the class of dihydropyridine anti-hypertensive agents, and it was approved by FDA in 1991. *In vitro* studies have revealed that FDP is highly vascular selective, and it does not cause orthostatic hypotension as they don't have any effect on venous smooth muscles in clinical dose. FDP is a lipophilic molecule that is soluble in methanol and is used as a solvent for UV-Visible spectroscopy to determine FDP concentrations in bulk and tablets. Spectrofluorometric method is highly selective, sensitive, simple to operate, cost-effective and doesn't require any derivatization. The developed HPTLC method is easy and inexpensive, and it can be used for routine analysis. The HPLC methods were used to determine FDP, and the results with the UV detector showed greater sensitivity, specificity, and accuracy. The separation is accomplished using a UPLC approach that does not require the use of an ion-pair reagent in the mobile phase. Gas chromatography methods for the determination of FDP is also developed where helium was used as carrier gas. To determine FDP and evaluate pharmacokinetic parameters and toxicological properties, several bioanalytical procedures like HPLC, UPLC, LC–MS/MS, LC–ESI–MS/MS, LC-Tandem MS have been developed. Biological matrices like plasma and serum as a single drug alone and also in association with other drugs have been used for the studies. All these methods utilized derivatization, protein precipitation, Liquid-Liquid extraction, and solid-phase extraction methods that are used for sample preparation in biological matrices.

Future developments in hyphenated methods may widen the path for analysing FDP in biological fluids and finished products, which could be more useful for FDP therapeutic monitoring. HPLC is the most extensively used analytical technique since it is cost-effective, has good sensitivity, and accurate and robust results are obtained hence it is used in routine analysis.

CONCLUSION

The present review examines the several analytical methodologies for estimating FDP that are available. For the estimation of FDP various analytical methods such as spectrophotometry, spectrofluorimetric, HPTLC, HPLC, UPLC are employed. HPLC, UPLC, LC–MS/MS, LC–ESI-MS/MS, LC-Tandem-MS, GCMS are the various bioanalytical techniques developed for the estimation of FDP in biological fluids. Since it is relatively easy, economical, and sensitive, HPLC is the most extensively used technique for the determination and quantification of FDP in bulk, formulations, and biological fluids. LC–MS/MS, LC–ESI-MS/MS, LC-Tandem-MS, GCMS are the hyphenated techniques for estimation of FDP. Analysts and skilled formulators should work together in the foreseeable future to develop more environmentally safe techniques for estimating FDP that use less toxic solvents. More HPLC approaches can help with FDP evaluation in biological fluids and bulk formulations. Further developments in UV spectrophotometric methods might help to estimate FDP in the future, as they are reliable and can be employed on regular basis.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Migliorança LH, Barrientos Astigarraga RE, Schug BS, Blume HH, Pereira AS, De Nucci G. Felodipine quantification in human plasma by high-performance liquid chromatography coupled to tandem mass spectrometry. J Chromatogr B Anal Technol Biomed Life Sci. 2005;814(2):217-23. doi: 10.1016/j.jchromb.2004.10.032, PMID 15639442.
2. Vadlamudi MK, Dhanaraj S. Stability indicating method for the determination of related substances in felodipine solid dosage form and in the drug substance by RP-HPLC. J Bioequiv Availab. 2016;8(4):153-66. doi: 10.4172/jbb.1000287.
3. Yedinak KC, Lopez LM. Felodipine: a new dihydropyridine calcium-channel antagonist. DICP. 1991 Nov;25(11):1193-206. doi: 10.1177/106002809102501109, PMID 1763537.
4. Saltiel E, Ellrodt AG, Monk JP, Langley MS. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. Drugs. 1988 Oct;36(4):387-428. doi: 10.2165/00003495-198836040-00002, PMID 3069435.
5. Elmfeldt D, Hedner T, Westerling S. Felodipine in hypertension-a review. J Cardiovasc Pharmacol. 1987 Jan 1;10 Suppl 1:S154-60. doi: 10.1097/00005344-198710001-00028, PMID 2442509.

6. Ljung B. Vascular selectivity of felodipine: experimental pharmacology. J Cardiovasc Pharmacol. 1990 Jan 1;15Suppl 4:S11-6. doi: 10.1097/00005344-199015004-00003, PMID 1693715.
7. Edgar B, Lundborg P, Regårdh CG. Clinical pharmacokinetics of felodipine. A summary. Drugs. 1987 Dec;34Suppl 3:16-27. doi: 10.2165/00003495-198700343-00005, PMID 3327676.
8. Baarnhielm C, Skanberg I, Borg KO. Cytochrome P-450-dependent oxidation of felodipine-a 1,4-dihydropyridine-to the corresponding pyridine. Xenobiotica. 1984 Jan 1;14(9):719-26. doi: 10.3109/00498258409151470, PMID 6516445.
9. Dunselman PH, Edgar B. Felodipine clinical pharmacokinetics. Clin Pharmacokinet. 1991 Dec;21(6):418-30. doi: 10.2165/00003088-199121060-00003, PMID 1782737.
10. Mohamed AM, Omar MA, Hammad MA, Mohamed AA. Spectrofluorimetric and micelle-enhanced spectrofluorimetric methods for determination of felodipine and nimodipine in pharmaceutical preparations and human plasma. Spectrochim Acta A Mol Biomol Spectrosc. 2015 Oct 5;149:934-40. doi: 10.1016/j.saa.2015.05.026, PMID 26005990.
11. Santosh SC, Sandeep SS, Vaibhav PP, Jugal M, Sanjay JK. Development and validation of UV spectrophotometric method for estimation of felodipine using green solvent in tablet formulation. Acta Sci Pharm Sci. 2018;4(2):13-5.
12. Walash MI, Belal FF, El-Enany NM, El-Maghrabey MH. Synchronous fluorescence spectrofluorimetric method for the simultaneous determination of metoprolol and felodipine in combined pharmaceutical preparation. Chem Cent J. 2011 Dec;5(1):70. doi: 10.1186/1752-153X-5-70, PMID 22059735.
13. Basavaiah K, Chandrashekar U, Prameela HC. Sensitive spectrophotometric determination of amlodipine and felodipine using iron(III) and ferricyanide. Farmaco. 2003 Feb 1;58(2):141-8. doi: 10.1016/S0014-827X(02)00018-6, PMID 12581780.
14. Jadhav NR, Kambar RS, Nadaf SJ. Dual wavelength spectrophotometric method for simultaneous estimation of atorvastatin calcium and felodipine from tablet dosage form. Advances in Chemistry. 2014;2014:1-6. doi: 10.1155/2014/131974.
15. Rajesh K, Rajalakshmi R, Vijayaraj S, Sreelakshmi T. assessment of thiruvarur region groundwater samples using physicochemical parameters. Asian J Res Chem. 2011;4(8):1202-5. doi: 10.5958/0974-4150.
16. Thorat VM, Pawar SS, Pande VV, Arote SR, Musmade Deepak S. Development and validation of UV spectrophotometric method for estimation of process related impurity in felodipine bulk and formulation. Der Pharm Lett. 2015;7:284-90.
17. Krishna NM, Rao SS, Rambabu C. Bromothymol blue and bromocresol purple as efficient reagents for the development and validation of visible spectrophotometric assay methods for felodipine. Int Pharm Drug Anal. 2017 Apr 8:108-15.
18. Gedil F, Ustun O, Atay O. Quantitative determination of felodipine in pharmaceuticals by HPLC and UV spectroscopy. Turk J Pharm Sci. 2004;1(2):65-76.
19. Nimje HM, Oswal RJ, Kshirsagar SS, Chavan M. Spectrophotometric analysis for estimation of felodipine in tablet dosage form by calibration curve method. Res J Pharm Technol. 2011;4(12):1805-6.
20. Basavaiah K, Chandrashekar U, Gowda NP. Titrimetric and spectrophotometric assay of felodipine in tablets using bromated-bromide, methyl orange and indigo carmine reagents. J Serb Chem Soc. 2005;70(7):969-78. doi: 10.2298/JSC0507969B.
21. Patre NG, Patil SS. Development and validation of stability indicating assay method for determination of felodipine in tablet dosage form. Int J Pharm Sci Drug Res. 2018 Jul;10(4):268-73.
22. Jain PS, Ansari NA, Surana SJ. HPTLC and RP-HPTLC method development and validation for the estimation of felodipine in bulk and pharmaceutical formulation. Pharm Anal Acta. 2018;9:599. doi: 10.4172/2153-2435.1000599.
23. Migliorança LH, Barrientosastigarraga RE, Schug BS, Blume HH, Pereira AS, Denucci G. Felodipine quantification in human plasma by high-performance liquid chromatography coupled to tandem mass spectrometry. Journal of Chromatography B. 2005 Jan 25;814(2):217-23. doi: 10.1016/j.jchromb.2004.10.032.
24. Strode III JT, Taylor LT, Howard AL, Ip D, Brooks MA. Analysis of felodipine by packed column supercritical fluid chromatography with electron capture and ultraviolet absorbance detection. J Pharm Biomed Anal. 1994 Aug 1;12(8):1003-14. doi: 10.1016/0731-7085(94)00048-4, PMID 7819374.
25. Walash M, Belal F, El-Enany N, Zayed S. Micellar liquid chromatographic determination of felodipine in tablets and human plasma with fluorescence detection: application to stability studies and content uniformity testing. Anal Methods. 2014;6(10):3401-9. doi: 10.1039/C3AY41570H.
26. Cardoza RM, Amin PD. A stability indicating LC method for felodipine. J Pharm Biomed Anal. 2002 Feb 1;27(5):711-8. doi: 10.1016/S0731-7085(01)00490-3.
27. Taha EA, Fouad MM, Attia AK, Yousef ZM. RP-HPLC method development and validation for simultaneous estimation of ramipril and felodipine. Eur J Chem. 2019 Jun 30;10(2):113-7. doi: 10.5155/eurjchem.10.2.113-117.1832.
28. Bhavana G, Indira PG, Apuroopa. Method development and validation of stability indicating RP-HPLC for the estimation of felodipine PR tablets. Asian J Pharm Anal. 2020;10(4):207-12. doi: 10.5958/2231-5675.2020.00038.1.
29. Jadhav NR, Kambar RS, Nadaf SJ. Com/storage/app/archive/pdf/AfDLePcalFplIJ4T7fh3Kq4Wku0TzLIhueSZlpJ8. pdf. J Curr Pharm Res. 2012 Jul 1;2(4):637.
30. Dhale C, Joshi S, Shete S. Development and validation RP-HPLC method for analysis of felodipine in bulk and pharmaceutical dosage form. Int Res J Pharm. 2014;5(10):770-2. doi: 10.7897/2230-8407.0510156.
31. Patel YP, Patil S, Bhoir IC, Sundaresan M. Isocratic, simultaneous reversed-phase high-performance liquid chromatographic estimation of six drugs for combined hypertension therapy. J Chromatogr A. 1998 Dec 18;828(1-2):283-6. doi: 10.1016/s0021-9673(98)00652-9, PMID 9916313.
32. Pandey VP, Soma Sekhar K, Shenoy KR. Pharmacology Online. 2010;2:36270.
33. Madhukar A, Kumar YG, Usha K, Srilatha M. Analytical method development and validation of felodipine in bulk and tablet dosage form by using rp-hplc techniques. Indo Am J Pharmacol Sci. 1;4(9):3248-53. doi: 10.5281/zenodo.987841.
34. Santhosh Kumar P, Srinivasa Rao V, Abdul K, Prasad UV, Nanda Kumar Y, Sarma PV. J Pharm Res. 2012;5:1838-40.
35. Hu L, Hu Q, Gao N. Int J Pharm Sci Res. 2013 Sep 1;4(9):3369. doi: 10.13040/IJPSR.0975-8232.4(9).3369-74.
36. Kallepalli P. A new stability indicating liquid chromatographic method for the quantification of felodipine. Asian J Pharm. 2018 Aug 18;12(02):S597-602. doi: 10.22377/ajp.v12i02.2400.
37. Basavaiah K, Chandrashekar U, Prameela HC. Determination of felodipine in bulk drug and in tablets by high-performance liquid chromatography. Indian J Chem. 2003;10:454-6.
38. Jarag RJ, Paradkar AR. Development and validation of method for quantitative estimation of felodipine agglomerates by high pressure liquid chromatography. Asian J Res Chem. 2011;4(1):88-90.
39. Ahmed S, Atia NN, Ali MF. Ultrasound assisted dispersive liquid-liquid microextraction coupled with high performance liquid chromatography designated for bioavailability studies of felodipine combinations in rat plasma. J Chromatogr B. 2017;1046:200-10. doi: 10.1016/j.jchromb.2017.01.034.
40. Sakamoto T, Ohtake Y, Itoh M, Tabata S, Kuriki T, Uno K. Determination of felodipine enantiomers using chiral stationary phase liquid chromatography and gas chromatography/mass spectrometry, and the study of their pharmacokinetic profiles in human and dog. Biomed Chromatogr. 1993 Mar;7(2):99-103. doi: 10.1002/bmc.1130070211, PMID 8485383.
41. Dru JD, Hsieh JY, Matuszewski BK, Dobrinska MR. Determination of felodipine, its enantiomers, and a pyridine metabolite in human plasma by capillary gas chromatography with mass spectrometric detection. J Chromatogr B Biomed Appl. 1995 Apr 21;666(2):259-67. doi: 10.1016/0378-4347(94)00579-t, PMID 7633602.
42. Kim H, Roh H, Yeom S, Joo Lee H, Beom Han S. Sensitive determination of felodipine in human and dog plasma by use of

liquid–liquid extraction and LC–ESI–MS–MS. Chromatographia. 2003 Aug;58(3-4):235-40. doi: 10.1365/s10337-003-0042-6.

43. Baranda AB, Mueller CA, Alonso RM, Jimenez RM, Weinmann W. Quantitative determination of the calcium channel antagonists amlodipine, lercanidipine, nitrendipine, felodipine, and lacidipine in human plasma using liquid chromatography-tandem mass spectrometry. Ther Drug Monit. 2005 Feb 1;27(1):44-52. doi: 10.1097/00007691-200502000-00010, PMID 15665746.
44. Kim SH, Lee HJ. Development and validation of a high-throughput method for the quantitative analysis of felodipine in human plasma using high-performance liquid chromatography with mass/mass spectrometer and its application to a bioequivalence study in healthy male Korean subjects. J Pharm Investig. 2012 Aug;42(4):177-84. doi: 10.1007/s40005-012-0028-1.
45. Lindmark B, Ahnoff M, Persson BA. Enantioselective determination of felodipine in human plasma by chiral normal-phase liquid chromatography and electrospray ionisation mass spectrometry. J Pharm Biomed Anal. 2002 Jan 15;27(3-4):489-95. doi: 10.1016/S0731-7085(01)00582-9.
46. Albu F, Sora I, Tache F, David V, Medvedovici A. On-line SPE on restricted access adsorbent for HPLC-MS/MS analysis of felodipine in plasma samples. Anal Lett. 2010 May 4;43(7-8):1330-43. doi: 10.1080/00032710903518740.
47. Kallem RR, Ramesh M, Seshagirirao JV. Validated LC-ESI-MS/MS method for simultaneous quantitation of felodipine and metoprolol in rat plasma: application to a pharmacokinetic study in rats. Biomed Chromatogr. 2013 Jun;27(6):784-91. doi: 10.1002/bmc.2861, PMID 23303553.
48. Li Y, Yin Y, Sun Z, Li X, Hu L, Li P. Sensitive and rapid quantification of felodipine by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) and its pharmacokinetics in healthy chinese volunteer. Chemical Research in Chinese Universities. 2006;22(4):479-83. doi: 10.1016/S1005-9040(06)60146-3.
49. Nishioka R, Umeda I, Oi N, Tabata S, Uno K. Determination of felodipine and its metabolites in plasma using capillary gas chromatography with electron-capture detection and their identification by gas chromatography-mass spectrometry. J Chromatogr. 1991;565(1-2):237-46. doi: 10.1016/0378-4347(91)80386-q, PMID 1874870.
50. Gabrielsson M, Hoffmann K, Gunnar Regardh C. Determination of four carboxylic acid metabolites of felodipine in plasma by high-performance liquid chromatography. Journal of Chromatography B: Biomedical Sciences and Applications. 1992;573(2):265-74. doi: 10.1016/0378-4347(92)80128-D.
51. Salunkhe NH, Jadhav NR, Bhinge SD. Validated RP-HPLC method for quantification of felodipine in rabbit plasma: application in a bioequivalence study. Ann Pharm Fr. 2019 Jan 1;77(1):15-27. doi: 10.1016/j.pharma.2018.08.002, PMID 30243471.
52. Kisan Chatki P, Tabassum S. Analytical methods of dihydropyridines based calcium channel blockers–amlodipine, lacidipine, isradipine, nifedipine, felodipine, cilnidipine and its related formulations: a review. AJRC. 2021;14(3):221-34. doi: 10.52711/0974-4150.2021.00039.
53. Palem CR, Gannu R, Yamsani SK, Yamsani VV, Yamsani MR. Development of a high-performance liquid chromatography method for simultaneous determination of pioglitazone and felodipine in pig serum: application to pharmacokinetic study. Biomed Chromatogr. 2011 Aug;25(8):952-8. doi: 10.1002/bmc.1553, PMID 21058416.
54. Utpal J, Anjan KM, Sovan LP, Prabal KM, Guru PM. Preparation and *in vitro* characterization of felodipine loaded eudragit® rs100 nanoparticles. Int J Pharm Pharm Sci. 2014;6(4):564-67.
55. Raghavendra Rao NG, Kulkarni U, Chitral MS. Comparative study on effect of different techniques used in the formulation of felodipine fast dissolving tablets. Int J Pharm Pharm Sci. 2010;2:152-9.
56. Keerthana M, Shirisha S, Sahoo Sunit K, Madhusudhan RY. Formulation and evaluation of bilayered felodipine transdermal patches: *in vitro* and ex vivo characterization. Asian J Pharm Clin Res. 2021;14(3):106-11. doi: 10.22159/ajpcr.2021.v14i3.40290.