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

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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

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 (4S)-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, 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 actin in, which causes smooth muscle contraction and vasoconstruction. FDP acts by binding to calmodulin protein, hence prevents calcium-calmodulin interaction [3]. Dilution 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 has 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 P450-dependent oxidation to its pyridine anologue [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.

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 30 000 between toluene and water.
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, taylor and 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 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.
Quantify FDP, its impurities, and degradation products, a simple and efficient method for determining FDP. To identify and accurately detect FDP, methods are developed. Table 3 represents the Ultra-high-performance liquid chromatography (UPLC) method for measuring FDP in the presence of impurities, employing a simple detection method.

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

<table>
<thead>
<tr>
<th>Method</th>
<th>Drug</th>
<th>Matrix</th>
<th>Diluent</th>
<th>Wavelength (nm)</th>
<th>Linearity (µg/ml)</th>
<th>LOD</th>
<th>LOQ</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectrophotometric FDP</td>
<td>Tablet</td>
<td>Ethanol</td>
<td>Method 1-Methanol (MeOH), Method 2-8% Tween 80 and distilled water</td>
<td>361.5</td>
<td>5-50</td>
<td>NA</td>
<td>NA</td>
<td>[11]</td>
</tr>
<tr>
<td>Spectrofluorometric FDP</td>
<td>Tablet/Pasta</td>
<td>Method 1-426 nm, Method 2-423 nm</td>
<td>Method 1-0.2-3.0ug/ml, Method 2-0.05-4.0 ug/ml</td>
<td>Method 1-0.045ug/ml, Method 2-0.025ug/ml</td>
<td>Method 1-0.12ug/ml, Method 2-0.05ug/ml</td>
<td>[10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spectrophotometric FDP</td>
<td>Tablet</td>
<td>Methanol</td>
<td>375 nm</td>
<td>0.2-2 µg/ml</td>
<td>1-5.0 µg/ml</td>
<td>NA</td>
<td>NA</td>
<td>[12]</td>
</tr>
<tr>
<td>Spectrophotometric FDP</td>
<td>Tablet</td>
<td>Water</td>
<td>760 nm</td>
<td>2 to 12 µg/ml</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[13]</td>
</tr>
<tr>
<td>Spectrophotometric FDP</td>
<td>Tablet</td>
<td>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)</td>
<td>268 nm, 245 nm</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[14]</td>
<td></td>
</tr>
<tr>
<td>Spectrophotometric FDP</td>
<td>Tablet</td>
<td>Methanol</td>
<td>366.5 nm</td>
<td>3 to 10 µg/ml</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[15]</td>
</tr>
<tr>
<td>Spectrophotometric FDP</td>
<td>Tablet</td>
<td>Methanol</td>
<td>237 nm</td>
<td>2-18 µg/ml</td>
<td>0.265</td>
<td>0.8835</td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Spectrophotometric FDP</td>
<td>Tablet</td>
<td>MeOH</td>
<td>234 nm and 360 nm</td>
<td>4-24µg/ml and 8-60ug/ml</td>
<td>2ug/ml and 2.5ug/ml</td>
<td>NA</td>
<td>NA</td>
<td>[17]</td>
</tr>
<tr>
<td>Spectrophotometric FDP</td>
<td>Tablet</td>
<td>MeOH</td>
<td>326.4 nm</td>
<td>10-100 µg/ml</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[18]</td>
</tr>
<tr>
<td>Spectrophotometric FDP</td>
<td>Tablet</td>
<td>MeOH</td>
<td>Method B (Methyl Orange)-Water, Method C (Indigo Carmine)-Water</td>
<td>Method B: 0.12-0.07µg/ml, Method C: 0.5-6.0µg/ml</td>
<td>Method B: 0.013µg/ml, Method C: 0.09µg/ml</td>
<td>Method B: 0.044µg/ml, Method C: 0.32µg/ml</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Method</th>
<th>Drug</th>
<th>Matrix</th>
<th>Stationary phase</th>
<th>Mobile phase</th>
<th>Wavelength (nm)</th>
<th>Rf</th>
<th>LOD and LOQ</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTLC</td>
<td>FDP Tablet</td>
<td>Precoated aluminium plates with silica gel 60 F254</td>
<td>n-hexane: ethyl acetate 6: 4 (v/v)</td>
<td>0.5±0.027</td>
<td>366 nm</td>
<td>NA</td>
<td>23.54ng/spot and 71.33 ng/spot</td>
<td>[21]</td>
</tr>
<tr>
<td>HPTLC</td>
<td>FDP Tablet</td>
<td>Pre-coated aluminium plates with 250 µm layer of silica gel 60 F254(NP), Silica gel 60 RP-18 TLC F2545(RP)</td>
<td>Toluene: Methanol (8:2 v/v)</td>
<td>(NP), acetonitrile: water: glacial acetic acid (8:2.1 v/v/v)(RP)</td>
<td>0.40(RP), 0.53(RP)</td>
<td>237 nm</td>
<td>300-1800 and 500-3000 ng/spot</td>
<td>11.51(NP), 34.90(RP) and 29.90(NP), 90.61(RP)</td>
</tr>
</tbody>
</table>

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

**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.

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

<table>
<thead>
<tr>
<th>Method</th>
<th>Drug</th>
<th>Matrix</th>
<th>Mobile phase</th>
<th>Flow rate</th>
<th>Column</th>
<th>Detection</th>
<th>Linearity</th>
<th>LOD and LOQ</th>
<th>Rt (min)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPE/UV, LC/UV</td>
<td>FDP Tablet</td>
<td>NA</td>
<td>6% (v/v) MeOH-modified C02, CAN-MeOH0.05 M Potassium phosphate buffer (40:20:40, v/v/v)</td>
<td>2 ml/min</td>
<td>HyperSil Silica (25 cm * 4.6 mm * 5 µm)</td>
<td>264 nm</td>
<td>NA</td>
<td>NA</td>
<td>&lt;6 min</td>
<td>[24]</td>
</tr>
<tr>
<td>HPLC-fluorescence detection</td>
<td>FDP Tablet</td>
<td>Pulverisation</td>
<td>25 mmol of sodium dihydrogen phosphate and 85 mmol of sodium dodecylsulfate with 6.5% v/v pentanol</td>
<td>1.5 ml/min</td>
<td>CLC-C18 (250 nm * 4.6 mm * 5 µm)</td>
<td>240 nm (excitation) 440 nm (emission)</td>
<td>0.05-15 mg/ml</td>
<td>0.011 mg/ml and 0.032 mg/ml</td>
<td>NA</td>
<td>[25]</td>
</tr>
</tbody>
</table>
### Table 4: Various methods for determining and estimating FDP in biological matrix (plasma and tissue).

<table>
<thead>
<tr>
<th>Method</th>
<th>Drug</th>
<th>Matrix</th>
<th>Sample preparation</th>
<th>Mobile phase</th>
<th>Flow rate</th>
<th>Column</th>
<th>Detection</th>
<th>Linearity</th>
<th>LOD and LOQ</th>
<th>Rt (min)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>Trituration</td>
<td>Methanol–potassium dihydrogen orthophosphate (75:25, v/v), Potassium di-hydrogen phosphate: MeOH:ACN 15:15:70 (v/v/v), Buffer: ACN, MeOH (2:2:1 v/v)</td>
<td>1.5 ml/min</td>
<td>LithoCart (250 mm × 4 mm * 5.0 μm)</td>
<td>238 nm</td>
<td>1-7 μg/ml</td>
<td>150ng/ml and 500ng/ml</td>
<td>NA</td>
<td>[26]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>Trituration</td>
<td>Hyperchom C18 (250 × 4.6 mm, 5.0 μm) Inertial ODS_5 C18 (100 × 4.6 mm, 3.0 μm)</td>
<td>1 ml/min</td>
<td>NA</td>
<td>210 nm</td>
<td>5-80 μg/ml</td>
<td>1.21 μg/ml</td>
<td>NA</td>
<td>[27]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>NA</td>
<td>Inertsil C18 (100 × 4.6 mm, 3.0 μm)</td>
<td>1 ml/min</td>
<td>NA</td>
<td>238 nm</td>
<td>1.71μg/ml</td>
<td>NA</td>
<td>[28]</td>
<td></td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>NA</td>
<td>ACN: water (70:30 v/v)</td>
<td>1 ml/min</td>
<td>NA</td>
<td>238 nm</td>
<td>5-30 μg/ml</td>
<td>0.12μg/ml and 0.34μg/ml</td>
<td>11.46 min</td>
<td>[29]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>NA</td>
<td>ACN:water(70:3v/v) Phenomenex C-18 (150 mm × 4.6 mm, 5.0 μm)</td>
<td>1 ml/min</td>
<td>NA</td>
<td>238 nm</td>
<td>2-10 μg/ml</td>
<td>0.000665μg/ml and 0.00214μg/ml</td>
<td>NA</td>
<td>[30]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>Dilution</td>
<td>ACN-0.01 M KH2PO4</td>
<td>1.5 ml/min</td>
<td>Jasco-metaphase ODS (250×3.0 mm) 5.0 μm</td>
<td>250 nm</td>
<td>25-3200 ng/ml</td>
<td>12.20 min</td>
<td>[31]</td>
<td></td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>NA</td>
<td>Acetonitrile: Methanol: Phosphate buffer (40:20:30v/v)</td>
<td>1.0 ml/min</td>
<td>Lichrosor C18 (150 × 4.6 mm, 5.0 μm)</td>
<td>326 nm</td>
<td>4.5ng/ml</td>
<td>NA</td>
<td>[32]</td>
<td></td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>NA</td>
<td>ACN: Water (80:20 V/V)</td>
<td>1.0 ml/min</td>
<td>ODS C18 (4.6 mm × 150 mm, 5.0 μm)</td>
<td>305 nm</td>
<td>15-75 μg/ml</td>
<td>0.19μg/ml and 0.64μg/ml</td>
<td>NA</td>
<td>[33]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>NA</td>
<td>ACN: water (80:20 v/v)</td>
<td>1.0 ml/min</td>
<td>Symmetry C18 (25 cm × 4.5 mm, 5.0 μm)</td>
<td>234 nm</td>
<td>25 to 200 μg/ml</td>
<td>0.125 ng/ml and 1.25 ng/ml</td>
<td>NA</td>
<td>[34]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>NA</td>
<td>Methanol: acetonitrile: water (50:15:35), v/v/v</td>
<td>1.0 ml/min</td>
<td>C18 (5µm, 250 × 4.6 mm)</td>
<td>238 nm</td>
<td>5.05-40.4ng/ml</td>
<td>6.5 min</td>
<td>[35]</td>
<td></td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>Trituration</td>
<td>Phosphate buffer: acetonitrile (20:80v/v)</td>
<td>1.2 ml/min</td>
<td>C18Zorbax (250 mm × 4 mm, 5.0 μm)</td>
<td>234 nm</td>
<td>0.1-150 μg/ml</td>
<td>0.0279/μg/ml and 0.00852/μg/ml</td>
<td>2.51 min</td>
<td>[36]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>Trituration</td>
<td>Acetonitrile-20 mmol aqueous ammonium acetate (80:20/v/v)</td>
<td>1.0 ml/min</td>
<td>RP-C18 (250×4.6 mm, 5.0 µm)</td>
<td>236 nm</td>
<td>2.49 to 99.60 μg/ml</td>
<td>0.6μg/ml and 1.60μg/ml</td>
<td>NA</td>
<td>[37]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>Trituration</td>
<td>MeOH-0.055M phosphate buffer (83:17:1 v/v)</td>
<td>0.7 ml/min</td>
<td>Luna C18 (250×4.6 mm, 5.0 µm)</td>
<td>275 nm</td>
<td>2-20μg/ml</td>
<td>0.4μg/ml and 1mg/ml</td>
<td>12.52 min</td>
<td>[18]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>Agglom erates</td>
<td>MeOH-0.055 M phosphate buffer (83:17:1:v/v)</td>
<td>0.8 ml/min</td>
<td>HG250 (250 mm × 4.6 mm, 5.0 µm)</td>
<td>232 nm</td>
<td>10-60μg/ml</td>
<td>0.8899/μg/ml and 1.42758/μg/ml</td>
<td>NA</td>
<td>[38]</td>
</tr>
<tr>
<td>HPLC</td>
<td>FDP</td>
<td>Tablet</td>
<td>NA</td>
<td>0.02 mmol Ammonium acetate and acetonitrile (55:45, v/v)</td>
<td>0.7 ml/min</td>
<td>Phenomenex Gemini C18 (150 × 2.0 mm, 5.0 μm)</td>
<td>240 nm</td>
<td>0.2-8.0 μg/ml</td>
<td>NA</td>
<td>[2]</td>
<td></td>
</tr>
</tbody>
</table>

*FDP*: Fluorescent diesters; *HPLC*: High Performance Liquid Chromatography; *GC/MS*: Gas Chromatography/Mass Spectrometry; *LC/MS*: Liquid Chromatography/Mass Spectrometry; *LC/MS*: Liquid Chromatography/Mass Spectrometry; *MS*: Mass Spectrometry; *API*: Active Pharmaceutical Ingredient; *Plasma*: Plasma; *Matrix*: Matrix; *Sample preparation*: Sample preparation; *Flow rate*: Flow rate; *Column*: Column; *Detection*: Detection; *Linearity*: Linearity; *LOD and LOQ*: Limit of Detection and Limit of Quantitation; *Rt*: Retention time; *Ref.*: Reference.
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**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 properties, several bioanalytical procedures like HPLC, UPLC, LC-MS/MS, LC-ESI-MS/MS, LC-Tandem MS, MCMS are the various bioanalytical techniques developed for the estimation of FDP in biological fluids. Future developments in UV spectrophotometric methods might help to estimate FDP in the future, as they are reliable and can be employed on regular basis.

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**AUTHORS CONTRIBUTIONS**

All the authors have contributed equally.

**CONFLICT OF INTERESTS**

Declared none

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