SYNOPSIS OF THE THESIS ENTITLED
Development of Stability Indicating RP-HPLC and UV-Spectrophotometric Methods for the Determination of Some Chosen Drugs and Application of Spectroscopic Methods for Identification of Impurities in an anti hypertensive agent

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BY

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SYNOPSIS

The pharmaceutical industry is one of the most regulated activity sectors, where regulation includes specific quality systems such as good laboratory practice (GLP), good clinical practice (GCP) and good manufacture practice (GMP). Quality control is an essential operation of the pharmaceutical industry. Drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. The supply of essential medicines of good quality was identified as one of the prerequisites for the delivery of health care. The number of drugs and drug formulations introduced into the market by pharmaceutical industries is increasing at a considerable rate. These drugs and formulations may be either new entities or partial modifications of existing ones. The complexity of these dosage forms poses challenge to the analytical chemist during the development of assay procedures. Development of newer analytical methods for the determination of drugs and their formulations is necessary due to various reasons.

Analytical methodology should be capable of resolving all potential impurities to be formed during the products’ entire shelflife at the designated storage conditions. UV-Visible Spectrophotometry, High performance liquid chromatography (HPLC), HPLC coupled with mass spectrometry (LC/MS), Gas chromatography (GC), GC coupled with mass spectrometry (GC/MS), Nuclear magnetic resonance (NMR) spectroscopy, Mass spectrometry (MS) and Infra red spectroscopy (IR) techniques are generally employed for separation and quantification of the desired molecule. Among the several instrumental techniques, UV-Visible spectrophotometric technique is very simple, sensitive and economic generally applied for the analyses of drugs in pure and formulations where as high sensitive chromatographic techniques (HPLC, NMR & LC/MS) are extensively used for the study of impurities present in bulk drugs to find out different degradation products generally formed during the degradation of active pharmaceutical ingredient (API) under different stressed conditions and also to quantify the drug in a few micrograms per milli liter.

In the present investigation, the author has chosen eight bulk drugs such as Everolimus (ERL), Belinostat (BLT), Ceritinib (CRB), Saroglitazar (SAR), Cobicistat
(CBT), Elvitegravir (ELT), Ibrutinib (IBR) and Dapoxetine hydrochloride (DAR) for
the study of assay and degradation. The entire investigation has been carried out by
adopting simple techniques like UV-spectrophotometry and FTIR methods and
sensitive HPLC and LC/MS/MS methods. The content of the thesis has been divided
into eleven chapters as follows:

I. General introduction

II. Stability indicating RP-HPLC method for the estimation of everolimus in
pharmaceutical formulations, published in American journal of pharmtech research.

III. RP-HPLC method validation and forced degradation studies for the
determination of belinostat in bulk and its pharmaceutical dosage form, published in
Elixir international journal.

IV. Forced degradation studies and RP-HPLC method validation for the
determination of ceritinib in bulk and its pharmaceutical dosage form, published in
Asian journal of pharmaceutical and clinical research.

V. Validated stability indicating RP-HPLC method development for the
determination of saroglitazar in bulk and pharmaceutical dosage form, published in
Indo-American journal of pharmaceutical research.

VI. Validated stability indicating RP-HPLC method for the determination of
cobicistat in bulk and pharmaceutical formulations, published in Analytical chemistry:
an indian journal.

VII. Isocratic stability indicating RP-HPLC method for the assay of
elvitegravir in pure and in dosage forms, published in Der pharmacia lettre.

VIII. Validation of stability indicating RP-HPLC method for the assay of
ibrutinib in pharmaceutical dosage form, published in Analytical chemistry: an indian
journal.
IX. Isocratic stability indicating RP-HPLC method for the assay of dapoxetine hydrochloride in pure and in dosage forms, communicated to Asian journal of pharmaceutical and clinical research.

X. Structural identification and characterization of potential impurities of azelnidipine

XI. UV spectrophotometric methods (A) A new and sensitive UV spectrophotometric method for the determination of belinostat in dosage forms, (B) UV spectrophotometric method development and validation of assay of ceritinib tablet formulation, and (C) UV spectrophotometric determination of ibrutinib in bulk and dosage forms.

Chapter I deals with the general introduction of drugs on the various techniques used for the assay. Chapter II to IX describes the estimation of drug content in API and dosage forms, and degradation of selected drugs by RP-HPLC methods. Chapter X contains the structural identification and characterization of potential impurities of Azelnidipine by spectroscopic techniques like FT-IR, UV, NMR and MS methods. Chapter XI describes the UV spectrophotometric methods for the determination of three drugs (BLT, CRB and IBR) in bulk and dosage forms. Appropriate references have been placed at the end of the thesis followed by the published papers.

Chapter-I, general introduction is divided into nine sections, Section-1.1, 1.3 to 1.8 includes a brief introduction on drugs, analysis of pharmaceuticals, study of impurities, analytical techniques, analytical method development and method validation and also statistical evaluation. Section-1.2 includes profile, physical properties, chemical aspects and structural features of chosen drugs ERL, BLT, CRB, SAR, CBT, ELT, IBR, DAP and AZL.

Everolimus (ERL) is a class of medications called kinase inhibitors used for treatment of different cancer. It is a 40-O-(2-hydroxyethyl) derivative of sirolimus and works similarly to sirolimus as an inhibitor of mammalian. Everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-\{(1R)-2-[\{(1S,3R,4R)-4-(2-hydroxyethoxy)3-methoxy cyclohexyl\}-1-methyl-ethyl\]-
19,30 dimethoxy 15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0] hexa triaconta-16,24,26,28-tetraene-2,3,10,14,20 pentaone. The chemical structure of ERL is represented in Fig 1.1.

Fig 1.1: Chemical structure of Everolimus

Belinostat (PXD101, trade name Beleodaq) is a drug under development by TopoTarget for the treatment of hematological malignancies and solid tumors. It is a histone deacetylase inhibitor. The chemical name of Belinostat (BLT) is (2E)-N-Hydroxy-3-[3-(phenyl sulfamoyl)phenyl] prop-2-enamide. The chemical structure of BLT is represented in Fig 1.2.

Fig 1.2: Chemical structure of Belinostat

Ceritinib(CRB), 5-Chloro-N\(^2\)-[2-iso propoxy-5-methyl-4 (4- piperidinyl) phenyl]-N\(^4\)-[2-(isopropyl sulfonyl)phenyl]-2,4-pyrimidine diamine, is an anaplastic lymphoma kinase (ALK) inhibitor which induces complete tumour regression in a xenograft model of EML4-ALK-positive lung cancer. The alternative names of Ceritinib are LDK 378, NVP-LDK 378, Zykdia\textsuperscript{TM}. The chemical structure of CRB is represented in Fig 1.3.
Saroglitazar (Lipaglyn) is indicated for the treatment of diabetic dyslipidemia and hyper triglyceridemia with type 2 diabetes mellitus not controlled by statin therapy. Saroglitazar is (2S) -2- Ethoxy -3- [4- (2- {2-methyl -5- [4- (methylsulfanyl)phenyl]-1H-pyrrol-1-yl}ethoxy)phenyl]propanoic acid. The chemical structure of SAR is represented in Fig 1.4.

Cobicistat, [1,3-thiazol-5-ylmethyl N-[(2R,5R)-5-[[[(2S)-2-[[methyl- [(2-propan-2-yl-1,3-thiazol-4-yl) methyl] carbamoyl] amino]-4-morpholin-4-ylbutanoyl] amino]-1,6-diphenylhexan-2-yl] carbamate], is used in the treatment of human immunodeficiency virus (HIV). In combination with three other drugs elvitegravir, emtricitabine, and tenofovir, Cobicistat is used in the treatment of HIV. The combination of the four drugs is popularly known as Quad – pill. The chemical structure of CBT is represented in Fig 1.5.
Elvitegravir (ELT), 6-[(3-Chloro-2-fluorophenyl)methyl]-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxoquinoline-3-carboxylic acid, is a newly introduced HIV-1 integrase strand transfer inhibitor. ELT is an integrase inhibitor used to treat HIV infection. The chemical structure of ELT is represented in Fig 1.6.

![Chemical structure of Elvitegravir](image)

Fig 1.6: Chemical structure of Elvitegravir

Ibrutinib (IBR) is an anticancer drug targeting β-cell malignancies (blood cancer treatment medicines). It was used for the treatment of mantle cell lymphoma and for the treatment of chronic lymphocytic leukaemia. It is an orally administered, selective and covalent inhibitor of the enzyme bruton's tyrosine kinase (BTK). The systematic (IUPAC) name of ibrutinib is given by 1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl] piperidin-1-yl] prop-2-en-1-one. The chemical structure of IBR is represented in Fig 1.7.

![Chemical structure of Ibrutinib](image)

Fig 1.7: Chemical structure of Ibrutinib

Dapoxetine Hydrochloride (DAP), (S)-N,N-Dimethyl-α-[2-(1-Naphthalenyl oxy) ethyl]benzene methanamine hydrochloride, drug is used for the treatment of premature ejaculation. It acts as selective serotonin re-uptake inhibitor (SSRI) as it is an antidepressant. The chemical structure of DAP is represented in Fig 1.8.
Azelnidipine (AZL) is a white crystalline powder and is used as cardiovascular agent. The therapeutic action of AZL is that it acts as anti-hypertensive agent and also as calcium channel blocker. The structure of possible impurities related to raw materials or degradants is identified by the various characterization techniques such as UV, IR, NMR and Mass Spectrography studies.

In the studies of AZL, four impurities were identified namely, propan-2-yl-2-(4-nitro benzylidene)-3-oxobutanoate[Impurity1]; propan-2-yl2-(3-nitrobenzylidene)-3-oxobutanoate[Impurity 2]; 3-[1-(diphenyl methyl)azetidin-3-yl] 5-propan-2-yl 2-amino-6-methyl-4-(4-nitro phenyl)-1,4-dihydro pyridine-3,5-dicarboxylate [Impurity 3]; and 3-[1-diphenyl methyl)azetidin-3 yl] 5-propan-2-yl 2-amino-6-methyl-4-(2-nitro phenyl)-1,4-dihydro pyridine-3,5-dicarboxylate [Impurity 4]. The chemical structures of impurities of AZL are represented in Fig 1.9 (a), (b), (c) and (d) respectively.

Section-1.9 includes the objective of the present investigation. The physical properties like appearance, solubility, formulation and characterization of the above chosen drugs were presented in Table 1.1.

Chapters II-IX, an experimental part describes stability indicating RP-HPLC experimental method selected for the present investigation. It is mainly focused on the development of new methods and developed optimized conditions. Validation (precision, accuracy, limit of detection, limit of quantification, specificity, linearity, ruggedness, robustness and stability) of developed analytical method are explained in these chapters. It also includes the forced degradation studies to detect the stability of the above chosen drugs. These chapters ends detailed notes about the objective of the present investigation and scope of the developed methods. The chromatographic
conditions of chosen drugs were given in Table 1.2 (a) and (b). All the methods developed were simple, specific and can easily be adapted for the estimation of the selected drugs in the bulk samples and pharmaceutical formulations for the regular quality control applications.

Fig 1.9 (a): Chemical structure of para impurity of AZL

Fig 1.9 (b): Chemical structure of azelnidipine intermediate

Fig 1.9 (c): Chemical structure of 4-nitro azelnidipine

Fig 1.9 (d): Chemical structure of 2-nitro azelnidipine
<table>
<thead>
<tr>
<th>Physical properties</th>
<th>Everolimus</th>
<th>Belinostat</th>
<th>Ceritinib</th>
<th>Saroglitazar</th>
<th>Cobicistat</th>
<th>Elvitegravir</th>
<th>Ibrutinib</th>
<th>Dapoxetine</th>
<th>Azelnidipine</th>
</tr>
</thead>
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<tr>
<td>Chemical formula</td>
<td>C_{53}H_{83}NO_{14}</td>
<td>C_{16}H_{36}ClN_{3}O_{5}</td>
<td>C_{25}H_{29}NO_{14}</td>
<td>C_{40}H_{33}N_{7}O_{5}S_{2}</td>
<td>C_{23}H_{23}ClFNO_{3}</td>
<td>C_{23}H_{24}NO_{2}</td>
<td>C_{21}H_{23}NO.HCl</td>
<td>C_{33}H_{34}N_{4}O_{6}</td>
<td></td>
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<tr>
<td>Molecular mass</td>
<td>958.2 g/mol</td>
<td>318.35 g/mol</td>
<td>558.14 g/mol</td>
<td>439.56 g/mol</td>
<td>776.023 g/mol</td>
<td>447.883 g/mol</td>
<td>440.497 g/mol</td>
<td>341.87 g/mol</td>
<td>582.65 g/mol</td>
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<tr>
<td>Appearance</td>
<td>White or off-white crystalline powder</td>
<td>White solid powder</td>
<td>White or light yellow powder</td>
<td>White crystalline powder</td>
<td>White or pale yellow solid</td>
<td>White to pale yellow solid</td>
<td>White to off-white solid</td>
<td>White crystalline powder</td>
<td>Pale yellow to white crystalline powder</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in acetonitrile</td>
<td>Soluble in dimethyl sulfoxide (DMSO) but insoluble in water</td>
<td>Soluble in DMSO, ethanol but slightly soluble in water</td>
<td>DMSO, methanol, ethanol, water and acetonitrile</td>
<td>soluble in water, DMSO, PBS buffer</td>
<td>soluble in DMSO, acetonitrile and methanol</td>
<td>soluble in DMSO, methanol, acetonitrile</td>
<td>DMSO, methanol, ethanol, chloroform, water and acetonitrile</td>
<td>soluble in ethanol; slightly soluble in methanol and water</td>
</tr>
<tr>
<td>Formulations</td>
<td>Zortres-1 mg, 10mg 100 mg tab Certican 1mg, 10mg, 100 mg tab Advacan 0.25 mg, 0.5 mg tab</td>
<td>Beleodaq - 500 mg/vial PXD 101 -10 mg, 100 mg, 500 mg, 1 kg</td>
<td>LDK 378-5 mg, 10 mg, 50 mg, 100 mg Zykadia™ -150 mg hard-gelatin capsule</td>
<td>Lipaglyn-4 mg tablet</td>
<td>Tybost-150 mg tablets and Vitekta - 85 mg, 150 mg tablets</td>
<td>Stribild-150 mg tablets</td>
<td>Ibruvica 140 mg capsule</td>
<td>Sustinex-30 mg, 60 mg capsules Prejac-60 mg capsule Kutub-30 mg, 60 mg capsules</td>
<td>Watsonnoke-30 mg, 60 mg tablets and Calblock® - 8 mg, 16 mg tablets</td>
</tr>
<tr>
<td>Characterization</td>
<td>Anti cancer drug</td>
<td>Anti cancer drug</td>
<td>Anti cancer drug</td>
<td>Anti diabetic drug</td>
<td>Anti HIV drug</td>
<td>Anti HIV drug</td>
<td>Anti cancer drug</td>
<td>Anti depressant drug</td>
<td>Anti hypertensive drug</td>
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Table 1.2 (a): Chromatographic conditions adopted for chosen drugs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Everolimus</th>
<th>Belinostat</th>
<th>Ceritinib</th>
<th>Saroglitazar</th>
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<td><strong>Chapter ID</strong></td>
<td><strong>Chapter-II</strong></td>
<td><strong>Chapter-III</strong></td>
<td><strong>Chapter-IV</strong></td>
<td><strong>Chapter-V</strong></td>
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<tr>
<td>Working solution</td>
<td>0.2 mg/mL</td>
<td>0.2 mg/mL</td>
<td>0.1 mg/mL</td>
<td>0.4 mg/mL</td>
</tr>
<tr>
<td>Analytical column</td>
<td>Kromasil C&lt;sub&gt;18&lt;/sub&gt; (100 mm x 4.6 mm, 5 µm)</td>
<td>Altima C&lt;sub&gt;18&lt;/sub&gt; (150 mm x 4.6 mm, 5 µm)</td>
<td>BDS C&lt;sub&gt;18&lt;/sub&gt; (150 mm x 4.6 mm, 5 µm)</td>
<td>Altima ODS C&lt;sub&gt;18&lt;/sub&gt; (150 mm x 3.9 mm, 5 µm)</td>
</tr>
<tr>
<td>Buffer solution</td>
<td><strong>Mobile Phase-A:</strong> 0.01M KH&lt;sub&gt;2&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;, pH adjusted to 3.0±0.05 with H&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td><strong>Mobile Phase-B:</strong> Acetonitrile and Water in the ratio of 90:10, v/v</td>
<td>0.01M potassium dihydrogen orthophosphate, pH adjusted to 3.0±0.05 with H&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1.41 gm of DSHP in 1 lit water, pH adjusted to 7.0 with ortho phosphoric acid</td>
</tr>
<tr>
<td>Mobile phase</td>
<td>Buffer and acetonitrile in 75:25 v/v ratio</td>
<td>Buffer and acetonitrile in 40:60 v/v ratio</td>
<td>Buffer and acetonitrile in 55:45 v/v ratio</td>
<td>Buffer and acetonitrile in 40:60 v/v ratio</td>
</tr>
<tr>
<td>Wavelength (nm)</td>
<td>270</td>
<td>210</td>
<td>320</td>
<td>294</td>
</tr>
<tr>
<td>Flow rate (mL.min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Injection volume</td>
<td>10 µL</td>
<td>20 µL</td>
<td>10 µL</td>
<td>10 µL</td>
</tr>
<tr>
<td>Run time (minutes)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Temperature °C</td>
<td>30°C</td>
<td>30°C</td>
<td>30°C</td>
<td>30°C</td>
</tr>
<tr>
<td>Diluent</td>
<td>Water</td>
<td>Methanol and water in 50:50 v/v ratio</td>
<td>Methanol and water in 50:50 v/v ratio</td>
<td>Water</td>
</tr>
</tbody>
</table>
Table 1.2 (b): Chromatographic conditions adopted for chosen drugs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cobicistat</th>
<th>Elvitegravir</th>
<th>Ibrutinib</th>
<th>Dapoxetine Hydrochloride</th>
</tr>
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<tr>
<td>Chapter ID</td>
<td>Chapter-VI</td>
<td>Chapter-VII</td>
<td>Chapter-VIII</td>
<td>Chapter-IX</td>
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<tr>
<td>Working solution</td>
<td>0.276 mg/mL</td>
<td>0.2 mg/mL</td>
<td>0.5 mg/mL</td>
<td>0.6 mg/mL</td>
</tr>
<tr>
<td>Analytical column</td>
<td>Hypersil BDS C_{18} (150mmx4.6mm, 5 µm)</td>
<td>Hypersil BDS C_{18} (150mm x 4.6 mm, 5 µm)</td>
<td>Inertsil ODS C_{18} (100mm x 4.6 mm, 5 µm)</td>
<td>Hypersil BDS C_{18} (100mmx4.6mm, 5 µm)</td>
</tr>
<tr>
<td>Buffer solution</td>
<td>1.6 gm of potassium dihydrogen orthophosphate in 1000 mL water, pH adjusted to 6.5 with ortho phosphoric acid</td>
<td>6.8 gm of potassium dihydrogen orthophosphate, pH adjusted to 5.0±0.05 with orthophosphoric acid</td>
<td>0.01M potassium dihydrogen orthophosphate, pH adjusted to 6.8 ± 0.05 with H_{3}PO_{4}</td>
<td>14.9 gm of ammonium phosphate in 1000 mL water, pH adjusted to 3.0 ± 0.1 with ortho phosphoric acid</td>
</tr>
<tr>
<td>Mobile phase</td>
<td>Buffer and acetonitrile in 90:10 v/v ratio</td>
<td>Buffer and acetonitrile in 60:40 v/v ratio</td>
<td>Buffer and acetonitrile in 70:30 v/v ratio</td>
<td>Buffer and acetonitrile in 60:40 v/v ratio</td>
</tr>
<tr>
<td>Wavelength (nm)</td>
<td>240</td>
<td>265</td>
<td>320</td>
<td>230</td>
</tr>
<tr>
<td>Flow rate mL.min^{−1}</td>
<td>1.0</td>
<td>1.0</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Injection volume</td>
<td>10 µL</td>
<td>10 µL</td>
<td>10 µL</td>
<td>20 µL</td>
</tr>
<tr>
<td>Run time (minutes)</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Temperature °C</td>
<td>30°C</td>
<td>30°C</td>
<td>30°C</td>
<td>30°C</td>
</tr>
<tr>
<td>Diluent</td>
<td>Mobile phase</td>
<td>Mobile phase</td>
<td>Methanol</td>
<td>Mobile phase</td>
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</table>
The author has also successfully identified and characterized the four impurities of Azelnidipine (AZL) namely para impurity, Azelnidipine intermediate, 4-Nitro Azelnidipine and 2-Nitro Azelnidipine and well separated by using UV, MS, IR and NMR spectroscopic methods and the results are included in Chapter-X.

Even though, UV spectrophotometric methods are available for certain chosen drugs, no attempts have been made to develop conditions for the determination of Belinostat, Ceritinib and Ibrutinib by UV spectrophotometrically. Hence, the author has attempted to develop conditions for UV spectrophotometric methods for the determination of BLT, CRB and IBR drugs. In this technique the rate of change of absorbance is measured as a function of wavelength. The application of derivative spectrophotometry for quantitative analysis is based on the validity of Beer’s law and the additivity of absorbances.

It starts with the investigation with a brief introduction experimental, method development, method validation, results and discussion. The absorption spectrum and $D^1$ and $D^2$ spectra for each of the concentration of each drug are recorded over the wavelength range 200-400 nm against a reagent blank under similar conditions. The absorption spectra of working standard solution BLT, CRB and IBR were recorded by scanning the absorbance values in the range of wavelength 200-400 nm and then first and second derivative spectra were also obtained from the spectrophotometer. From the absorption spectra, it was found that the wavelengths of maximum absorbance were found to be 238.9, 319.6 and 249.6 nm respectively. The detailed description of UV methods are discussed in Chapter-XI (A), (B) and (C).

Finally, the author has been described the summary of all the nine drugs used in the present investigation. The references which are used in general introduction, RP-HPLC methods for the assay of EVR, BLT, CRB, SAR,CBT, ELT, IBR and DAP, impurity profiling of AZL drug and UV spectrophotometric methods for the development of BLT, CRB and IBR drugs are given at the end of the thesis.

The developed chromatographic methods were found to be simple, sensitive, precise and accurate. The proposed methods were proved to be linear, robust and rugged. The pharmaceutical formulations were successfully analyzed by the proposed
methods. Therefore, these methods may be suggested as alternative methods for routine quality control analysis.

The present research will enrich practical subject knowledge significantly on novel chromatographic and spectroscopic studies on identification and characterization of impurities in pharmaceutical ingredients. The results in the present investigation are well supported by the research publications of reputed national as well as international journals. This research will add new dimensions to the existing literature on chromatographic and spectroscopic studies on pharmaceutical products. These developed methods are of great asset in quality monitoring of the selected products towards development of pharmaceutical dosage forms and may be claimed as a novel, noteworthy feature of the research work.

LIST OF PUBLISHED PAPERS


**LIST OF SUPPORTING PUBLISHED PAPERS**


