IJBPAS, January, 2026, 15(1): 165-184

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)
'A Bridge Between Laboratory and Reader'

www.ijbpas.com

COMPARATIVE ANALYSIS OF DIFFERENT CHROMATOGRAPHIC TECHNIQUES FOR STABILITY INDICATING ANALYSIS OF ANTIPSYCHOTIC DRUGS

DADHEECH P* AND GOYAL A

B N Institute of Pharmaceutical Sciences, B N University, Udaipur, Rajasthan

*Corresponding Author: Dr. Pankaj Dadheech: E Mail: dadheechpankaj007@gmail.com

Received 13th Sept. 2024; Revised 25th Nov. 2024; Accepted 14th Jan. 2025; Available online 1st Jan. 2026

https://doi.org/10.31032/IJBPAS/2026/15.1.9727

ABSTRACT

Stability indicating analysis of antipsychotic drugs is critical in ensuring the efficacy and safety of pharmaceutical formulations. Chromatographic techniques play a pivotal role in this process, providing reliable and accurate data on the stability and degradation products of these drugs. This review presents a comprehensive analysis of the comparative effectiveness of different chromatographic techniques, including High-Performance Liquid Chromatography (HPLC), Ultra Performance Liquid Chromatography (UPLC), High-Performance Thin Layer Chromatography (HPTLC), Capillary Electrophoresis (CE), Super Critical Fluid Chromatography (SFC) and Gas Chromatography (GC), in the stability indicating analysis of antipsychotic drugs. By evaluating the strengths, limitations, and applications of each technique, this review aims to provide insights into their suitability for different types of drug formulations and highlight the emerging trends and future prospects in this vital area of pharmaceutical analysis.

Keywords: High-Performance Liquid Chromatography (HPLC), Ultra Performance Liquid Chromatography (UPLC), and Gas Chromatography (GC), Antipsychotic Drugs, Chromatographic Techniques

INTRODUCTION

Antipsychotic drugs play a pivotal role in the treatment of various psychotic disorders, benefiting a substantial global population. Their significance in managing psychiatric conditions, particularly in schizophrenia therapy, has amplified in recent times **[1]**. Moreover, these medications find application in addressing bipolar disorder, severe depression, and postoperative delirium in surgical units. Despite their introduction in 1952, it took decades of research before a comprehensive understanding of their mechanisms of action surfaced. Antipsychotics are commonly categorized as typical or atypical based on their tendency to induce motor adverse effects, a widely accepted classification in the field **[2, 3]**. First-generation antipsychotics, commonly referred to as typical antipsychotics, function as dopamine receptor antagonists (DRA). They encompass a range of compounds, such as phenothiazines (trifluoperazine, perphenazine, prochlorperazine, acetophenazine, triflupromazine, mesoridazine), butyrophenones (haloperidol), thioxanthenes (thiothixene, chlorprothixene), dibenzoxazepines (loxapine), dihydroindoles (molindone), and diphenylbutylpiperidines (pimozide) **[4-6]**.

On the other hand, second-generation antipsychotics, known as atypical antipsychotics, operate as serotonin-dopamine antagonists. The Food and Drug Administration (FDA) sanctioned 12 atypical antipsychotics as of 2016, which include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone, iloperidone, cariprazine, brexpiprazole, and clozapine **[7]**. Stability-indicating assays play a critical role in the forced degradation analysis of both pharmaceutical products and active pharmaceutical ingredients **[8]**. They are instrumental in identifying any degradation and alterations in the concentration of the active pharmaceutical ingredient within the product. According to the guidance documents by the United States Food and Drug Administration (FDA), a stability indicating method is a validated quantitative analytical procedure specifically designed to assess the stability of a drug substance. It enables the measurement of changes in drug substance concentration without any interference from other present substances, including degradation impurities, excipients, and other potential components **[9]**.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline Q3B, Impurities in New Drug Products, mandates the provision of documented evidence to validate that the analytical methods are suitable for detecting and quantifying degradation products and impurities. These validated methods should be reliable, specific, and capable of effectively differentiating impurities from the API and other pharmaceutical substances. A variety of methods have been employed as stability-indicating assays, including high-performance liquid chromatography (HPLC), gas chromatography (GC), high-performance thin-layer chromatography (HPTLC), capillary electrophoresis (CE), and supercritical fluid chromatography (SFC) **[10, 11] (Figure 1)**. Antipsychotic drugs, maintain their stability and potency throughout their shelf life. Stability indicating analysis using chromatographic techniques is essential to monitor the degradation products and impurities that may affect the efficacy and safety of these drugs. While several chromatographic techniques have been employed for stability indicating analysis, it is imperative to evaluate their comparative efficacy and applicability in the context of antipsychotic drugs.

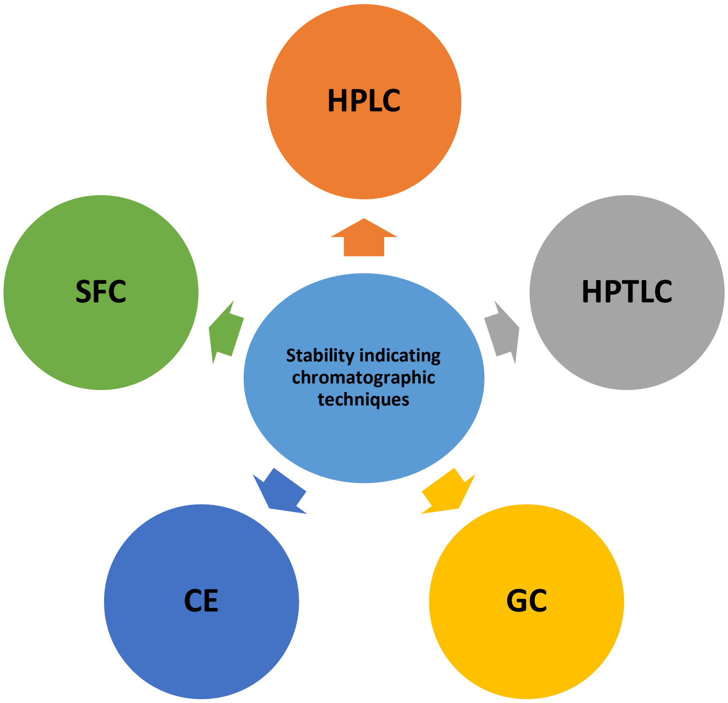

Figure 1: Stability indicating chromatographic techniques

COMPARATIVE ANALYSIS OF CHROMATOGRAPHIC TECHNIQUES

This review systematically compares the effectiveness of different chromatographic techniques, focusing on HPLC, UPLC, and GC. It examines the principles, instrumentation, and operating conditions of each technique, highlighting their respective advantages and limitations in the stability indicating analysis of antipsychotic drugs. The review discusses the specific parameters relevant to stability indicating analysis, including resolution, sensitivity, selectivity, and robustness, and evaluates how each chromatographic technique performs in addressing these parameters.

High Performance Liquid Chromatography Techniques for Antipsychotic Drugs

HPLC remains the prominent technique in pharmaceutical analysis, involving the use of a chromatographic column where a solid or liquid sample is dissolved in a suitable solvent **[9, 12]**. This system is known for its simplicity of operation, versatility, minimal sample preparation requirements, and its ability to provide high resolution and excellent recovery **[13]**. It is well-suited for a wide range of compounds with varying polarity, molecular mass, volatility, and thermal sensitivity. The elution of the analytes can be conducted in either isocratic or gradient elution mode (Table 1). HPLC's separation results are presented in a chromatogram, with each analyte in the sample appearing as a distinct peak at a specific time **[14]**. This technique is highly advantageous for drug stability assessment due to its specificity, speed, sensitivity, and robustness. Notably, HPLC offers the flexibility of employing various detection wavelengths, adjusting the flow rate, and customizing the mobile phase elution profile **[15]**.

Table 1: Stability Indicating HPLC Methods for Drug Substances and their Elution Conditions for Antipsychotic Drug Analysis

S. No.	Drug Substances	Elution Methods	Analysis Time	References
1.	Clozapine, Olanzapine and Quetiapine, several Beta-blockers and their metabolites	Gradient mixture of acetonitrile and potassium dihydrogen phosphate buffer pH 3.1 (containing 10% methanol) as a mobile phase at a flow rate of 1 mL/min.	40 min	[16]
2.	Ziprasidone and its impurities in pharmaceutical dosage forms	Gradient with mobile phase A [buffer-acetonitrile (80+20, v/v)] and mobile phase B [buffer-acetonitrile (10+90, v/v)], buffer was 0.05 M KH_2PO_4 solution with an addition of 10 mL triethylamine/L solution, adjusted to pH 2.5 with orthophosphoric acid and flow rate was 1.5mL/min.	30min	[17]
3.	Olanzapine and Aripiprazole in human plasma	Gradient elution was performed with a mobile phase consisting of phosphate buffer (pH 3.14, 20 mM) and acetonitrile with flow rate 0.8mL/min.	10 min	[18]
4.	Pimozide in bulk and its tablet dosage form	Acetonitrile: 50 mM Disodium hydrogen phosphate buffer (pH 6.2, adjusted by 1 % ortho phosphoric acid) in the ratio of 60: 40 %v/v with a flow rate of 1 ml/min	10 min	[19]
5.	Risperidone in Bulk & Dosage Forms	Water 35: Methanol 65 (PH 5.5 aq.phase) with a flow rate of 0.9ml/min	10 min	[20]
6.	Asenapine maleate	Acetonitrile:10 mM phosphate buffer (30:70, *v/v*) and its pH was adjusted to 3.5 using orthophosphoric acid with a flow rate of 1.0 mL/min.	10 min	[21]
7.	Haloperidol (HAL) and Trihexyphenidyl hydrochloride (THP)	0.5 mL triethylamine 0.05 M phosphate buffer having pH 3.75: acetonitrile: (65:35 v/v), a flow rate of 1.2 mL.min-1	10 min	[22]
8.	Asenapine maleate	Water: methanol (60:40, v/v) was used. The flow rate was 1.0 mL min−1	10 min	[23]
9.	Lurasidone	Ammonium acetate(pH 5.5): acetonitrile: methanol in the ratio of 35:30:35, v/v/v at a retention time of 7.39 minute and flow rate of 1ml/min	10 min	[24]

10.	**Stress Degradation of Paliperidone**	**Hypersil BDS C18 (250 mm × 4.6 mm, 5 µm) thermostated at 45°C was used for the separation. 0.05 M ammonium dihydrogen orthophosphate buffer was prepared by dissolving 5.75 ± 0.10 g ammonium dihydrogen orthophosphate in 1000 mL of water**	**35 min**	**[25]**
11.	**Quetiapine**	**The assessment was performed utilizing a C8 reversed-phase column (150×4.6 mm i.d., 5 µm), employing a mobile phase comprising acetonitrile, methanol, and pH 1.9 phosphate buffer. Triprolidine served as the internal standard.**	**10 min**	**[26]**
12.	**Aripiprazole and its impurities in pharmaceuticals**	**Phenomenex Luna® C18 column (5.0 µm particle size, 250 × 4.6 mm id) using a gradient mobile phase A (phosphate buffer pH 3.0) and mobile phase B (acetonitrile) at the working temperature of 25°C**	**10min**	**[27]**
13.	**Olanzapine and related impurities**	**Agilent Octyldecyl silica column (TC-C_{18}, 4.6 mm × 250 mm, 5 µm) using a gradient HPLC method**	**-**	**[28]**

High-Performance Liquid Chromatography (HPLC) enables the simultaneous detection of various analytes in pharmaceutical formulations, as depicted in **Table 1**. Widely employed as a stability-indicating assay for both bulk drugs and drug products, HPLC facilitates the concurrent separation of drug substances and degradation impurities. For instance, Cui *et al*. (2011) developed a stability-indicating assay using RP-HPLC to separate 8 impurities from bulk drug through gradient elution. The separation achieved excellent results, with perfectly resolved peaks in the chromatogram.

Optimizing parameters for effective separation of multiple drugs is achievable in HPLC through response surface methodology. In the case of tablets the retention time responses create surfaces, and the intersection of these surfaces is essential for identical retention times of the drugs. Maintaining an optimal capacity factor is crucial in achieving good chromatography, avoiding values that are too low or too high. The development of the HPLC separation method involves the optimization of the mobile phase, considering parameters such as the concentration of the organic modifier and pH. The pH of the mobile phase plays a significant role as it influences the degrees of ionization of analytes, the stationary phase, and mobile phase additives. Changes in pH affect selectivity and the retention times of analytes.

Moreover, Jadhav *et al*. (2011) successfully created and validated a method for the simultaneous determination of Paliperidone along with their respective degradation products in commercial formulations. This method exhibited excellent specificity, high precision, accuracy, sensitivity, and robustness, aligning with ICH guidelines and making it suitable for routine quality-control analysis. During forced degradation under hydrolytic, oxidative, photolytic, and thermal stress conditions, degradation was observed specifically in the oxidative and acidic stress conditions. A newly developed RP-LC method successfully detected five process-related impurities (Imp-A to Imp-E) in a test sample of paliperidone. Notably, among these five, Imp-C and Imp-D were identified as degradants. The Hypersil BDS C18 column (250 × 4.6 mm, 5 μm) facilitated excellent resolution between peaks corresponding to degradation products and process-related impurities from the analyte.

HPLC has been consistently employed in the development of studies for Ziprasidone, Pimozide, and Risperidone (Pavlovic*et al*., 2011; Kabra *et al*., 2014; Kokane *et al*., 2019). Various combinations of mobile phases, including isocratic elution and weak acidic mobile phases with buffers and organic solvents, were utilized to achieve enhanced separation for different antipsychotics drugs. Numerous studies have highlighted HPLC's promising attributes such as sensitivity, reliability, linearity, accuracy, precision, repeatability, robustness, limit of detection (LoD), and limit of quantification (LoQ), making it highly useful as a stability-indicating method for diverse pharmaceutical ingredients and products. This is why HPLC remains a popular technique for drug stability evaluation, with the flexibility to customize conditions based on the physicochemical properties of drugs.

Despite its advantages, HPLC does have limitations. The use of organic solvents in the mobile phase can make this method expensive and environmentally unfriendly, requiring proper waste disposal for the eluted organic wastes from the HPLC system. Additionally, HPLC lacks a universal detector for stability testing. Although the ultraviolet-visible (UV-vis) detector is commonly employed for chromophoric compounds, no single detector can detect all chemical compounds. HPLC may exhibit low sensitivity for certain compounds, and some may go undetected if irreversibly adsorbed to the HPLC packing materials. While HPLC is user-friendly, its operation can be time-consuming. To employ HPLC as a stability-indicating method, five essential steps are involved: (1) selecting the type of methods, (2) gathering information on the sample and analyte, (3) method development, (4) method optimization, and (5) method validation.

Gas Chromatography Techniques for Antipsychotic Drugs

Gas chromatography (GC) is a technique that utilizes gases for the separation and analysis of compounds that can be vaporized without undergoing decomposition. To conduct a sample analysis using GC, the sample is dissolved in a solvent before injection into the system. The sample undergoes vaporization before analytes are separated between stationary and mobile phases. A chemically inert gas, such as helium or nitrogen, carries the analytes through the heated column, facilitating the separation and partition of analytes. GC operates similarly to HPLC and thin-layer chromatography (TLC), differing in the use of a liquid stationary phase and a gaseous mobile phase.

GC demonstrates high precision, accuracy, sensitivity, and resolution in sample analysis and peak separation. Since the 1980s, it has been employed as a stability-indicating assay for various pharmaceutical substances and products **[29]**. GC/GC-MS techniques for the development of antipsychotic drugs is given in **Table 2**.

Table 2: Stability Indicating GC/GC-MS Methods for Drug Substances and their Elution Conditions for Antipsychotic Drug Analysis

S. No.	Drug Substances	Elution Methods	Analysis Time	References
1.	Chlorpromazine (CPZ), haloperidol (HAL), cyamemazine, quetiapine, clozapine, olanzapine (OLZ), and levomepromazine	A capillary column (30 m×0.25 mm I.D., 0.25 µm film thickness) with 5 % phenylmethylsiloxane (HP-5 MS). The oven temperature started at 120 °C for 2 min, followed by an increase of 20 °C/min to achieve the final temperature of 300 °C.	25 min	[30]
2.	Chlorpromazine, Levomepromazine, Cyamemazine, Clozapine, Haloperidol, and Quetiapine	Separation of the selected APDs was achieved with a capillary column (30 m × 0.25 mm ID, 0.25-µm film thickness) with 5% phenylmethylsiloxane (HP-5MS. The initial oven temperature was held at 120 °C for 2 min, then raised to 300 °C at a 20 °C/min rate	25 min	[31]
3.	Carbamazepine, Amitriptyline, doxepin, trihexyphenidyl, chlorpromazine, chlorprothixene, trifluoperazine, clozapine and haloperidol	AC-5 capillary column (15m X0.25mm i.d.). The temperature program was set at 180°C, increased at 10 °C/min until 270°C.	10min	[32]
4.	Blonanserin	Capillary column, DB5-MS (30 m × 0.25 mm i.d., 0.25 µm film thickness, 100°C (1-min hold) up to 300°C (5-min hold) at 20°C/min; injection and interface temperatures, 290°C and 280°C.	15min	[33]
5.	Blonanserin	DB-624 wide bore column, 30 m × 0.53 mm i.d., 3 µm film thickness, Helium, 4.5 mL/min (constant flow), 40°C (held 5 min) to 120°C at 10°C/min ramp, then to 220°C at 40°C/min ramp	[15]	[34]

GC, known for its high precision, accuracy, sensitivity, and resolution in sample analysis and peak separation, has served as a stability-indicating assay for various pharmaceutical substances and products since the 1980s. Peng *et al.*, (2012) validated gas chromatographic (GC) method for the simultaneous determination of residual solvents in blonanserin. This method was demonstrated to be specific, linear, sensitive, accurate, precise and robust. The easily operated and cost-effective direct-injection method proved to have no column contamination and matrix effects.

Notably, GC is considered more environmentally friendly than HPLC as it minimizes environmental pollution and conserves organic solvents **[35]**. However, the GC system is limited to the analysis of volatile samples and samples with lower melting points. Compounds with a molecular weight above 1000 Da pose challenges in vaporization since they are rarely volatile, making GC more suitable for smaller-sized molecules. Additionally, thermally unstable molecules are not well-suited for GC analysis. Furthermore, samples to be analyzed by GC must be salt-free and devoid of ions **[36]**.

High Performance Thin Layer Chromatography (HPTLC) Techniques for Antipsychotic Drugs

High-Performance Thin-Layer Chromatography (HPTLC) represents an advanced version of TLC, offering improved separation efficiency suitable for both qualitative and quantitative analyses **[37]**. This method is characterized by its rapid and cost-effective nature, providing reproducible results while allowing for the simultaneous analysis of a large number of samples with a small amount of mobile phase. HPTLC permits the use of various combinations of organic solvents as the mobile phase **(Table 3)**. These mobile phases can encompass mixtures of non-polar and polar organic solvents **[38]**, as well as combinations of organics with acidic or alkaline solvents. This flexibility extends to samples requiring mobile phases with extreme pH, where the ionization state of analytes is pH-dependent in the mobile phases. The vast range of mobile phase combinations enables the simultaneous separation of analytes in drug samples. Particularly suited for samples necessitating a combination of mobile phases, HPTLC excels where other analytical methods, notably HPLC, may face limitations. The HPTLC system is also applicable to suspension samples, producing colored bands and retention factors for analyte identification **[39, 40]**.

Table 3: Stability Indicating HPTLC Methods for Drug Substances and their Elution Conditions for Antipsychotic Drug Analysis

S. No.	Drug Substances	Elution Methods	References
1.	Olanzapine and fluoxetine	methanol:toluene (4:2 v/v) as the mobile phase and spectrodensitometric scanning-integration was performed at a wavelength of 233 nm using a Camag TLC Scanner III	[41]
2.	Olanzapine	Mobile phase comprising of toluene: methanol (5:5 v/v) and aluminum plate pre-coated with silica gel 60 F_{254} as a stationary phase. Densitometric analysis of olanzapine carried out at 297 nm gave sharp symmetrical peak with R_f value of 0.50.	[42]

3.	**Clozapine and Aripiprazole**	**HPTLC aluminum plates pre-coated with silica gel 60 F_{254} as the stationary phase, while the solvent system was toluene–methanol–ethyl acetate–ammonia (6.5:2.5:1:0.1, *v*/*v*). The R_F values were observed to be 0.43 and 0.60 for clozapine and aripiprazole. Densitometric analysis was carried out in absorbance mode at 218nm.**	**[43]**
4.	**Quetiapine fumarate**	**Stationary phase was silica gel and the mobile phase toluene–methanol 8:2 (v/v). Quetiapine fumarate RF value is 0.37 ± 0.02), Densitometric analysis at 254 nm**	**[44]**
5.	**Enalapril maleate**	**precoated silica gel F 254 HPTLC plates using a mixture of 1-buthanol, glacial acetic acid and water (12:3:5, v/v) as a mobile phase. Quantitative analysis was carried out at a wavelength of 207 nm.**	**[45]**
6.	**Asenapine Maleate**	**Precoated with silica gel G60 F_{254} on aluminium sheet as a stationary phase and methanol as a mobile phase, densitometric analysis at 235nm.**	**[46]**
7.	**Lurasidone**	**Plates precoated with silica gel 60 F 254 . The mobile phase used was Toluene: Methanol in the ratio of 9.5:0.5 v/v. The drug showed considerable absorbance at 231nm**	**[47]**
8.	**Quetiapine fumarate**	**Silica gel and the mobile phase toluene-methanol 8:2 (v/v). This system gave compact bands for quetiapine fumarate (RF 0.37 ± 0.02). Densitometric analysis of quetiapine fumarate was performed in absorbance mode at 254 nm.**	**[48]**
9.	**Olanzapine and Fluoxetine**	**Silica gel 60 F[sub] 254 TLC plate using methanol:toluene (4:2 v/v) as the mobile phase and spectrodensitometric scanning-integration was performed at a wavelength of 233 nm using a Camag TLC Scanner III. Rf value was found at 0.63 and 0.31.**	**[49]**

Numerous studies have demonstrated the specificity of HPTLC in drug stability analysis. For example, Shah *et al*. (2008) utilized HPTLC a rapid, selective and stability-indicating high performance thin layer chromatographic method for the estimation of olanzapine and fluoxetine in combined tablet dosage form. Ahmed *et al*. (2021) reported an accurate, precise, and economical stability indicating high performance thin layer chromatographic (HPTLC) method developed to assess the safety of olanzapine in pharmaceutical formulations. Olanzapine was subjected to forced degradation studies to assess the effect of environmental conditions on its stability. Stress conditions such as hydrolysis under acidic and alkaline environment, degradation and oxidation by heat, light and air were used to study the stability of olanzapine. Patel *et al*., (2018) developed a sensitive and precise high-performance thin-layer chromatographic (HPTLC) method for the simultaneous estimation of clozapine and aripiprazole in combination. The method employed HPTLC aluminum plates pre-coated with silica gel 60 F_{254} as the stationary phase, while the solvent system was toluene–methanol–ethyl acetate–ammonia (6.5:2.5:1:0.1, *v*/*v*). The R_F values were observed to be 0.43 and 0.60 for clozapine and aripiprazole, respectively. Densitometric analysis was carried out in absorbance mode at 218 nm. Dhaneshwar *et al.*, (2009) established and validated a sensitive, selective, precise, and stability indicating HPTLC method for quantitative analysis of quetiapine fumarate both as the bulk drug and in formulations. This method can effectively separate the drug form its degradation products, it can also be used for the stability determination.

However, HPTLC has several limitations. The separation bed is short, with a limited developing distance and lower plate efficiency. This limitation may result in ineffective separation if the retention factors (Rf values) and polarities of analytes are similar, leading to the overlap of spots and peaks. In such cases, the spots and peaks of analytes may overlap, rendering the separation less effective **[50]**.

Capillary Electrophoresis for Antipsychotic Drugs

Capillary electrophoresis (CE) is a highly efficient separation method conducted in narrow-bore capillaries under the influence of an external electric field. This versatile technique is applicable to various substances, including inorganic ions, chiral biomolecules, biotechnological samples, biopolymers, and clinical samples. CE offers selective, precise, and efficient separation, making it suitable for the analysis of complex mixtures with minimal sample size requirements (in the microliter range or below) and reduced need for reagents. CE presents several advantages over HPLC and GC. The method is versatile, allowing for short separation times and suitability for thermally unstable compounds. It is particularly effective in separating structurally similar compounds, such as chiral molecules. Compared with HPLC and gas chromatography, CE boasts distinct advantages, including automation, minimal sample preparation, cost-effectiveness of capillary columns, and the use of very small amounts of organic solvents and chemicals **[51, 52]**.

In stability-indicating assays, CE has become a complementary and alternative method, particularly for the separation of drugs and impurities with similar structures and chemical properties in pharmaceutical formulations. Samples analyzed using CE often require little or no pre-treatment before analysis. The CE system is applicable to water-insoluble, charged, and neutral drug substances, making it suitable for various pharmaceutical product analyses, including stability studies, determination of drug impurities, main component assays, chiral separation, and detection of drug residue. For example, the stability of metformin hydrochloride in tablets was successfully evaluated using CE, demonstrating good linearity, accuracy, precision, sensitivity, selectivity, and robustness, with successful resolution of metformin hydrochloride from its major degradation products **[53, 54]**.

Stability indicating capillary electrophoresis methods for drug substances and their elution conditions for antipsychotic drug analysis is given in **Table 4**.

Table 4: Stability Indicating Capillary Electrophoresis Methods for Drug Substances and their Elution Conditions for Antipsychotic Drug Analysis

S. No.	Drug Substances	Elution Methods	References
1.	Aripiprazole	Fused silica capillary column (30.2 cm x 75 µm ID), a background electrolyte containing 6 mmol L^{-1} ammonium formate buffer (pH 3) with 5% methanol under a potential of 15 kV and detection at 214 nm.	[55]
2.	Zolpidem Tartrate	Separation was achieved using background electrolyte of 20 mM disodium hydrogen phosphate adjusted with phosphoric acid (85%); pH, 5.50 and detection was at 254 nm.	[56]
3.	Asenapine	Phosphate buffer (15 mM, pH: 3.1) with 25.7 kV voltage and 20 °C capillary temperature.	[57]
4.	Quetiapine and its impurities	Background electrolyte (BGE) composed of ammonium acetate dissolved in a mixture of acetonitrile and methanol including acetic acid to protonate the substances	[58]
5.	Asenapine	SunFire C18, 5 µm column having 250×4.6 mm i.d. in isocratic mode, with mobile phase containing 0.02 M potassium dihydrogen phosphate: acetonitrile (95:05, v/v, pH 3.5 adjusted with 1% o-phosphoric acid) was used. The flow rate was 1.0 mL min−1 and effluents were monitored at 232 nm.	[59]

A notable limitation of CE as a stability-indicating method is its challenge in separating analytes with varying polarity and water solubility. This limitation was evident in the stability study of quetiapine, an antipsychotic drug used for treating schizophrenia **[60]**. The drug exhibited a series of impurities generated during synthesis, acid hydrolysis, and oxidative degradation, including desethanol quetiapine, N-formyl-quetiapine, quetiapine carboxylate, N-ethylpiperazinyl thiazepine, ethylquetiapine, bis(dithiazepine) (dimer), and N- and S-oxides. The diverse water solubility of these impurities made CE unsuitable for their analysis **[61]**.

Ultra-Performance Liquid Chromatographic methods for Antipsychotic Drugs

In the realm of pharmaceutical analysis, High-Performance Liquid Chromatography (HPLC) has long been a stalwart method. Nevertheless, as technology progresses, Ultra-Performance Liquid Chromatography (UPLC) has emerged as a compelling alternative. Both methodologies are indispensable in Quality Control (QC) laboratories, aiding pharmaceutical companies in guaranteeing the safety and efficacy of their products. Conversely to HPLC, UPLC employs diminutive particles, typically 1.7 µm or smaller in size, to enhance the speed and efficiency of separations. Stability indicating UPLC methods for drug substances and their elution conditions for antipsychotic drug analysis is given in **Table 5**.

Table 5: Stability Indicating UPLC Methods for Drug Substances and their Elution Conditions for Antipsychotic Drug Analysis

S. No.	Drug Substances	Elution Methods	References
1.	Quetiapine	Agilent Eclipse Plus C18, RRHD 1.8 µm (50 mm x 2.1 mm) column using gradient elution. The optimized mobile phase consists of 0.1 % aqueous triethylamine (pH 7.2) as a solvent-A and 80:20 v/v mixture of acetonitrile and methanol as solvent-B, within a run time of 5min.	[62]
2.	Olanzapine	Acquity UPLC BEH 100-mm, 2.1-mm, and 1.7-µm C-18 columns, and the gradient eluted within a short runtime, i.e., within 10.0 min, at 250 nm, the flow rate was 0.3 mL/min, and the column oven temperature was maintained at 27 °C	[63]
3.	Amisulpride, Risperidone, Paliperidone, Ziprasidone, Aripiprazole and Lurasidone	Acquity UPLC@BEH shield RP C18 (100 mm X 2.1 mm id, 1.7 m particle size), only 7 min with a 0.3 ml/min flow rate, 1 µl injection volume and a 45 °C column oven temperature	[64]
4.	Quetiapine	Agilent Eclipse Plus C18, RRHD 1.8 µm (50 mm x 2.1 mm) column using gradient elution. The optimized mobile phase consists of 0.1 % aqueous triethylamine (pH 7.2) as a solvent-A and 80:20 v/v mixture of acetonitrile and methanol as solvent-B at 252 nm.	[65]
5.	Ziprasidone	Acquity UPLC BEH 100-mm, 2.1-mm, and 1.7-µm Shield RP-18 columns, within 8.0 min. The eluted compounds were monitored at 230 nm, the flow rate was 0.3 mL/min, and the column oven temperature was maintained at 27°C.	[66]
6.	Iloperidone	Acquity UPLC® HSS C18 (2.1 mm × 100 mm, 1.8 micron) column thermostated at 35°C with a short runtime of 10 min. Quantification is achieved with photodiode array detection at 225 nm over the concentration range of 0.03 - 0.15 µg/mL	[67]
7.	Lacosamide and Quetiapine	Acquity BEH C18 column (50mmX2.1mm, 1.7µm) having used the phosphate buffer pH 2.5 and acetonitrile in the ratio of 75:25 v/v with a flow rate of 0.2mL/min at 210nm with run time 5 min.	[68]
8.	Ziprasidone	Supelco analytical column (100x2.1 mm i.d., 2.7 ?m) with 10 mM ammonium acetate buffer (pH: 6.7) and acetonitrile (ACN) as mobile phase with the ratio (55:45-Buffer:ACN) at a flow rate of 0.35 ml/ min at 318nm and the run time is 3 min.	[69]
9.	Paliperidone	Acquity ultra-performance liquid chromatograph (BEH 100 mm, 2.1 mm, 1.7 µm C-18 column) employing 0.01 M potassium dihydrogen phosphate buffer (pH 2.0) as mobile phase A and acetonitrile–water (9:1) as mobile phase B. A linear gradient (mobile phase A, mobile phase B in the ratio of 84:16) with a 0.45 mL/min flow rate was chosen	[70]

The reduction in column particle size and dimensions in UPLC, as opposed to HPLC, results in a notable reduction in analysis time and significant savings in solvent consumption, leading to cost reduction. UPLC exhibits peaks with decreased noise and an improved signal-to-noise ratio. The use of UPLC allows for the generation of sharp and narrow peaks, providing clearer information compared to peaks obtained through HPLC. This technological advancement creates new avenues for enhancing business profitability in a highly efficient manner.

APPLICATIONS IN ANTIPSYCHOTIC DRUG ANALYSIS

Furthermore, the review delves into the applications of each chromatographic technique in the analysis of various types of antipsychotic drugs, considering their chemical properties and formulation complexities. It discusses case studies and research findings that illustrate the successful application of these techniques in the determination of degradation pathways, impurity profiles, and related substances in different pharmaceutical formulations containing antipsychotic drugs.

CURRENT TRENDS AND FUTURE PROSPECTS

The review also highlights the emerging trends and advancements in chromatographic technology, including the integration of hyphenated techniques such as LC-MS (Liquid Chromatography-Mass Spectrometry), UPLC and the development of novel stationary phases and columns for enhanced separation and sensitivity. It discusses the potential implications of these advancements for improving the accuracy, efficiency, and reliability of stability indicating analysis in the context of antipsychotic drugs. Additionally, the review outlines the future prospects and potential research directions that could further advance the field of chromatographic analysis for antipsychotic drugs.

CONCLUSION

In conclusion, this review provides a comprehensive understanding of the comparative analysis of different chromatographic techniques for stability indicating analysis of antipsychotic drugs. It underscores the importance of selecting the most appropriate chromatographic technique based on the specific requirements of the drug formulation and highlights the potential for further advancements and innovations in this critical area of pharmaceutical analysis.

REFERENCES

[1] de Bartolomeis A, Barone A, Begni V, Riva MA. Present and future antipsychotic drugs: A systematic review of the putative mechanisms of action for efficacy and a critical appraisal under a translational perspective. Pharmacological research. 2022 Feb 1;176:106078.

[2] Rani A, Aslam M, Pandey G, Pant BN. A review on synthesis of FDA-approved antipsychotic drugs. Tetrahedron. 2023 Apr 24:133430.

[3] Remington G, Hahn MK, Agarwal SM, Chintoh A, Agid O. Schizophrenia: Antipsychotics and drug development. Behavioural Brain Research. 2021 Sep 24;414:113507.

[4] Chokhawala K, Stevens L. Antipsychotic medications. InStatPearls [Internet] 2023 Feb 26. StatPearls Publishing.

[5] Drummond N, McCleary L, Freiheit E, Molnar F, Dalziel W, Cohen C, Turner D, Miyagishima R, Silvius J. Antidepressant and antipsychotic prescribing in primary care for people with dementia. Canadian Family Physician. 2018 Nov 1;64(11):e488-97.

[6] Jennings AA, Guerin N, Foley T. Development of a tool for monitoring the prescribing of antipsychotic medications to people with dementia in general practice: a modified eDelphi consensus study. Clinical interventions in aging. 2018 Oct 23:2107-17.

[7] Faden J, Citrome L. Resistance is not futile: treatment-refractory schizophrenia–overview, evaluation and treatment. Expert opinion on pharmacotherapy. 2019 Jan 2;20(1):11-24.

[8] Haddad PM, Correll CU. The acute efficacy of antipsychotics in schizophrenia: a review of recent meta-analyses. Therapeutic advances in psychopharmacology. 2018 Nov;8(11):303-18.

[9] Chew YL, Khor MA, Lim YY. Choices of chromatographic methods as stability indicating assays for pharmaceutical products: A review. Heliyon. 2021 Mar 1;7(3).

[10] Blessy MR, Patel RD, Prajapati PN, Agrawal YK. Development of forced degradation and stability indicating studies of drugs—A review. Journal of pharmaceutical analysis. 2014 Jun 1;4(3):159-65.

[11] Rawat T, Pandey IP. Forced degradation studies for drug substances and drug products-scientific and regulatory considerations. Journal of pharmaceutical Sciences and research. 2015 May 1;7(5):238.

[12] Ravisankar P, Swathi V, Srinivasa Babu P, Shaheem Sultana Md GS. Current trends in performance of forced degradation studies and stability indicating studies of drugs. IOSR Journal of Pharmacy and Biological Sciences. 2017;12(6):17-36.

[13] Khan MR, Wabaidur SM, Azam M, AlAmmari AM. Assessment of inorganic ion in drinking water using new method based on ultra-performance liquid chromatography-mass spectrometry. Journal of King Saud University-Science. 2020 Jun 1;32(4):2329-35.

[14] Alsohaimi IH, Khan MR, Alothman ZA, Wabaidur SM, Siddiqui MR, Alotaibi NF, Ghfar AA. Quantitative analysis of some inorganic anions (nitrate and nitrite) in metropolitan and bottled water samples using ultra-performance liquid chromatography/electrospray ionization mass spectrometry.

Desalination and Water Treatment. 2018;103:232-9.

[15] Aljerf L, AlMasri N. High resolution chromatography and sensitive retention: optimization of the experimental conditions for proteins extraction by preparative HPLC. J. Prog. Res. Mod. Phys. Chem. 2018;3(1):97-103.

[16] Silva Gracia M, Köppl A, Unholzer S, Haen E. Development and validation of an HPLC-UV method for the simultaneous determination of the antipsychotics clozapine, olanzapine and quetiapine, several beta-blockers and their metabolites. Biomedical Chromatography. 2017 Oct;31(10):e3968.

[17] Pavlovic M, Malesevic M, Nikolic K, Agbaba D. Development and validation of an HPLC method for determination of ziprasidone and its impurities in pharmaceutical dosage forms. Journal of AOAC International. 2011 May 1;94(3):713-22.

[18] Atila Karaca S, Yeniceli Ugur D. Development of a validated HPLC method for simultaneous determination of olanzapine and aripiprazole in human plasma. Journal of Research in Pharmacy. 2018;22(4).

[19] Kabra P, Nargung LV, Srinivasa Murthy M. RP-HPLC method for estimation of an antipsychotic drug-Pimozide. Asian J Pharm Clin Res. 2014;7(4):49-51.

[20] Kokane BA, Kokane JV, Dabhade PS, Kawada SN. RP-HPLC method development and validation for estimation of Risperidone in bulk & dosage forms. Int. J. Pharm. Sci. Rev. Res. 2019; 54(1):29-32.

[21] Al-Nimry SS, Khanfar MS. Validation of an RP-HPLC Method for the Determination of Asenapine Maleate in Dissolution Media and Application to Study In Vitro Release from Co-Crystals. Scientia Pharmaceutica. 2021 Mar 8;89(1):14.

[22] Patel KN, Gajjar UH, Patel PU, Pancholi SS. Development and validation of RP-HPLC method for simultaneous estimation of haloperidol and trihexyphenidyl hydrochloride in tablet dosage form. Asian Journal of Pharmaceutical Analysis. 2022;12(4):253-7.

[23] Patel KI, Joshi DE, Kumbhani JA, Prajapati VI. HPLC Method Development for Estimation of Dissolution of Antipsychotic Drug as Sublingual Film Dosage Form. J. Chem. Sci. 2018;7:420.

[24] Sangeetha RK. Method Development and Validation For The Estimation of Lurasidone By RP-HPLC and HPTLC. Eur. J. pharm. and med. Res. 2015;2:529-40.

[25] Jadhav SA, Landge SB, Choudhari PM, Solanki PV, Bembalkar SR, Mathad VT. Stress degradation behavior of paliperidone, an antipsychotic drug, and development of suitable stability-indicating RP-LC method. Chromatography Research International. 2011;2011.

[26] Mandrioli R, Fanali S, Ferranti A, Raggi MA. HPLC analysis of the novel antipsychotic drug quetiapine in human plasma. Journal of pharmaceutical and biomedical analysis. 2002 Nov 7;30(4):969-77.

[27] Djordjević Filijović N, Pavlović A, Nikolić K, Agbaba D. Validation of an HPLC method for determination of aripiprazole and its impurities in pharmaceuticals. Acta Chromatographica. 2014 Mar 1;26(1):13-28.

[28] Cui D, Li Y, Lian M, Yang F, Meng Q. Development of a simple and stability-indicating RP-HPLC method for determining olanzapine and related impurities generated in the preparative process. Analyst. 2011;136(15):3149-56.

[29] Yik-Ling C, Hon-Kent L, Lokesh VS. New Stability Indicating Method for Estimation of Purity of Flibanserin Active Pharmaceutical Ingredient. Indian Drugs. 2020 Apr 1;57(4).

[30] Da Fonseca BM, Moreno IE, Barroso M, Costa S, Queiroz JA, Gallardo E. Determination of seven selected antipsychotic drugs in human plasma using microextraction in packed sorbent and gas chromatography–tandem mass spectrometry. Analytical and bioanalytical chemistry. 2013 May;405:3953-63.

[31] Caramelo D, Rosado T, Oliveira V, Rodilla JM, Rocha PM, Barroso M, Gallardo E. Determination of antipsychotic drugs in oral fluid using dried saliva spots by gas chromatography-tandem mass spectrometry. Analytical and bioanalytical chemistry. 2019 Sep 1;411:6141-53.

[32] Shen M, Xiang P, Wu H, Shen B, Huang Z. Detection of antidepressant and antipsychotic drugs in human hair. Forensic science international. 2002 Apr 18;126(2):153-61.

[33] Bhole RP, Wankhede SB, pandey M. Stability indicating HPTLC method for simultaneous estimation of empagliflozin and linagliptin in pharmaceutical formulation. Analytical Chemistry Letters. 2017 Jan 2;7(1):76-85.

[34] Hattori H, Iwai M, Ogawa T, Mizutani Y, Ishii A, Suzuki O, Seno H. Simple analysis of blonanserin, a novel antipsychotic agent, in human plasma by GC-MS. Forensic Toxicology. 2010 Jul;28:105-9.

[35] Peng M, Liu J, Lu D, Yang YJ. Development and validation of a stability-indicating gas chromatographic method for quality control of residual solvents in blonanserin: a novel atypical antipsychotic agent. Journal of chromatographic science. 2012 Sep 1;50(8):727-32.

[36] Subasranjan A, Suresh P, Srinivasulu C, Hemant R. A validated stability-indicating gas chromatography method for determination of divalproex sodium impurities in pharmaceutical preparation. Drug Testing and Analysis. 2010 Apr;2(4):182-7.

[37] Feng T, Sun M, Song S, Zhuang H, Yao L. Gas chromatography for food quality evaluation. InEvaluation technologies for food quality 2019 Jan 1 (pp. 219-265). Woodhead Publishing.

[38] Choukaife AE, Aljerf L. A novel method to chromatographically resolution of sulphonamides by vapour-programmed Thin-Layer Chromatography. MOJ Biorg Org Chem. 2017;1(4):00024.

[39] Padh H, Parmar S, Patel B. Stability indicating HPTLC method for estimation of mangiferin in bulk and dosage form. Int J Pharm Biol Sci. 2017;7:71-.

[40] Loescher CM, Morton DW, Razic S, Agatonovic-Kustrin S. High performance thin layer chromatography (HPTLC) and high performance liquid chromatography (HPLC) for the qualitative and quantitative analysis of Calendula officinalis—Advantages and limitations. Journal of Pharmaceutical and Biomedical Analysis. 2014 Sep 1;98:52-9.

[41] Shah CR, Suhagia BN, Shah NJ, Patel DR, Patel NM. Stability-indicating simultaneous HPTLC method for olanzapine and fluoxetine in combined tablet dosage form. Indian journal of pharmaceutical sciences. 2008 Mar;70(2):251.

[42] Ahmed R, Bhusari KP, Tajne MR, Khan SA. Development of a stability indicating HPTLC method for the estimation of olanzapine in pharmaceutical dosage forms. Journal of the Indian Chemical Society. 2021 Nov 1;98(11):100215.

[43] Patel VB, Shah DA, Gohil HB, Chhalotiya U. Stability-indicating high-performance thin-layer chromatographic method for the estimation of antipsychotic drug combination clozapine and aripiprazole. JPC–Journal of Planar Chromatography–Modern TLC. 2018 Oct;31:397-403.

[44] Dhaneshwar SR, Patre NG, Mahadik MV. Stability-indicating HPTLC method for quantitation of quetiapine fumarate in the pharmaceutical dosage form. Acta chromatographica. 2009 Mar 1;21(1):83-93.

[45] Mennickent SC, Rivas C, Vega MA, De Diego MG. A stability-indicating HPTLC method for quantification of enalapril maleate in tablets. Journal of the Chilean Chemical Society. 2013;58(2):1737-40.

[46] Patel RB, Naregalkar NS, Patel MR. Stability-indicating HPTLC method for quantitative estimation of asenapine maleate in pharmaceutical formulations, equilibrium solubility, and ex vivo diffusion studies. Journal of Liquid Chromatography & Related Technologies. 2015 Nov 26;38(19):1731-9.

[47] Polawar AR, Damle MC. Development and Validation of Stability Indicating HPTLC Method for Quantification Of Lurasidone HCL. Pharma Science Monitor. 2014 Jul 1;5(3).

[48] Dhaneshwar SR, Patre NG, Mahadik MV. Stability-indicating HPTLC method for quantitation of quetiapine fumarate in the pharmaceutical dosage form. Acta chromatographica. 2009 Mar 1;21(1):83-93.

[49] Shah CR, Suhagia BN, Shah NJ, Patel DR, Patel NM. Stability-indicating simultaneous HPTLC method for olanzapine and fluoxetine in combined tablet dosage form. Indian journal of pharmaceutical sciences. 2008 Mar;70(2):251.

[50] Kamboj A, Saluja AK. Development of validated HPTLC method for quantification of stigmasterol from leaf and stem of Bryophyllum pinnatum. Arabian journal of Chemistry. 2017 May 1;10:S2644-50.

[51] Al Azzam KM, Saad B, Tat CY, Mat I, Aboul-Enein HY. Stability-indicating micellar electrokinetic chromatography method for the analysis of sumatriptan succinate in pharmaceutical formulations. Journal of pharmaceutical and biomedical analysis. 2011 Dec 15;56(5):937-43.

[52] El Deeb S, Wätzig H, Abd El-Hady D. Capillary electrophoresis to investigate biopharmaceuticals and pharmaceutically-relevant binding properties. TrAC Trends in Analytical Chemistry. 2013 Jul 1;48:112-31.

[53] Altria KD. Analysis of pharmaceuticals by capillary electrophoresis. Springer Science & Business Media; 2013 Apr 17.

[54] Hamdan II, Jaber AB, Abushoffa AM. Development and validation of a stability indicating capillary electrophoresis method for the determination of metformin hydrochloride in tablets. Journal of pharmaceutical and biomedical analysis. 2010 Dec 15;53(5):1254-7.

[55] Fajardo FA, Tavares MF, Rashid A, Prado MS. Novel Eco-Friendly Stability Indicating Capillary Zone Electrophoresis Method for Determination of Aripiprazole in Tablet Dosage form: DoE Directed Optimization, Development and Method Validation. Journal of Pharmaceutical Sciences. 2022 Dec 1;111(12):3340-51.

[56] Al Azzam KM, Yit LK, Saad B, Shaibah H. Development and validation of a stability-indicating capillary electrophoresis method for the determination of zolpidem tartrate in tablet dosage form with positive confirmation using 2D-and 3D-DAD fingerprints. Scientia Pharmaceutica. 2014 Jun;82(2):341-56.

[57] Aliyeva S, Atila Karaca S, Uğur A, Dal Poçan AG, Yeniceli Uğur D. A novel capillary electrophoresis method for the quantification of asenapine in pharmaceuticals using Box-Behnken design. Chemical Papers. 2020 Dec;74:4443-51.

[58] Borst C, Belal F, Holzgrabe U. Possibilities and limitations of capillary electropherosis in pharmaceutical analysis. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2013 Jul 15;68(7):526-30.

[59] Chhalotiya UK, Bhatt KK, Shah DA, Patel JR. Stability-indicating liquid chromatographic method for the quantification of the new antipsychotic agent asenapine in bulk and in pharmaceutical formulation. Scientia Pharmaceutica. 2012 Jun;80(2):407-18.

[60] Hillaert S, Snoeck L, Van den Bossche W. Optimization and validation of a capillary zone electrophoretic method for the simultaneous analysis of four atypical antipsychotics. Journal of Chromatography A. 2004 Apr 16;1033(2):357-62.

[61] Borst C, Belal F, Holzgrabe U. Possibilities and limitations of capillary electropherosis in pharmaceutical analysis. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2013 Jul 15;68(7):526-30.

[62] Trivedi RK, Patel MC. Development and validation of a stability indicating RP-UPLC method for determination of quetiapine in pharmaceutical dosage form. Scientia pharmaceutica. 2011 Mar;79(1):97-112.

[63] Krishnaiah C, Murthy MV, Kumar R, Mukkanti K. Development of a stability-indicating UPLC method for determining olanzapine and its associated degradation products present in active pharmaceutical ingredients and pharmaceutical dosage forms. Journal of pharmaceutical and biomedical analysis. 2011 Mar 25;54(4):667-73.

[64] Jebaliya H, Shah A, Karad SC, Nakum S, Dabhi B. Quantification of panel of most potent antipsychotic medicines by high throughput UPLC method. Results in Chemistry. 2022 Jan 1;4:100427.

[65] Trivedi RK, Patel MC. Development and validation of a stability indicating RP-UPLC method for determination of quetiapine in pharmaceutical dosage form. Scientia pharmaceutica. 2011 Mar;79(1):97-112.

[66] Raj S, Kumari KS, Krishnaiah C, Rao AN. Development of a stability-indicating UPLC method for determining ziprasidone hydrochloride and its associated degradation products present in active pharmaceutical ingredients and pharmaceutical dosage forms. Journal of Liquid Chromatography & Related Technologies. 2013 Mar 1;36(7):968-82.

[67] Landge SB, Jadhav SA, Vishwambar SP, Solanki PV, Bembalkar SR, Mathad VT. Development and validation of RP-UPLC method for the determination of iloperidone, its related compounds and degradation products in bulk and dosage form. American Journal of Analytical Chemistry. 2014 Sep 30;5(14):969.

[68] Sivaganesh T, Rao TS, Ramasrinivas K, SeshamRaju U, Shasikiran YM, Raja G. Development and validation of stability indicating rp-uplc assay method for the determination of lacosamide and quetiapine fumarate in bulk and tablet dosage forms. Bulletin of Faculty of Pharmacy, Cairo University. 2019 Dec 1;57(2):157-66.

[69] Mittal S, Gupta A, Narasimhan B, Srinivas K, Gupta R, Semwal V. Development and validation of stability indicating UPLC assay method for ziprasidone active pharma ingredient. Chronicles of Young Scientists. 2012 Oct 1;3(4):286-.

[70] Bindu KH, Reddy IU, Anjaneyulu Y, Suryanarayana MV. A stability-indicating ultra-performance liquid chromatographic method for estimation of related substances and degradants in paliperidone active pharmaceutical ingredient and its pharmaceutical dosage forms. Journal of chromatographic science. 2012 Apr 1;50(4):368-72.