



Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry

Journal home page: www.ajpamc.com

<https://doi.org/10.36673/AJPAMC.2026.v14.i01.A03>



NEW ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF UV-VISIBLE SPECTROSCOPY FOR THE ESTIMATION OF VORTIOXETINE: A SYSTEMATIC REVIEW

K. Nandankumar*¹, S. Sumanth¹, Y. S. Sonalika¹, Y. Vinutha¹

¹*Department of Pharmaceutical Analysis, Bharathi College of Pharmacy, Bharathinagara, Maddur, Mandya, Karnataka, India.

ABSTRACT

Analytical method development is a fundamental component of pharmaceutical research, supporting drug discovery, formulation development, quality control, stability assessment and regulatory compliance. The rapid emergence of complex drug molecules, biologics, Nano medicines and combination therapies has increased the demand for analytical techniques that are highly sensitive, selective, rapid, robust and environmentally sustainable. This review critically examines recent advances in pharmaceutical analytical method development, with emphasis on conventional and emerging technologies employed for qualitative and quantitative analysis of Vortioxetine in bulk and tablet dosage form. Major analytical platforms, including ultraviolet-visible (UV-Vis) spectroscopy, Fourier-transform infrared (FTIR) spectroscopy are comprehensively discussed with respect to their principles, applications, strengths and limitations. In addition, recent progress in green analytical chemistry, miniaturized analytical systems, and regulatory expectations for method validation according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines is critically evaluated. The integration of advanced analytical technologies with data-driven approaches is transforming pharmaceutical analysis by enabling faster, more accurate, cost-effective and environmentally responsible methodologies.

KEYWORDS

Vortioxetine, UV Spectroscopy, FTIR and ICH Guidelines.

Author for Correspondence:

Nandankumar K,
Department of Pharmaceutical Analysis,
Bharathi College of Pharmacy, Bharathinagara,
Maddur, Mandya, Karnataka, India.

Email: knandankumar@gmail.com

INTRODUCTION

Vortioxetine is a novel antidepressant primarily used for the treatment of major depressive disorder (MDD) in adults. It belongs to the class of serotonin modulators and stimulators (SMS) and differs from conventional selective serotonin reuptake inhibitors (SSRIs) because it combines inhibition of the

serotonin transporter with modulation of several serotonin (5-HT) receptor subtypes.

Vortioxetine increases the availability of serotonin in the brain by inhibiting its reuptake while acting as an agonist, partial agonist, or antagonist at different serotonin receptors, including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT₃ and 5-HT₇ receptors. This multimodal mechanism is believed to improve mood, reduce anxiety and enhance cognitive functions such as attention, learning, and memory, which are often impaired in patients with depression.

Vortioxetine is administered orally, usually once daily, with recommended doses ranging from 5mg to 20mg, depending on the patient's response and tolerability. It undergoes extensive hepatic metabolism, primarily via the CYP2D6 enzyme and dosage adjustments may be necessary when used with strong CYP2D6 inhibitors or in poor metabolizers.

Serotonin Reuptake Inhibition

Vortioxetine inhibits the serotonin transporter (SERT)

This reduces the reuptake of serotonin (5-HT) into the presynaptic neuron.

As a result, the concentration of serotonin in the synaptic cleft increases, enhancing serotonergic neurotransmission.

Serotonin Receptor Modulation

Through these combined actions, Vortioxetine:

Increases serotonin availability.

Modulates the release of norepinephrine, dopamine, acetylcholine and histamine in specific brain regions.

Enhances synaptic plasticity and neuronal communication.

Improves mood, anxiety symptoms, and cognitive performance in patients with depression.

REVIEW OF LITERATURE

Karajgi *et al*, (2023)¹ has created a first-order derivative UV spectrophotometric technique to measure the amount of vortioxetine hydrochloride in drug formulations. Since no UV derivative approach had previously been described for the quantitative analysis of vortioxetine hydrochloride,

the investigation was carried out to build a straightforward, precise and repeatable analytical procedure. The medication exhibited maximal absorbance at 230nm while adhering to Beer-Lambert's law in the concentration range of 10-50µg/mL when methanol was used as the solvent. Recovery studies verified the accuracy and precision of the approach, which was validated in accordance with ICH principles. For regular analysis, the results showed adequate reproducibility and dependability. The authors came to the conclusion that vortioxetine hydrochloride in pharmaceutical dosage forms can be quantitatively estimated using the suggested first-order derivative UV spectrophotometric approach. By offering a straightforward and affordable analytical technique for the regular measurement of vortioxetine hydrochloride, this work supports pharmaceutical quality control.

Karajgi *et al*² Vortioxetine hydrochloride in pharmaceutical formulations can now be quantitatively estimated using a validated area under curve (AUC) UV spectrophotometric technique. Since no UV spectrophotometric approach based on the area under curve technique had previously been published for the medication, the study was conducted to build a straightforward, accurate, precise, and repeatable analytical procedure. The measurement was conducted in the wavelength range of 220-240nm using methanol as the solvent; vortioxetine hydrochloride showed its maximum absorbance at 230nm. Recovery experiments were conducted to verify the accuracy of the approach, which was validated in accordance with ICH recommendations. The outcomes showed adequate accuracy, precision and repeatability, demonstrating the method's dependability. The authors came to the conclusion that vortioxetine hydrochloride in pharmaceutical dosage forms can be routinely quantitatively estimated using the suggested area under curve UV spectrophotometric approach. By offering a straightforward and affordable analytical method for quality control applications, this study advances pharmaceutical analysis.

Naik *et al*³ to assess the exposure-response
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relationship of vortioxetine in patients with major depressive disorder (MDD), population pharmacokinetic (PK) and pharmacokinetic–pharmacodynamic (PK/PD) models were developed. Understanding the connection between vortioxetine plasma levels and its therapeutic efficacy in depressed individuals was the focus of the investigation. Compartmental PK models and Emax pharmacodynamics models were used to examine pharmacokinetic data from 12 clinical studies with 3160 patients and effectiveness data from seven MDD studies with 2537 individuals. A two-compartment model with first-order absorption and elimination provided the best description of vortioxetine's pharmacokinetics. The findings showed that the effectiveness of vortioxetine rose with plasma concentration and plateaued at increasing exposure levels. The authors came to the conclusion that the created PK/PD models supported the approved therapeutic dose range and accurately described the exposure-response connection of vortioxetine. By offering insightful information on the pharmacokinetic behaviour, effectiveness, and dose optimisation of vortioxetine in patients with major depressive disorder, this study advances clinical pharmacology.

Milan Meloun *et al*⁴ used a UV–VIS multiwavelength pH-titration approach to examine the overlapping thermodynamic dissociation constants of vortioxetine. By contrasting potentiometric and spectrophotometric pH-titration methods, the study sought to ascertain the dissociation constants of vortioxetine hydrobromide. The overlapping dissociation constants were assessed using a chemometric method that involved nonlinear regression analysis over a pH range of 5-10. Reliable measurement of the two dissociation constants from variations in the vortioxetine absorption spectra was made possible by the UV–VIS spectrophotometric approach. Spectrophotometric investigation yielded thermodynamic dissociation constants of $pK_{a1} = 7.22$ and $pK_{a2} = 8.67$ at 25°C and $pK_{a1} = 7.27$ and $pK_{a2} = 8.79$ at 37°C. Similar outcomes from potentiometric analysis supported the suggested method's dependability. Additionally, the study

showed that the chromophore's protonation had little effect on the absorption spectra and provided theoretical predictions using MARVIN and ACD/Percepta software to corroborate the experimental results. The authors came to the conclusion that a dependable and efficient way for figuring out the thermodynamic dissociation constants of vortioxetine is the UV–VIS multiwavelength pH-titration method.

KE Pravallika *et al*⁵ created and verified two quick, accurate, selective, and straightforward UV spectrophotometric techniques for measuring vortioxetine hydrobromide in pharmaceutical dosage forms and bulk. The goal of the project was to develop affordable analytical techniques that could be used for regular quality control analysis with two distinct solvents. Method B used a 50:50 (v/v) mixture of water and methanol with detection at 224nm, whereas Method A used methanol as the solvent with detection at 228nm. Over concentration ranges of 2-12µg/mL for Method A and 3–15µg/mL for Method B, both approaches complied with Beer–Lambert's law, demonstrating exceptional linearity with a correlation coefficient (R^2) of 0.999. $Y = 0.061x + 0.01$ for Method A and $Y = 0.061x + 0.03$ for Method B were the regression equations that were found. With mean recovery values for procedures A and B ranging from 98.3–100.7% and 98.5–100.3%, respectively, the devised procedures showed acceptable accuracy. Good reproducibility was demonstrated by precision studies with standard deviation values less than 1% and %RSD less than 2%. The ICH guidelines for accuracy, precision, robustness, ruggedness, limit of detection and limit of quantification were followed in the validation of both approaches. The authors came to the conclusion that the suggested UV spectrophotometric techniques are appropriate for routine quantitative assessment of vortioxetine hydrobromide in pharmaceutical formulations and are dependable and accurate.

Ancy Mathew *et al*⁶ Created and verified a straightforward, accurate, precise, and cost-effective absorbance ratio UV spectrophotometric approach for the simultaneous measurement of aripiprazole
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and vortioxetine in a synthetic mixture. The goal of the study was to develop a trustworthy analytical technique appropriate for regular quality control examination of the combined medications. Vortioxetine was measured at 255nm and 225nm using the absorbance ratio method, while aripiprazole was examined at the same wavelengths. Over the concentration range of 2-20µg/mL for vortioxetine and 2-32µg/mL for aripiprazole, the technique demonstrated excellent linearity. With correlation values (R^2) of 0.9992 and 0.9971, respectively, the regression equations for vortioxetine were $y = 0.0321x + 0.0223$ at 255 nm and $y = 0.0536x + 0.0055$ at 225nm. The suggested method's reliability for quantitative estimate was shown by its satisfactory precision and accuracy. The technique is appropriate for routine pharmaceutical quality control because validation studies verified satisfactory analytical performance. The authors came to the conclusion that vortioxetine and aripiprazole in pharmaceutical dose forms can be determined simultaneously using the suggested absorbance ratio UV spectrophotometric approach.

Melou *et al*⁷ Use potentiometric pH-titration and UV-Vis multiwavelength spectrophotometric methods to examine the overlapping thermodynamic dissociation constants of vortioxetine. To precisely ascertain the ionisation behaviour of vortioxetine at 25°C and 37°C, the study used chemometric data analysis. The spectrophotometric and potentiometric approaches showed good agreement in the successful estimation of two dissociation constants. The results offer essential insights into the physicochemical characteristics of vortioxetine, which are crucial for comprehending its stability, solubility, and pharmaceutical formulation.

Meliha Merve Çicekliyur *et al*⁸ used both in vivo and in silico methods to examine vortioxetine's potential for cytotoxicity and genotoxicity. By analysing vortioxetine's effects on genetic material, the study sought to determine the drug's long-term safety. Chromosome aberration (CA) and micronucleus (MN) assays were used to assess genotoxicity in cultured human peripheral blood

cells, whilst the mitotic index (MI) was used to assess cytotoxicity. Agarose gel electrophoresis and UV titration were used for DNA interaction investigations, and Attraction Cavities and AutoDock Vina were used for molecular docking. The findings showed that vortioxetine cleaves pBR322 DNA in the presence of hydrogen peroxide and attaches to calf thymus DNA through groove-binding interactions with a binding constant (K_b) of $6.25 \times 10^3 \text{ M}^{-1}$. Similar to escitalopram, molecular docking experiments revealed binding affinities of -7.29kcal/mol (Attraction Cavities) and -6.01kcal/mol (AutoDock Vina). Under the tested circumstances, both medications showed possible genotoxic effects. The authors came to the conclusion that long-term vortioxetine use may present a genotoxic risk, underscoring the significance of additional long-term safety assessment and cautious clinical monitoring.

Ayman A. Goud *et al*⁹ have created and verified straightforward, sensitive, accurate, and easy-to-use visible spectrophotometric techniques for the quantitative measurement of vortioxetine hydrobromide (VOR) in pharmaceutical formulations and pure drugs. Using N-bromosuccinimide (NBS) as a green oxidising agent in conjunction with amaranth (AM), methylene blue (MB) and indigocarmine (IC) dyes, the study sought to develop cost-effective analytical techniques. Excess NBS oxidised vortioxetine HBr in an acidic solution and the unreacted NBS was measured spectrophotometrically using the chosen dyes. At 520nm (AM), 663nm (MB) and 609nm (IC), absorbance was observed with correlation values ranging from 0.9993 to 0.9996, the suggested approaches demonstrated outstanding linearity spanning concentration ranges of 1.0–15µg/mL, 0.5–12µg/mL and 0.50–10µg/mL. With LOD values of 0.30, 0.15 and 0.15µg/mL and LOQ values of 1.0, 0.50 and 0.50µg/mL for the AM, MB and IC procedures, respectively, the techniques demonstrated high sensitivity. Excellent accuracy, precision and dependability were established by validation investigations and the methods' application was further shown by recovery studies employing the usual addition approach. There was

no discernible difference between the suggested and reference procedures, according to a statistical comparison using Student's t-test and F-test. The authors came to the conclusion that vortioxetine hydrobromide in pharmaceutical formulations can be routinely analysed for quality using these visual spectrophotometric techniques.

Karol Wróblewski *et al*¹⁰ for the measurement of vortioxetine hydrobromide in bulk medication and tablet formulations, a straightforward, quick, accurate, precise, and stability-indicating HPLC-DAD method has been developed and validated. In order to guarantee drug purity, efficacy, and safety, the study sought to develop a trustworthy analytical technique that could quantify vortioxetine in the presence of its primary degradation product. The medication was exposed to oxidative, hydrolytic, and photolytic stress conditions. Significant degradation was seen under oxidative stress, which resulted in the development of a major degradation product that was detected by ESI-MS/MS. A C18 column with a mobile phase of acetonitrile and water containing acetic acid and triethylamine in isocratic mode was used to accomplish chromatographic separation. At a flow rate of 1.0 mL/min, detection was carried out at 228nm. Over the concentration range of 25–125µg/mL, the technique demonstrated exceptional linearity. Validation investigations showed satisfactory selectivity, recovery ranging from 100.0 to 101.6% and good precision with %RSD below 1.8%. Vortioxetine in tablet formulations was successfully quantitatively estimated using the approved method. The authors came to the conclusion that the suggested HPLC-DAD technique is dependable, specific, and appropriate for regular vortioxetine quality control and stability investigations.

Vanita M. Lasan *et al*¹¹ A straightforward, accurate, specific, and precise HPTLC method for estimating vortioxetine hydrobromide in bulk drugs has been developed and validated. The goal of the study was to develop a trustworthy analytical technique appropriate for regular quality control analysis. Chloroform: methanol: glacial acetic acid (92:8:5, v/v/v) was used as the mobile phase for chromatographic separation on TLC aluminium

plates that had been pre-coated with silica gel G60 F254. Vortioxetine hydrobromide showed an R_f value of 0.65 ± 0.03 when densitometric analysis was carried out at 230nm. With a correlation coefficient (R²) of 0.9932, the approach showed good linearity across the concentration range of 500–900ng/spot. The approach demonstrated satisfactory precision, accuracy, specificity, and sensitivity when validated in accordance with ICH recommendations. The results showed that the LOD and LOQ were 37.81 ng/spot and 114.6ng/spot, respectively. Excellent accuracy and reproducibility were demonstrated by intermediate precision and repeatability studies with %RSD values less than 1%. The authors came to the conclusion that the devised HPTLC method is sensitive, dependable, and appropriate for routine quantitative estimation of vortioxetine hydrobromide.

Nagarjuna Chary Ragi *et al*¹² Vortioxetine's forced degradation behaviour has been studied, and its degradation products have been found using sophisticated analytical techniques. The study's objectives were to assess vortioxetine's stability under different stress scenarios in compliance with ICH Q1A (R2) recommendations and to describe the degradation products that were produced. Thermal, acidic, alkaline, neutral hydrolytic, photolytic and oxidative stress conditions were applied to vortioxetine. Six breakdown products were formed as a result of the drug's substantial deterioration under photolytic and oxidative stress, although it remained stable under thermal and hydrolytic conditions. High-resolution LC/MS, LC/MS/MS and ESI-Q-TOF-MS/MS techniques were used to identify and characterise these degradation products. Through synthesis and structural characterisation using ¹H and ¹³C Nuclear Magnetic Resonance (NMR) spectroscopy, the main degradation products were further verified. The authors developed a degradation route to explain the generation of degradation products under oxidative and photolytic conditions based on the analytical results. The study came to the conclusion that the devised analytical approach successfully detected and characterised vortioxetine degradation products, offering useful data for quality control, stability

evaluation, and the creation of stable pharmaceutical formulations.

CallRubeena Sulthana *et al*¹³ have created and verified a quick, accurate, and trustworthy RP-HPLC method for the measurement of vortioxetine in tablet and bulk medication dosage forms. The goal of the study was to develop a straightforward analytical technique appropriate for regular vortioxetine quality control analysis. Using an ODS C18 column (4.6 × 250mm, 5µm) and 100% acetonitrile as the mobile phase at a flow rate of 1.0mL/min, chromatographic separation was performed. Vortioxetine demonstrated a retention time of 2.252 ± 0.02 minutes when detection was carried out at 274nm. Over the concentration range of 10–50µg/mL, the suggested technique demonstrated satisfactory linearity. Excellent repeatability and reproducibility of the approach were proven by validation studies, which showed good precision with %RSD values below 2.0%. For the quantitative estimation of vortioxetine, the devised RP-HPLC method was shown to be straightforward, precise, and accurate. The validated method is appropriate for routine quality control analysis of vortioxetine in pharmaceutical tablet formulations and bulk drugs, the authors found.

Mandal *et al*¹⁴ have released a study design for a randomised, double-blind, placebo-controlled superiority trial to assess vortioxetine's safety and effectiveness as an additional treatment for OCD patients. The purpose of the trial is to ascertain whether vortioxetine, when added to standard medication, improves OCD symptoms, cognitive function, and overall clinical outcomes while preserving a safe profile. It describes the trial design and procedures like a research protocol but does not present clinical outcomes. It is anticipated that the trial's results will offer proof of vortioxetine's possible use as an adjunctive treatment for OCD.

Papalexi *et al*¹⁵ Over the course of three months, 336 outpatients with major depressive disorder (MDD) participated in an evaluation of vortioxetine's practical efficacy. Sheehan Disability Scale (SDS) ratings significantly decreased from baseline, and the study showed notable improvements in functional outcomes. After three

months of treatment, about half of the patients had made a functional recovery. Functioning improved more with higher doses of vortioxetine (15–20mg/day) than with lower doses (5–10mg/day). The results corroborate vortioxetine's efficacy in reducing depression symptoms and enhancing day-to-day functioning in standard clinical practice.

Meeker *et al*¹⁶ to assess the safety and effectiveness of vortioxetine in the acute treatment of major depressive disorder (MDD), a systematic review and meta-analysis have been carried out. Eleven randomised controlled trials with 6,145 individuals were included in the study. When compared to a placebo, the results demonstrated that vortioxetine considerably increased response and remission rates, especially at dosages of 10mg and 20mg. Nausea and vomiting were the most often reported side effects, and they got worse as dosages increased. Vortioxetine is an efficient and generally well-tolerated therapy choice for people with MDD, according to the study's overall findings.

Leiser *et al*¹⁷ Vortioxetine's effects on cortical neuronal oscillations were examined in conscious rats using quantitative EEG. Vortioxetine was observed to promote wakefulness and improve frontal cortical activity in a dose-dependent manner when compared to escitalopram and duloxetine. In particular, it enhanced theta, alpha, and gamma oscillations-effects that duloxetine and escitalopram did not consistently show. The results imply that vortioxetine's multimodal serotonergic mechanism enhances cortical functioning, which may be connected to its possible cognitive advantages in the treatment of depression.

Gizem Tiris *et al*¹⁸ created and verified a quick, precise, and stability-indicating RP-HPLC method to measure vortioxetine in pharmaceutical formulations and bulk. The goal of the study was to develop a trustworthy analytical technique for the drug's regular assay and stability assessment. A Waters Symmetry C18 column with a mobile phase of methanol and 0.05M potassium dihydrogen phosphate buffer (30:70, v/v; pH 3.0 ± 0.05) was used to accomplish chromatographic separation. At 225nm, detection was done. With a mean recovery of 100.7% and a regression coefficient (R²) of January – March

0.9998, the technique demonstrated excellent linearity over the concentration range of 10.0–70.0µg/mL. Forced degradation investigations under acid, alkali, oxidation and UV stress conditions verified stability-indicating capacity. The technique showed acceptable linearity, accuracy, precision, specificity, limit of detection, and limit of quantification after being verified in accordance with ICH guidelines. For routine quality control analysis and stability investigations of vortioxetine in pharmaceutical dosage forms, the authors came to the conclusion that the suggested RP-HPLC method is dependable and appropriate.

Sankar *et al*¹⁹ to assess the impact of vortioxetine on metabolic syndrome (MetS) risk markers in individuals with major depressive disorder, a comprehensive evaluation of randomised controlled trials was carried out. Eight RCTs measuring blood pressure, central adiposity, fasting plasma glucose, triglycerides, and high-density lipoprotein levels were included in the review. The results revealed conflicting and scant information about the effect of vortioxetine on metabolic risk variables. Nonetheless, a number of included studies demonstrated that vortioxetine is both safe and effective in treating depression. The authors came to the conclusion that more well-planned research is required to determine its metabolic safety profile.

Table No.1: SERT inhibition, Vortioxetine acts on several serotonin receptors

S.No	Receptor	Action	Effect
1	5-HT _{1A}	Full agonist	Produces antidepressant and anxiolytic effects
2	5-HT _{1B}	Partial agonist	Enhances serotonin release and neurotransmission
3	5-HT _{1D}	Antagonist	Increases serotonin release by blocking inhibitory auto receptors
4	5-HT ₃	Antagonist	Improves cognition, reduces nausea and increases acetylcholine and norepinephrine release
5	5-HT ₇	Antagonist	May improve mood, cognition and circadian rhythm

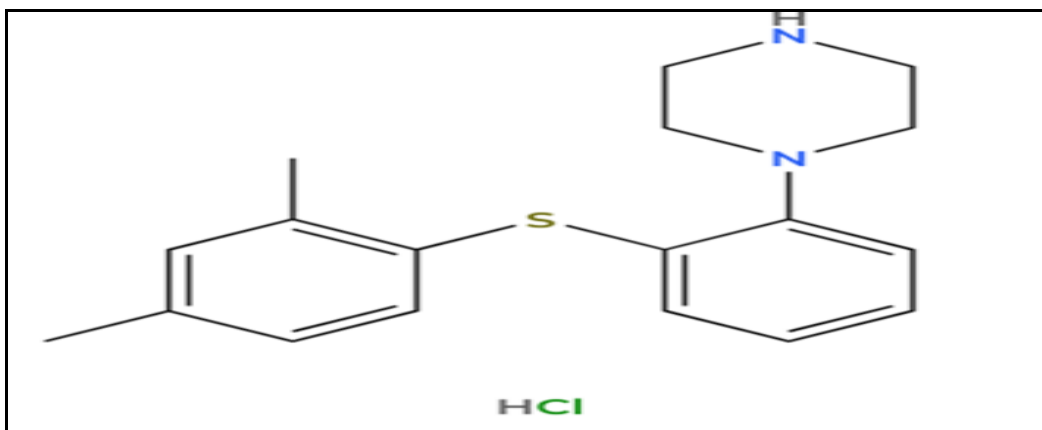


Figure No.1: Structure of vortioxetine

CONCLUSION

A review of the literature revealed that a number of UV [1-7] and a small number of single and simultaneous approaches were created and documented. Therefore, techniques are created based on its solubility and maximal absorbances at specific ultraviolet wavelengths (200-400nm). According to ICH guidelines, the published methods were validated for a number of parameters. The presented approaches were shown to be selective and repeatable by statistical analysis. Therefore, it can be said that Vortioxetine as an API and medicinal dosage form can be successfully estimated using stated and published methodologies.

ACKNOWLEDGMENT

The authors wish to express their sincere gratitude to Department of Pharmaceutical Analysis, Bharathi College of Pharmacy, Bharathinagara, Maddur, Mandya, Karnataka, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Nandankumar K *et al.* New analytical method development and validation of UV- visible spectroscopy for the estimation of vortioxetine: A systematic review, *Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry*, 14(1), 2026, 20-28.