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A SYSTEMATIC REVIEW ON STABILITY INDICATING HPTLC METHOD DEVELOPMENT AND VALIDATION FOR ESTIMATION ON VORTIOXETINE IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

Depression is a prevalent mental health disorder characterized by persistent sadness, loss of interest in daily activities, and impaired cognitive function. Pharmacological treatment using antidepressant drugs plays a vital role in the management of major depressive disorder (MDD). Vortioxetine is a novel multimodal antidepressant approved for the treatment of MDD in adults. It acts by inhibiting the serotonin transporter and modulating multiple serotonin receptors, This multimodal mechanism enhances serotonergic neurotransmission and contributes to improved mood and cognitive function. Vortioxetine shows good oral absorption, extensive distribution, and hepatic metabolism primarily through cytochrome P450 enzymes. Several analytical techniques such as UV spectrophotometry and high-performance liquid chromatography (HPLC) have been reported for the

determination of vortioxetine in bulk drug and pharmaceutical formulations. However, official pharmacopeial methods are still unavailable. This review focuses on depression, antidepressant classification, pharmacological properties, mechanism of action, pharmacokinetics, and reported analytical methods for vortioxetine hydrobromide.

KEYWORDS: Vortioxetine, antidepressant, major depressive disorder, UV, HPLC.

1. INTRODUCTION TO DEPRESSION

Depression is one of the most common psychiatric disorders worldwide and significantly affects emotional, physical, and social well-being. It is characterized by persistent sadness, lack of interest in activities, fatigue, sleep disturbances, and impaired concentration. If untreated, depression can lead to severe consequences such as reduced productivity, impaired relationships, and suicidal tendencies.

Various therapeutic approaches are used for the treatment of depression, including psychotherapy, lifestyle modifications, and pharmacological therapy. Among these approaches, antidepressant medications play a key role in managing depressive disorders by altering neurotransmitter levels in the brain.

1.2 Types of Depression

Depression can occur in different forms depending on the severity, duration, and underlying causes. Some common types include:

- **Major Depressive Disorder (MDD):** Characterized by persistent low mood and loss of interest in daily activities.
- **Bipolar Depression:** Occurs in individuals with bipolar disorder and alternates with manic episodes.
- **Postpartum Depression:** Develops after childbirth due to hormonal and psychological factors.
- **Premenstrual Dysphoric Disorder:** A severe form of premenstrual syndrome with emotional symptoms.

2. Introduction to Antidepressant Drugs

Antidepressants are a class of medications used primarily for the treatment of depressive disorders and other psychiatric conditions such as anxiety disorders, obsessive–compulsive disorder, panic disorder, and post-traumatic stress disorder. These drugs act mainly by

regulating the levels of neurotransmitters in the brain, particularly serotonin (5-HT), norepinephrine (NE), and dopamine (DA), which play a crucial role in mood regulation, emotional balance, and cognitive function.

In patients with depression, the levels or activity of these neurotransmitters may be reduced or dysregulated. Antidepressant medications work by enhancing the availability of these neurotransmitters in the synaptic cleft either by inhibiting their reuptake, preventing their breakdown, or modulating receptor activity. This leads to improved neuronal communication and alleviation of depressive symptoms such as sadness, fatigue, loss of interest, and impaired concentration.

The development of antidepressant drugs has evolved significantly over the years. Early antidepressants such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were effective but often associated with significant side effects and safety concerns.

Later, selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) were developed to provide improved safety and tolerability. More recently, newer agents such as multimodal antidepressants, including vortioxetine, have been introduced. These drugs not only inhibit serotonin reuptake but also modulate multiple serotonin receptors, resulting in improved therapeutic outcomes and cognitive benefits in patients with major depressive disorder.

3. Introduction to Vortioxetine

Vortioxetine hydrobromide is a novel antidepressant belonging to the class of multimodal serotonergic agents used for the treatment of major depressive disorder (MDD) in adults. It was developed by H. Lundbeck A/S in collaboration with Takeda Pharmaceutical Company and received approval from the U.S. Food and Drug Administration in 2013 for the management of depression. The drug is widely prescribed due to its unique pharmacological profile and improved tolerability compared with some traditional antidepressants.

Vortioxetine differs from conventional antidepressants because it acts through a multimodal mechanism, combining serotonin transporter inhibition with direct modulation of multiple serotonin receptors. This unique activity allows the drug to influence several neurotransmitter systems involved in mood regulation, including serotonin, dopamine, norepinephrine, acetylcholine, and histamine pathways. As a result, vortioxetine not only improves depressive

symptoms but may also provide beneficial effects on cognitive function, including memory, attention, and executive function in patients with depression.

Clinically, vortioxetine is used for the treatment of major depressive disorder, a chronic and recurrent psychiatric condition characterized by persistent low mood, reduced interest in activities, and impaired daily functioning. Studies have demonstrated that vortioxetine is effective in reducing depressive symptoms while also improving cognitive deficits associated with depression. In addition, it has shown a favourable safety profile with relatively lower incidence of certain side effects commonly associated with other antidepressants, such as sexual dysfunction and weight gain.

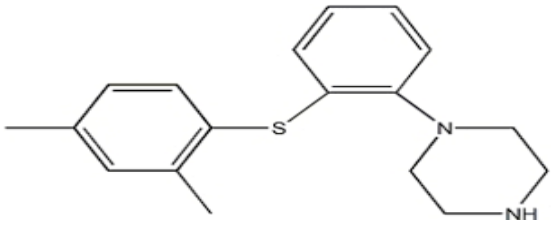

Figure1: Chemical Structure of Vortioxetine.

3.1 MECHANISM OF ACTION OF VORTIOXETINE

Vortioxetine hydrobromide is a multimodal antidepressant that exerts its therapeutic effects through a combination of serotonin transporter inhibition and direct modulation of several serotonin (5-HT) receptors.

The primary mechanism involves inhibition of the serotonin transporter (SERT), which reduces the reuptake of serotonin from the synaptic cleft into the presynaptic neuron. As a result, the concentration of serotonin in the synaptic cleft increases, leading to enhanced serotonergic neurotransmission and improvement in depressive symptoms.

In addition to serotonin reuptake inhibition, vortioxetine directly modulates multiple serotonin receptor subtypes. It acts as a 5-HT_1A receptor agonist, which contributes to antidepressant and anxiolytic effects. The drug also functions as a partial agonist at 5-HT_1B receptors and as an antagonist at 5-HT_3, 5-HT_1D, and 5-HT_7 receptors. Through these receptor interactions, vortioxetine regulates the release of various neurotransmitters such as dopamine, norepinephrine, in different regions of the brain.

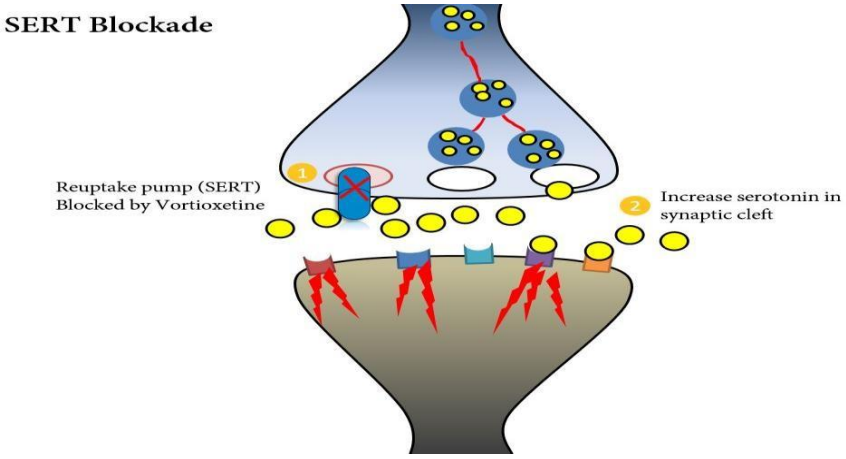

Figure 2: Mechanism of action of Vortioxetine.

LITERATURE REVIEW OF VORTIOXETTINE

- Official method for vortioxetine is not available in any pharmacopoeia
- Only reported methods are available for vortioxetine

Table 3.1: Reported Methods for the Assessment of Vortioxetine.

Sr no	TITLE	DESCRIPTION	REF NO.
UV- VISIBLE SPECTROSCOPY			
1	Development and validation of **UV-spectrophotometric** methods for the estimation of vortioxetine hydrobromide in bulk and pharmaceutical dosage forms.	**Solvent:** Methanol **Wavelength:** 228 nm **Linearity:**2-12 µg/mL	**23**
2	Vortioxetine estimation in its drug formulation by first order derivative **UV-spectrophotometric** method	**Solvent:** Methanol **Wavelength:** 230 nm **Linearity:** 10-50 µg/mL	**24**
3	Quantification of Vortioxetine in Pharmaceutical preparations by validated area under curve UV-Spectrophotometric Analytical method	**Solvent:** Methanol **wavelength:** 230 nm **Linearity:** 10-50 µg/mL	**25**
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY			
4	Analytical method development and validation for estimation of Vortioxetine from dosage form	**Stationary phase:** C18 column (250 x 4.6 mm, 5 µm) **Mobile phase:** Acetonitrile: Potassium dihydrogen buffer (pH- 7.4) (55:45 %v/v) **Flow rate:** 1 mL/min **Wavelength:** 227 nm	**26**
5	Development and validation of **RP-HPLC** method for estimation of vortioxetine in bulk and pharmaceutical dosage form	**Stationary phase:** C18 column (250 × 4.6 mm, 5 µm) **Mobile phase:** Acetonitrile: Methanol (70:30 %v/v)	**27**

		Flow rate: 1 mL/min **Wavelength:** 274 nm.	
6	Method development and validation of Vortioxetine hydrobromide in tablet dosage form by **UPLC**	**Stationary phase:**C8 column (100 x 2.1mm, 1.7µ) **Mobile phase:** Buffer (pH-3.5): Acetonitrile: Methanol: (55 : 35 :10 %v/v/v) **Flow rate:** 0.4 mL/min **Wavelength:** 274 nm.	**28**
7	Development of the validated stability-indicating method for the determination of Vortioxetine in bulk and pharmaceutical formulation by **HPLC-DAD**, stress degradation kinetics studies	**Stationary phase**: Synergi Polar RP column (150 × 4.6 mm × 4 µm) **Mobile phase:** Acetonitrile :Methanol: Acetate buffer(pH-3.5):water(30:30:20:20%v/v/v/v) **Flow rate:** 1mL/min	**29**
	and detection of degradation Products by LC-ESI-QTOF- MS	**Wavelength:** 226 nm	
8	Development and validation of **RP-HPLC** method and force degradation studies for estimation of Vortioxetine HBR in bulk drug and dosage form.	**Stationaryphase:**C18column(250mm x 4.6mm x 5µm) **Mobile phase:** Ammonium acetate(pH-3.5) : Acetonitrile (40:60 %v/v/) **Flow rate:** 1mL/min **Wavelength:** 226 nm	**30**
9	Determination of vortioxetine in human serum and saliva samples by **HPLC–DAD** and **HPLC–MS**	**Stationary phase:** Synergi Polar RP column (150× 4.6 mm × 4 µm) **Mobile phase:** Methanol: Acetate buffer (pH-3.5) : water(70:20:10 %v/v/v) **Flow rate:** 1mL/min **Wavelength:** 235 nm	**31**
10	A novel stability-indicating method for determination of a new antidepressant effect of vortioxetine in a pharmaceutical formulation by using **RP-HPLC**	**Stationary phase:** C18 column (100 × 4.6 mm, 3.5 µm) **Mobile phase:** Methanol: potassium dihydrogen phosphate (pH-3) (30:70, %v/v) **Flow rate** -1.3 mL/min **Wavelength:** 225.0 nm	**32**
11	Validated **RP-HPLC** method for the estimation of vortioxetine in bulk and in tablets	**Stationary phase:** C18 (250 x 4.6 mm, 5 µm) **Mobile phase:** Acetonitrile (100%v) **Flow rate** -1mL/min **Wavelength:** 274 nm	**33**
12	Method development and validation for estimation of vortioxetine hydrobromide through **HPLC** method	**Stationary phase:** BDS (150 x 4.6 mm, 5 µm) **Mobile phase:** Acetonitrile: potassium dihydrogen phosphate((60:40 %v/v) **Flow rate** -1 mL/min **Wavelength:** 260 nm	**34**

HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY			
13	Development and validation of analytical method for the estimation of Vortioxetine hydrobromide.	**Mobile phase:** Chloroform: Methanol: Glacial acetic acid (92:8:0.5 %v/v/v) **Stationary phase:** TLC aluminium plates pre-coated with silica gel G60 F25 **Flow rate** -1mL/min **Wavelength:** 230 nm	**35**

CONCLUSION

Vortioxetine hydrobromide is a novel multimodal antidepressant used for the treatment of major depressive disorder. Its unique mechanism involving serotonin transporter inhibition and modulation of multiple serotonin receptors differentiates it from conventional antidepressants. The drug exhibits favorable pharmacokinetic properties, including good oral bioavailability and long elimination half-life. Various analytical methods such as UV spectrophotometry and HPLC have been developed for its determination in pharmaceutical formulations. However, further research is required to develop robust and stability-indicating analytical methods for routine quality control and regulatory purposes.

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