International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056
Volume: 10 Issue: 04 | Apr 2023 www.irjet.net p-ISSN: 2395-0072

Analytical Methods Development And Validation For Estimation Of Rivastigmine Drug Used For Alzheimer's Disease: A Systematic Review

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Abstract - *Quality assurance and quality control of pharmaceutical formulations and bulk pharmaceuticals both heavily rely on pharmaceutical analysis. The demand for innovative analytical techniques has increased as a result of the pharmaceutical industries' rapid expansion and medication production across the globe. Development of analytical methods has therefore evolved into the core function of analysis. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory defeat and impairment in behaviour, language, and visuospatial skills. Rivastigmine is a carbamate-derived acetylcholine esterase inhibitor that is primarily used to treat mild to moderate Alzheimer's disease. The primary goal of this review was to highlight spectrophotometric, reverse phase high performance liquid chromatography (RP-HPLC), high-performance liquid chromatography (HPLC), high-performance thin layer chromatography (HPTLC), and liquid chromatography-mass spectroscopy (LC-MS) techniques that can be used for method development and validation for Rivastigmine drug . The review is a collection of information that includes the various analytical techniques used, the various columns used, the mobile phase used, flow rate, various detectors, and detection wavelength and retention time. The purpose of this review is to stimulate research into the creation of new, more accurate, precise, and specific methods for estimation of rivastigmine.*

***Key Words*: Alzheimer's disease, Rivastigmine, Dementia, Method development, Analytical techniques.**

1.INTRODUCTION

Alzheimer's disease (AD) is the most prevalent serious neurocognitive impairment in the world today, affecting up to 47 million individuals. It is the sixth most common cause of death in the US, accounting for 29.4 fatalities per 100,000 people, according to the most recent statistics from the Centers for Disease Control and Prevention (CDC). cardiovascular disease deaths have fallen by 14% between 2000 and 2014, whereas complications from AD have shot up by 89% during the same period. The stress that carers go through is equally significant, and it has an impact on their physical and emotional health. In low to middle income and high income nations, respectively, barely 5-10% and 40–50% of individuals have gotten a formal diagnosis of AD, in spite of its societal impact.[19]

It is believed that Dr. Alois Alzheimer, a German psychiatrist and neuropathologist, first described the dementing illness that subsequently came to be recognised as AD. [5] The financial cost of Alzheimer's disease (AD) is among the highest in the world. 50 million people worldwide were estimated to have Alzheimer's disease in 2019.[14]

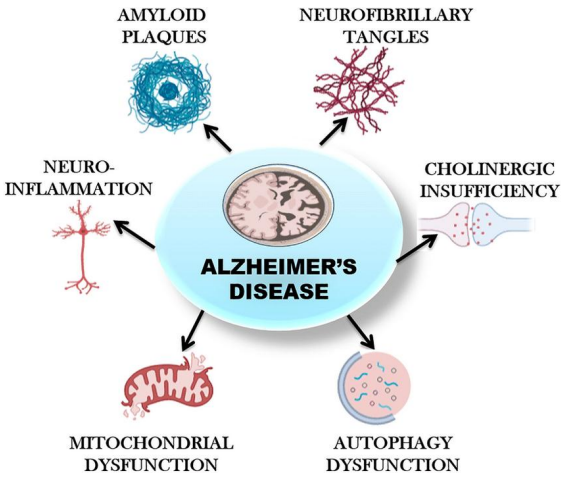

Fig 1.1

The hallmarks of Alzheimer's disease (AD), a neurodegenerative disorder, are neuritic plaques and neurofibrillary tangles in the medial temporal lobe and neocortical regions of the brain. Clinically, the disease shows up as a gradual decline in cognitive and behavioural abilities. Dementia, the most common form of the illness, already affects 50 million people globally, and by 2050, experts expect that number to increase to 152 million cases, doubling every five years.[4] Dementia is a clinical condition (a collection of related signs and symptoms) that is characterised by a steady decline in mental capacity.

Dementia can impair a variety of cognitive functions, including memory, language, thinking, decision-making, visuospatial function, attention, and orientation. Changes in personality, emotional control, and social behaviours are frequent coexisting symptoms

of cognitive impairments in dementia patients. Dementia affects a person's capacity to carry out daily tasks including driving, shopping, cleaning the house, cooking, managing finances, and taking care of oneself. This is significant since these changes in cognition and behaviour can interfere with job, social interactions, and relationships.[5]

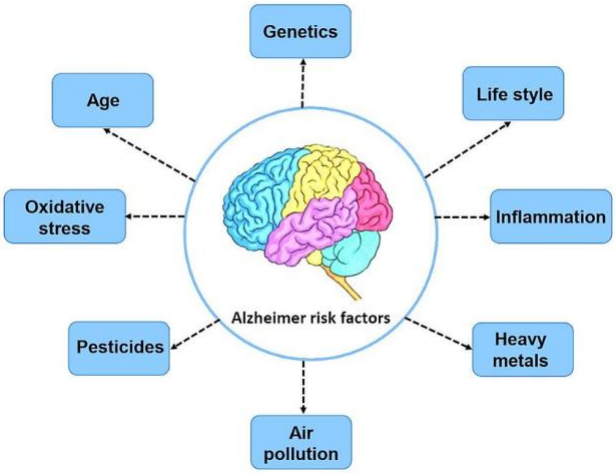

Fig 1.2

It is unclear what causes Alzheimer's disease. It is estimated that hereditary factors, usually involving numerous genes, account for around 70% of the aetiology. A history of head traumas, depression or hypertension, hypercholesterolemia, obesity, etc. are possible contributing factors. The diagnosis is made using the patient's medical history, cognitive testing, and blood tests to rule out other potential problems. Early symptoms are frequently confused with ageing. A definitive diagnosis requires the examination of brain cells. The risk of AD may be lowered via mental and physical exercise, as well as by avoiding smoking, high blood pressure, diabetes, and obesity.[12] The first-line treatment for Alzheimer's disease and some other dementias, such as dementia in Parkinson's disease, is thought to be a cholinesterase inhibitor, such as donepezil, galantamine, and rivastigmine. According to one theory, cholinesterase inhibitors function by preventing the enzyme acetylcholinesterase (AChE), which degrades the neurotransmitter acetylcholine, from doing its job. For more uncommon dementias linked to neurological disorders, cholinesterase inhibitors may also result in clinical improvement.[20]

A parasympathomimetic and reversible cholinesterase inhibitor called rivastigmine is recommended for treating mild to severe Alzheimer's-related dementia. [7] Rivastigmine is a carbamate derivative that is structurally unrelated to donepezil and tacrine but is linked to physostigmine. Rivastigmine's exact mechanism is still unknown, however it is hypothesised that it inhibits acetylcholinesterase and butyrylcholinesterase by binding to and inactivating them, preventing acetylcholine from being hydrolyzed and increasing the amount of acetylcholine at cholinergic synapses. Rivastigmine's anticholinesterase activity is more focused on brain acetylcholinesterase and butyrylcholinesterase than it is on peripheral tissues.[8] Cholinergic neuronal pathways that connect the basal forebrain to the cerebral cortex and hippocampus are involved in pathological alterations in AD. Memory, attention, learning, and other cognitive processes are thought to be tightly related to these pathways. They are carried out by lowered levels of acetylcholine, which are controlled by the cholinesterase enzyme. This enzyme, which is neuronal in origin, breaks down acetylcholine at synapses throughout the nervous system. Acetylcholine, a neurotransmitter that supports human memory and cognition, is broken down by cholinesterase. Acetylcholine is made more readily available to the patient for memory and cognitive function by suppressing cholinesterase. Since AD patients have much lower amounts of acetylcholine than persons who are otherwise healthy. . The enzyme that deactivates the transmitter in the synaptic cleft is blocked by these medications. It should be mentioned that ChEI treat AD's symptoms rather than its cause. Acetylcholine levels in the brain are raised by ChEI. Levels of butyrylcholinesterase rise while levels of acetylcholinesterase gradually decrease as AD advances and cortical neurons are destroyed. When acetylcholinesterase is gone, butyrylcholinesterase can and does take over the role of metabolising acetylcholine at the synapses. Rivastigmine, but not its rivals, blocks the activity of both acetylcholinesterase and butyrylcholinesterase by covalently attaching to their active sites. The first and most crucial stage in the degradation of rivastigmine, which is not metabolised in the liver, is the breaking of these covalent bonds. [21]

2.RESULTS AND DISCUSSION:

Rivastigmine

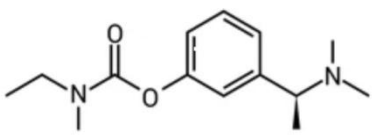

Fig 2.1

Rivastigmine is a carbamate of 3-[(1S)-1-(dimethyl amino) ethyl]phenyl.[8] It is offered as a capsule under the brand names Exelon, Rivagem-3, and Rivamer. It has a molecular weight of 250.3, a pKa of 8.85, a LogP of 2.3, a therapeutic dosage of 3 mg/day, a half-life of 1 h, a half-life of 1.5 h, 40% protein binding, and 36% oral bioavailability.[15] The development and validation of Rivastigmine drug used in Alzheimer's disease estimated quantitatively by spectrophotometric, reverse phase high performance liquid chromatography (RP-HPLC), high-performance liquid chromatography (HPLC), high-performance thin layer chromatography (HPTLC), and liquid chromatography-mass spectroscopy (LC-MS) method. Method development and validation of Rivastigmine can be studied by chromatographic techniques by various authors, the results can be discussed as below.

For the analysis of Rivastigmine in pharmaceutical dosage forms, an isocratic RP-HPLC method has been created and validated. Thermo Hypersil C4 column (25 cm X 4.6 mm, 5 m) with a mobile phase of orthophosphoric acid and acetonitrile (60:40, v/v) adjusted to pH 4.0 at a flow rate of 1.0 mL min-1 produced the best separation. At 220 nm, UV detection was carried out. An internal standard was atrovastatin. Rivastigmine and Atrovastatin have retention times of

4.75 and 8.83 minutes, respectively. Specificity, linearity, precision, accuracy, limit of quantification, limit of detection, robustness, and solution stability of the method were all validated.[6]

Another author proposed and validated a simple, accurate, and efficient RP-HPLC method for the estimation of Rivastigmine effect by improving cholinergic function, in bulk and pharmaceutical dosage form. Ortho phosphoric acid was used to bring the pH of the mobile phase, which was 2.02 g of 1-octane sodium sulfonate, to 3.0 before filtering through a 0.45 mm Pal Pharma nylon 66 membrane filter. By combining buffer and acetonitrile in a 70:30 v/v ratio, the mobile phase was created. Column 4.6 mm'250 mm, ODS, Xterra RP18, 5 mm or similar, flow rate 1.0 ml/min, detection 217 nm, injection volume 40 ml, and run duration 15 min are the specifications of the chromatographic system.[7]

The different conditions applied by another author using RP-HPLC for the determination of Rivastigmine from Bulk dosage form by reverse phase HPLC. The C18 column (Inertsil, C18, 250 x 4.6mm. 5) was utilized. The sample was analyzed using Potassium phosphate mono basic buffer (pH 2.5± 0.05): Acetonitrile (70:30) as a mobile phase at a flow rate of 1.0ml/min. uv detection done at 217 nm. Rivastigmine's retention time was found to be 3.66 minutes. According to ICH guidelines, the stability assay was carried out and validated for accuracy, precision, linearity, specificity, and sensitivity. The method was validated and found to be precise, rapid, accurate, specific, reliable, and reproducible.[8]

For the analysis of rivastigmine hydrogen tartrate in transdermal drug administration system, a rapid simple sensitive exact, accurate and reproducible RP-HPLC method was designed and validated. Water was used as the solvent because rivastigmine tartrate is water soluble. The C-18 RP-HPLC column, which was maintained at room temperature, was used to conduct the separation. The mobile phase, which was delivered at a rate of 1ml/min, was made of 0.01M ammonium acetate buffer and acetonitrile (70:30 v/v). Using a UV detector with a 219nm wavelength, the analysis was found. The method's accuracy, precision, robustness, linearity, and range are all validated. For the concentration range of 50–100 g/ml, the technique was discovered to be linear (r2 = 0.999). It was discovered that rivastigmine had a retention time of 4.40 minutes. The chromatogram's overall run time was around 10 minutes. A % R.S.D. value of less than 2 shows accuracy of the procedure. . The mentioned method was a simple and cost-effective quality-control tool for analysing Rivastigmine Hydrogen Tartrate in Transdermal Drug Delivery System on a regular basis.[11]

Spectrofluorimetric approach was created For the quantification of rivastigmine in bulk and pharmaceutical formulations, that is rapid, accurate, simple, and cost effective. In triple-distilled water, rivastigmine's relative fluorescence intensity was determined at 220 nm for excitation and 289 nm for emission. The range of linearity was found to be 100 to 4000 ng/ml. According to ICH guidelines and USP standards, the procedure was validated for a number of parameters. The quantitation and detection limits were found to be 20.5 and 62.1 ng/ml, respectively. The results show that the method is quick, simple, accurate, precise, and reproducible. The outcomes and label claims were discovered to be in good agreement.[22]

The development and validation of a sensitive, focused, and precise HPLC technique for the measurement of rivastigmine (RSM) in rat urine. The procedure calls for the straightforward liquid-liquid extraction of RSM and pyridostigmine as an internal standard (IS) from rat urine using tertiary methyl butyl ether. RSM and IS were separated chromatographically using a Kromasil KR-100 with a 20 mm ammonium acetate buffer (pH 6.5) and acetonitrile (65:35, v/v) given at flow rate of 1 mL/min. The technique had a linear range of 50 to 5000 ng/mL. The validation was carried out in accordance with FDA regulations, and the outcomes satisfied the requirements for acceptance.[23]

A rapid and sensitive liquid chromatography–tandem mass spectrometry (LC–MS/MS) method has been developed and validated for the estimation of rivastigmine

in human plasma. Rivastigmine was extracted from human plasma by using solid-phase extraction technique. Zolpidem was used as the internal standard. A Betabasic-8 column provided chromatographic separation of analytes followed by detection with mass spectrometry. The mass transition ion-pair was followed as m/z 251.20 → 206.10, for a linear range of 0.2–20.0 ng/ml with a correlation coefficient ≥0.9988. The intra-run and inter-run precision and accuracy were within 10.0%. The overall recoveries for rivastigmine and zolpidem were 86.28% and 87.57%, respectively. The total run time was 2.0 min.[24]

To create a faster separation method with shorter runtimes, a precise and accurate stability-indicating gradient reverse phase ultra-performance liquid chromatographic (RP-UPLC) method was developed. This method uses a photodiode array detector to quantitatively determine RIV and its impurities in both the drug substance and drug product. The method was applied to the active pharmaceutical ingredient, its pharmaceutical dosage form, degradation products, and process-related impurities. The Acquity UPLC BEH Phenyl column was used for chromatographic separation, with a mobile phase containing a gradient mixture of solvents A and B. The compounds eluted in just 10 minutes and were monitored at 210 nm with a flow rate of 0.4 mL/min and a column oven temperature of 40°C. The resolution of RIV and its eleven impurities (positional and potential) was greater than 2.0 for all pairs of components. This newly developed method was validated as per ICH guidelines with respect to specificity, linearity, limit of detection, limit of quantification, accuracy, precision, and robustness.[25]

The stability-indicating high-performance thin-layer chromatographic technique for rivastigmine analysis in the bulk drug and in a capsule formulation has been developed and validated. Chloroform-methanol 4:6 (v/v) was used as the mobile phase, and chromatographic separation was achieved on aluminum-backed silica gel 60F 254 HPTLC plates. At 210 nm, absorbance mode was used for the densitometric measurement of rivastigmine. The technique produced a compact spot for rivastigmine (RF 0.53 0.02) and was found to enable effective separation of a rivastigmine degradation product (RF 0.32 0.02). The method's accuracy, precision, linearity, recovery, detection and quantitation limits, robustness, and other properties were all validated. Excellent linearity was seen in the concentration range of 200–1600 ng per spot; the correlation coefficient was 0.9916–0.008. Limits of detection and quantitation were 30 and 100, respectively.[26]

86.20 for rivastigmine and m/z 308.10 → 235.10 for zolpidem. The method involves a rapid solid-phase extraction from plasma, simple isocratic chromatographic conditions and mass spectrometric detection that enables detection at sub-nanogram levels. The proposed method has been validated

For the quantitative determination of Rivastigmine hydrogen tartrate, a cholinesterase inhibitor in bulk medications and pharmaceutical dosage forms, an isocratic, reversed-phase liquid chromatographic (RPLC) method was developed. The established approach is also useful for the analysis of Rivastigmine Hydrogen Tartrate in Bulk Drugs, a related chemical. Aqueous 0.01 M sodium-1-heptane sulphonate (pH: 3.0 with dilute phosphoric acid)-acetonitrile (72:28, v/v) was used as the mobile phase to produce the chromatographic separation on a Waters X Terra RP18 (250 mm 4.6 mm, 5 m) column. limit of detection (LOD) and limit of quantitation (LOQ) were discovered to be 100 and 300 ng/ml, respectively.[27]

For the purpose of quantifying rivastigmine in rat plasma and brain, a high-performance liquid chromatographic fluorescence detection method has been developed and validated. RSM was extracted from brain and plasma, respectively, using protein precipitation and one-step liquid-liquid extraction procedures, accompanied with an internal standard. With the use of a column inertsil ODS-3V and a mobile phase made up of acetonitrile and ammonium acetate buffer (20 mM, pH 4.5) and delivered at a flow rate of 1 ml/min, the chromatographic separation was accomplished. For both matrices, the developed method's lower limit of quantification was 10 ng/mL.[28]

Drug name	Method	Column used	Mobile phase	Flow rate	Detection	Retention time
	RP-HPLC (Isocratic mode)	Thermo Hypersil C4 column (25 cm X 4.6 mm, 5 m)	orthophosphoric acid and acetonitrile (60:40, v/v)	1.0 mL min-1	220 nm	4.75 minutes
	RP-HPLC	4.6 mm'250 mm, ODS, Xterra RP18, 5 mm	Ortho phosphoric acid: acetonitrile (70:30 v/v)	1.0 ml/min	217 nm	15 min
	RP-HPLC	C18 column (Inertsil, C18, 250 x 4.6mm. 5)	Potassium phosphate mono basic buffer (pH 2.5± 0.05):	1.0ml/min	217 nm	3.66 min

Rivastig-mine			Acetonitrile (70:30)			
	RP-HPLC	C-18 RP-HPLC column	0.01M ammonium acetate buffer and acetonitrile (70:30 v/v)	1ml/min	219nm wavelength	4.40 minutes
	Spectrofl uori-metry	-	-	-	220 nm for excitation and 289 nm for emission	-
	HPLC	Kromasil KR-100	20 mm ammonium acetate buffer (pH 6.5) and acetonitrile (65:35, v/v)	1 mL/min	-	-
	LC–MS/MS	Betabasic-8 column	-	-	-	4.40 minutes
	RP-UPLC	UPLC BEH Phenyl column	gradient mixture of solvents A and B	0.4 mL/min	210 nm	10 minutes
	HPTLC	aluminum-backed silica gel 60F 254 HPTLC plates	Chloroform-methanol 4:6 (v/v)	-	210 nm	2.38 min
	RPLC	Waters X Terra RP18 (250 mm 4.6 mm, 5 m) column.	Aqueous 0.01 M sodium-1-heptane sulphonate (pH: 3.0 with dilute phosphoric acid)-acetonitrile (72:28, v/v)	-	-	-
	HPLC fluorescence detection method	inertsil ODS-3V	acetonitrile and ammonium acetate buffer (20 mM, pH 4.5)	1 ml/min	220nm for excitation and 293nm for emission	-

3. CONCLUSIONS

An attempt was made to review current trends in the method development and validation for rivastigmine in this article. Well designed, independent cost effective analyses of Rivastigmine are lacking. According to a review, there may be cost effective method for Rivastigmine. There is a lot of current research being done on developing and validating analytical methods as targets for treating AD with Rivastigmine. Hence, it is hoped that the combination of all these ongoing research areas will result in a better understanding.

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