RESEARCH ARTICLE

A Novel Eco-Friendly Approach using the Concept of Hydrotropy for Analytical Estimation of Mirtazapine by HPLC used to Treat Depression

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Received: 20th Sep 2024; Revised: 21st Oct, 2024; Accepted: 19th Nov, 2024; Available Online: 25th Dec, 2024

ABSTRACT

Introduction: In the pharmaceutical field, it is often required to prepare aqueous solutions of a variety of insoluble drugs. The ability to increase aqueous solubility can be a valuable aid for increasing the efficacy and reducing adverse effects for certain drugs.

Most quantitative analyses of poorly water-soluble drugs involve the use of various organic solvents. Hydrotropic solutions may be a proper choice to preclude the use of organic solvents, providing a simple, accurate, novel, safe, and precise method for drug analysis.

Objective: Current research work includes development and validation of ecofriendly HPLC method using the novel concept of Hydrotropy for analytical estimation of Mirtazapine with comparative greenness with literature method.

Methodology: The method was developed using 0.2% Ortho phosphoric acid in water as the mobile phase and Xterra C18 (250mm*4.6mm) 5µm column. The flow rate was set to 1.0 mL/min, and detection was done at 314 nm.

Results: The linearity range of 50%-150% met the correlation coefficient > 0.998. The %RSD for method precision was < 2.0%. The recovery range of 50-150% met 98-102%.

Conclusion: Hydrotropic method developed was successfully validated as per ICH Q2 (R1) with sufficient Specificity, Linearity, Accuracy and Precision. Additionally, the developed method was greener and ecofriendly compared to other literature method.

Keywords: Mirtazapine, Green LC, Hydrotropy, Analytical Estimation, Greenness, ICH Q2(R1)

How to cite this article: Harsh D Adhvaryu, Vandana B Patel. A Novel Eco-Friendly Approach using the Concept of Hydrotropy for Analytical Estimation of Mirtazapine by HPLC used to Treat Depression. International Journal of Pharmaceutical Quality Assurance. 2024;15(4): 2487-91. doi: 10.25258/ijpqa.15.4.49

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

In the pharmaceutical industry, solubility plays a significant role in the efficacy of poorly water-soluble drugs. Aqueous solubility is a critical factor for bioavailability.

Hydrotropes, which enhance the solubility of poorly soluble compounds, offer a green alternative to the traditional use of organic solvents.

The present study focuses on developing an eco-friendly, accurate, and precise analytical method using hydrotropy for the estimation of Mirtazapine without the use of organic solvents and comparative greenness of development method with literature method was evaluated.

Objective

Current research paper includes hydrotropic method development and validation for analytical estimation of Mirtazapine by HPLC and comparative greenness of developed method with literature method.

METHODOLOGY

Optimized Chromatographic Conditions

- Mobile phase: 0.2% Ortho phosphoric acid in water (Inorganic Hydrotrope)
- Column: Xterra C18 (250mm * 4.6mm) 5µm
- Flow rate: 1.0 ml/min
- Temperature: Ambient temperature
- Injection volume: 20 µl
- Detection wavelength: 314 nm
- Sample concentration: 100 ppm

Buffer Preparation

Accurately weigh 2 ml of Ortho phosphoric acid in 1000 mL of Milli-Q water.

Mobile Phase Preparation

Use the buffer as the mobile phase.

Standard Solution Preparation (100 ppm)

Weigh 100 mg of Mirtazapine standard into a 100 mL volumetric flask, add 70 mL of diluent, sonicate to dissolve, and dilute to volume with the diluent. Pipette out 5 mL of the standard stock solution into a 50 mL volumetric flask and dilute to the mark with diluent.

Sample Solution Preparation (100ppm)

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Table 1: Linearity Study Data
(The table presents the % linearity levels, the volume of stock solution added, dilution, and resulting concentration in µg/mL.)

S. No.	% Linearity Level	Linearity Stock Solution to be Added (mL)	Dilution	Concentration (µg/mL)
1	50	5	100	50
2	85	8.5	100	85
2	100	10	100	100
2	120	12	100	120
2	150	15	100	150

Table 2: Accuracy Solutions Preparation
(This table presents the accuracy levels, the amount of API spiked, dilution, and the resulting concentration in µg/mL.)

S. No.	Accuracy Level (%)	Stock of API Spiked (mg)	Dilution (mL)	Volume	Dilution (mL)	Concentration * (µg/mL)
1	50	50	100	5.0	50	50.0
2	100	100	100	5.0	50	100.0
3	150	150	100	5.0	50	150.0

*Prepare 3 sets of each accuracy level of 50%, 100% and 150%.

Weigh 100 mg of Mirtazapine API sample into a 100 mL volumetric flask, add 70 mL of diluent, sonicate to dissolve, and dilute to volume with the diluent. Pipette out 5 mL of the standard stock solution into a 50 mL volumetric flask and dilute to the mark with diluent.

The Developed Method is Validated as per ICH Q2R1 with below Listed Parameters

- System suitabilit
- Specificity/selectivity
- Linearity
- Accuracy
- Method precision

Preparation of Solution

Linearity Solution Preparation

Prepare a stock solution containing 1000µg/mL of Mirtazapine. Prepare a series of linearity solutions as shown in Table 1 and inject into the chromatography.

Accuracy Solution Preparation

Method Precision

Sample Preparation

Weigh 100 mg of Mirtazapine API sample into a 100 mL volumetric flask, add 70 mL of diluent, sonicate to dissolve,

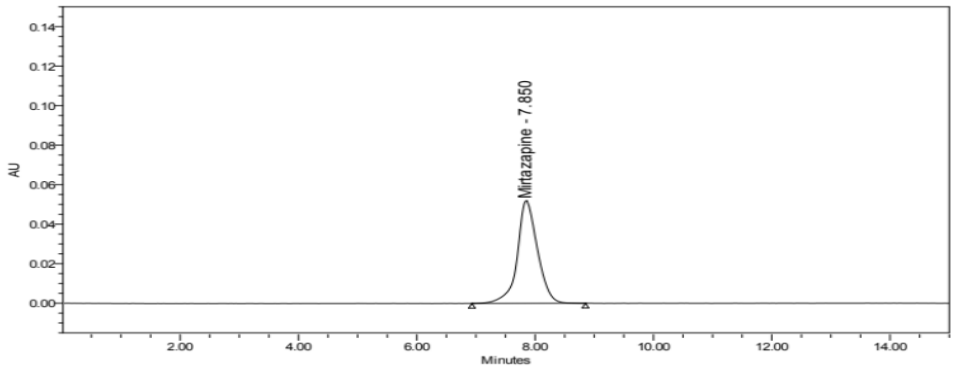

Figure 1: Standard chromatogram

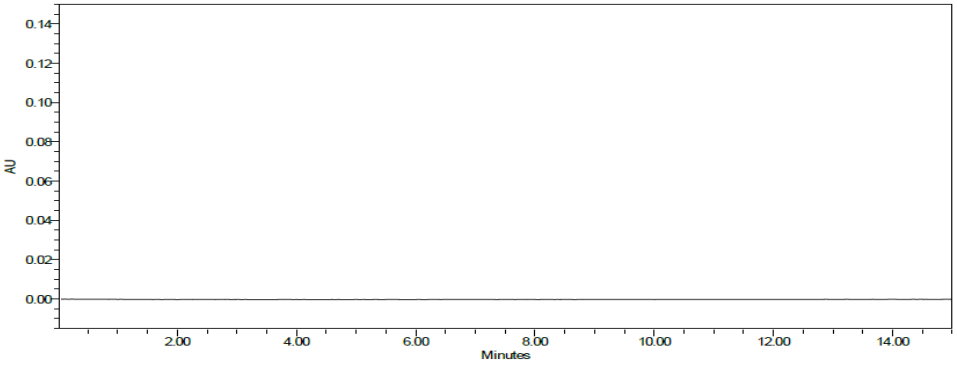

Figure 2: Blank chromatogram

Table 3: System suitability details

Sr. No	System suitability	Observation	Acceptance criteria
1	Retention Time (min)	7.8	-
2	Theoretical Plates	2802	NLT 2000
3	Tailing Factor	1.0	NMT 2.0
4	Mean Area	1227007	-
5	% RSD	0.43	NMT 2.0%

and dilute to volume with the diluent. Pipette out 5 mL of the standard stock solution into a 50 mL volumetric flask and dilute to the mark with diluent.
Prepare other 5 sets as per above procedure.

RESULTS AND DISCUSSION

System Suitability

Table 4: Linearity Results

Linearity Range	Concentration (ppm)	Area
50%	50.75	547348
85%	86.275	1057512
100%	101.5	1221188
120%	121.8	1521526
150%	152.25	2005716
Correlation Coefficient	0.998	
Slope	10450	
Intercept	60311	

Acceptance Criteria

- The tailing factor of the standard peak in the first injection of standard solution-1 should be NMT 2.0.
- The Theoretical plate of the standard peak in the first injection of standard solution-1 should be NLT 2000.

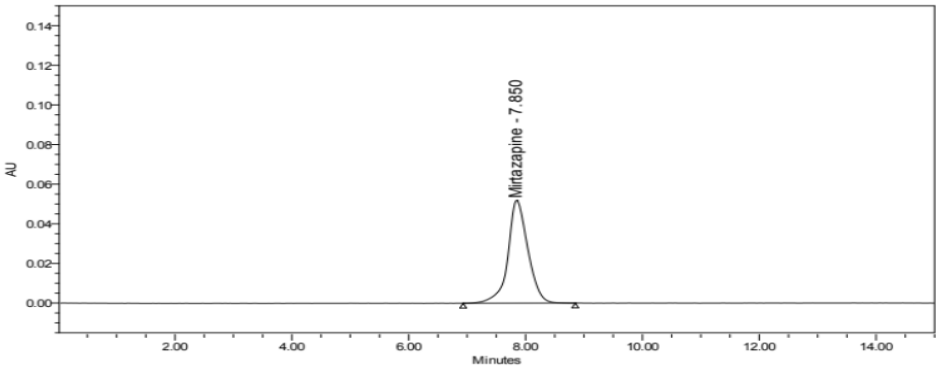

Figure 3: Standard chromatogram

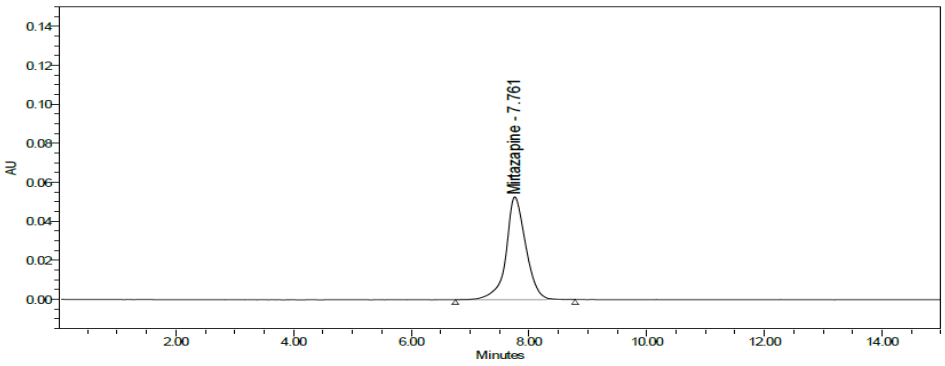

Figure 4: Sample chromatogram

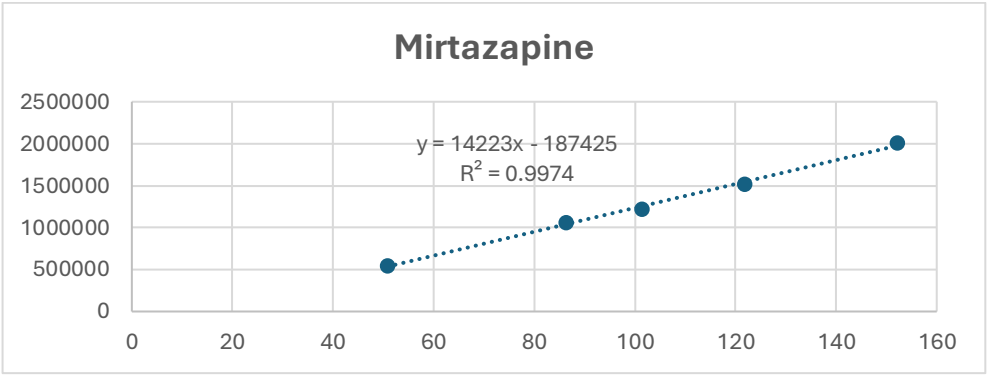

Figure 5: Linearity Graph

Table 5: Accuracy Results

Levels	Actual Concentration (ppm)	Obtained Concentration (ppm)	% Recovery	Mean % recovery	% RSD
	54.5	54.1	99.2		
50 %	52.8	53.6	101.6	99.7	1.65
	56.0	55.1	98.4		
	99.5	100.4	100.9		
100 %	99.8	101.0	101.2	101.1	0.19
	100.1	101.4	101.3		
	164	165.5	100.9		
150%	163.1	165.9	101.7	101.5	0.54
	162.9	166.2	102.0		

Table 6: Results of Method Precision

Injection no.	%Assay
1	99.6
2	99.9
3	99.9
4	99.5
5	100.1
6	100.3
Mean	99.9
SD	0.286
% RSD	0.29

- The relative standard deviation of the peak area for the 5 replicate injections of standard should be NMT 2.0%.

Conclusion

All System suitability parameters are well within acceptance criteria. Hence method is suitable for indented use.

Specificity/Selectivity

Acceptance Criteria

There should not be any interference at the retention time of Mirtazapine.

Conclusion

There is no interference of blank at the retention time of Mirtazapine in standard and sample. Hence it is concluded that test method is specific for estimation of Mirtazapine.

Linearity

Acceptance Criteria

Coefficient of determination (r2) should be not less than 0.998.

Conclusion

From the above results, Coefficient of correlation (r) meets the pre-defined acceptance criteria. Hence it is concluded that this method is Linear over the range of 10-150%.

Accuracy

Acceptance Criteria

Individual and mean % recovery of Ascorbic acid should be between 98.0 to 102.0.

Conclusion

From the results it is concluded that the method is accurate in the range of 50% to 150% of initial test concentration.

Method Precision

Acceptance Criteria

The RSD of six preparations should not be more than 2.0%

Conclusion

Table 7: Comparison of Developed method and Literature method

Criteria	Literature Method (Organic Solvent-Based)	Developed Method (Hydrotropy-Based)
Environmental Impact	Higher, due to organic solvents (e.g., acetonitrile)	Lower, as it uses water-based systems and non-toxic hydrotropes
Chromatographic System	HPLC with a 290-nm detector and a 4.6-mm × 25-cm column containing packing L1	HPLC with a 314-nm detector and a 4.6-mm × 25-cm column containing packing L1
Mobile Phase	Acetonitrile, methanol, tetrahydrofuran, and Buffer (15:12.5:7.5:65)	0.2% Ortho phosphoric acid in water
Retention Time	About 25 min	About 7.8 min
Detection	UV detector at 290 nm	UV detector at 314 nm
Degree of Greenness	Use of toxic solvents- Methanol, Acetonitrile and Tetrahydrofuran	High, uses less toxic solvents and is more environmentally friendly
Safety	Risks from toxic, flammable organic solvents	Safer, as water and hydrotropes are typically non-toxic
Sustainability	Less sustainable due to high solvent use and waste disposal	More sustainable with water-based solutions and biodegradable agents
Cost	Higher due to solvent costs and waste disposal	Potentially lower due to cheaper hydrotropes and less waste disposal
Efficiency	Well-established, high precision, but more hazardous	May require more optimization, but can achieve similar efficiency
Waste Management	Complex and costly (organic solvent disposal)	Easier and cheaper (water-based waste)

From the above results, % RSD of assay results of Mirtazapine meets the pre-defined acceptance criteria. Hence it is concluded that the method is Precise.

CONCLUSION

The proposed method was found to be simple, rapid, accurate, green, and economical for the estimation of Mirtazapine by HPLC using the concept of hydrotropy. This method provides a more sustainable and safer alternative compared to traditional organic solvent-based methods. It can be applied effectively for routine testing and has a lower environmental impact.

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