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Development and Validation of HPLC-UV Method for Determination of Paraquat in Raw and Commercial Samples

Ahmed Yar[1], Tariq Mahmood Ansari[1]*, Asad Raza[2] and Suryyia Manzoor[1]

[1]*Institute of Chemical Sciences, Bahauddin Zakariya University Multan, 68000, Pakistan.*
[2]*Department of Chemistry, Govt. Graduate College Civil Lines Multan, Punjab, Pakistan.*
**Corresponding Author Email: drtariq2000@gmail.com*

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Abstract

A new, rapid, efficient, low cost, robust, accurate and reproducible analytical method for the determination of Paraquat has been developed using reverse phase high performance liquid chromatography with UV-Visible detector (HPLC-UV). Paraquat is a frequently used herbicide. This method is useful for the detection and quantification of paraquat in raw materials and commercial samples with excellent recoveries upto almost 100%. pH of the mobile phase (acetonitrile:methanol:water 1:1:2) was optimized as 2.5 with ortho-phosphoric acid. This analytical method was validated with excellent linearity R^2 = 0.999. LOD and LOQ were calculated to be 0.74 mg/L and 2.45 mg/L, respectively. The method showed a high precision (RSD%) value of 0.32, while the accuracy measured in terms of percentage recovery was almost 100% under optimized conditions. The robustness of the method was studied by changing the flow rate and the mobile phase concentration ratios, and the results obtained were within the permissible accepted values.

Keywords: Paraquat, HPLC-UV, Commercial samples, Determination, Validation.

Introduction

Paraquat Dichloride (IUPAC: 1, 1'-dimethyl-4, 4'-bipyridinediium dichloride, Fig.1) is Colorless, hygroscopic crystals and decomposes at 340 ºC.

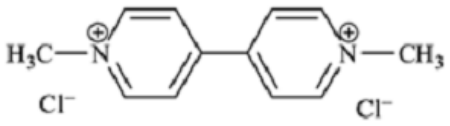

Figure 1. **Structure of Paraquat**

It exhibits a solubility of 62 g/100 mL at 20ºC in water, whereas practically insoluble in most organic solvents. Though it can be readily hydrolysed in an alkaline medium yet it is quite stable in neutral and acidic media. The role of paraquat as a herbicide was discovered in 1955 and first marketed in 1962. Paraquat (1, 1'-dimethyl-4, 4'-bipyridinediium dichloride) was manufactured and sold by ICI in early 1962 with the trade name Gramoxone and is widely used today among the most frequent herbicides. In the United States of America (USA), paraquat mainly exists as a solution with a variety of strengths. It is classified as "restricted use, " meaning it can be used by licensed applicators only. The approximate use of paraquat in US agriculture is mapped by the US Geological Survey and

shows a doubling from 2013 to 2017. It's use has been estimated to be 10,000,000 pounds annually [1]. There is an ongoing international movement for a global ban, but the inexpensive and, therefore, popular paraquat continues to be unrestricted in most developing countries [2]. A long term exposure to paraquat can lead to Parkinson's disease. The rate of Parkinson's disease diagnosis increased by 107% from 2013 to 2017 in the USA, which seems to be a strong link with enhanced use of paraquat.

Paraquat serves as a non-selective contact herbicide and desiccant. Its mechanism of action involves absorption by the foliage followed by the translocation in the xylem. Paraquat is used as pre-harvest desiccation of major crops like cotton, flax, alfalfa, clover, lupins etc. It is also used in the destruction of potato-haulms and stripping of hops. It may be used to control annual broad-leaved weeds in vines, bush fruit, strawberries (also control of runners), citrus fruit, olives, vegetables, ornamental plants and shrubs, emergent and submerged aquatic weeds [3].

Analytical methods reported for the quantitative determination of paraquat include LC and Ion Pair chromatography. These techniques have been used to analyse the pesticide in plasma, urine, whole blood, and serum samples of affected patients. Furthermore, the study of paraquat in wastewater, drinking water, residues sandy clay, loam soil, vegetables, residue in oil matrix, food, human exposure samples and post-mortem human blood samples are also well described in the literature [4-25]. GC-MS has been applied for the determination of paraquat in plasma and urine samples, extracted through solid-phase microextraction [26-27]. UV-Visible spectrophotometric detection of paraquat with acute poisoning in patients is also reported [28-30]. However, a few standard analytical methods are available in the literature for the analysis of paraquat in herbicide formulations, such as UV technique to determine paraquat salt in aqueous solutions of herbicide formulation [31] and HPLC-MS analysis of paraquat herbicide formulation [32].

All of these reported methods have been specifically designed for certain applications for extraction and determination of paraquat residues in fruits, vegetables, wastewater, drinking water, oil, fruits, serum and plasma but none of the HPLC-UV methods has been adopted as an Official Method by CIPAC, AOAC and FAO yet. It has also been observed that most local agrochemical industrial units have simple HPLC-UV systems in their quality control laboratories. In this scenario, they need a simple, accurate, reproducible, economical and valid HPLC-UV analytical method to follow in their quality control laboratories.

The present study aimed to develop a rapid, easy, economical, accurate, reproducible and valid HPLC-UV method for paraquat determination in raw materials and pesticide dosage formulations at a commercial scale in quality control laboratories.

Materials and Methods

Chemicals and Reagents

Acetonitrile and Methanol (HPLC gradient grade) from Duksan Pure Chemicals Korea, Water (HPLC Grade) from VWR Chemicals (BDH) prolabo, ortho-Phosphoric Acid 85% (Lab Grade) from VWR Chemicals (BDH) prolabo, Paraquat dichloride hydrate standard of Known Purity (99.5%) from Chem Services USA were obtained. A sample of 20% SL (soluble liquid) paraquat product marketed by name of Pointer was collected from Solex Chemicals Quality Control Laboratory Multan, Pakistan and other formulations of paraquat were collected from

the local market of Multan, Pakistan. A bench top pH meter (Model HI-2211) from Hanna Instruments was used for pH measurement. Buffer Solutions of pH 4, 7 and 9 were purchased from VWR Chemicals (BDH) prolabo.

Instruments and Apparatus

A filtration assembly (Glasco) with a filtration pump was used for mobile phase filtration. Filter papers of 0.25 µm and 0.45 µm (Sartorius) were used for filtration of mobile phase. Whatman No 42 filter paper from Sartorius was used for filtration of sample. Weighing of the sample and standard was performed using an Analytical weighing balance ranging from 0.01 g – 220 g Model No.AB204-S, Mettler, Toledo). An ultrasonic water bath (GT Sonic D3 China) was used for the extraction of the sample and standard analyte. Certified glassware from Iwaki Pyrex was used during the whole practical work. HPLC analysis of paraquat was performed with Shimadzu Japan HPLC system (LC-20AT pump and SPD-20A UV-VIS Spectrophotometric detector). A zorbax 250 mm x 4.6 mm (i.d) packed C18 column with 5 µm (particle size) from Agilent Technology was used.

Chromatographic Conditions and Method Optimization

Different chromatographic parameters were set by changing mobile phase compositions, flow rate, and detector wavelength. Ratios of HPLC gradient grade solvents (acetonitrile, methanol and water) were varied to optimize the best separation of the analyte. Flow rates of the mobile phase were changed between 0.5 mL/min to 1 mL/min at changing interval of 0.1 mL/min. During the whole analysis process, the isocratic elution mode was used. Degassing of the mobile phase was done by an ultrasonic water bath after passing it through 0.45 µm nylon membrane filter paper using a vacuum pump filtration system. Process of separation of analyte was done using C-18 column at room temperature (25^oC). Different wavelengths of UV range between 200 to 300 nm at an interval of 10 nm were tested to decide λ_{max} and optimum chromatographic response to minimize interferences from inert materials present in the formulated products. The optimum flow rate and wavelength were changed deliberately to perform the robustness test. Comparison of the results was achieved by changing each parameter accordingly.

Preparation of Standard Stock Solution

100 mg/L stock solution of pure Paraquat dichloride (Equal to 72.45 mg/L of Paraquat as Paraquat dichloride) was prepared with the accuracy of ±0.0001 mg/L into a separate 100 mL volumetric flask. Dissolved the analytical standard Paraquat dichloride into 10 mL of mobile phase (methanol: acetonitrile: water 1:1:2) by sonication moderately and cooled this standard solution to room temperature and made up the volume to 100 mL with mobile phase and shaken vigorously to homogenize the standard solution. This stock solution was found to be stable for 24 hours at a cooling temperature in the refrigerator.

Preparation of Working Standard Solutions

Working standards of 2.5, 5.0, 7.5, 10, 12.5, and 15 mg/L of Paraquat dichloride were prepared from the 100 mg/L stock solution by diluting up to the mark 100 mL with mobile phase (methanol :acetonitrile: water 1:1:2). These dilutions were vigorously shaken for homogeneity and maintained at room temperature. All the working standard solutions were filtered with 0.45 µm membrane filter paper and analyzed through HPLC. The data was recorded in the form of

chromatograms, and the percentage recovery was calculated. The experiments were performed in triplicates.

Preparation of Sample Solutions

A 10 mg/L of paraquat dichloride (equal to 7.25 mg/L of paraquat pure contents) was prepared by taking out the contents from Pointer 20% SL (paraquat 20% SL) product sample in 100 mL volumetric flask, make up the volume with mobile phase (methanol: acetonitrile: water 1:1:2). The product sample solution was shaken vigorously and mixed thoroughly for homogeneity. The sample was filtered with 0.45µm membrane filter paper, run through HPLC, and chromatograms were obtained. The percentage recovery was calculated by repeating the whole process three times.

Proposed HPLC Method

Isocratic elution mode of RP-HPLC was used for the determination of paraquat contents in raw and dosage forms using a single mobile phase (acetonitrile: methanol: water 1:1:2). The pH of the mobile phase was set as 2.5 using 0.1 M Ortho-phosphoric Acid. The flow rate used during the analysis was 1 mL/min. Sample volume injected was 20 µL. The micro glass syringe with stainless steel piston of 50 µL was arranged from SGE. Paraquat peak was measured at 257 nm. Paraquat contents in samples were quantified by comparing the peak areas of the samples and standards at a retention time of 2.4 minutes.

Paraquat contents were calculated by using the following equation (Eq.1):

$$\text{Paraquate Content } \%\,(w/w) \times 1 = \frac{A_2 \times m_1 \times P}{A_1 \times m_2} \qquad (1)$$

Paraquate content % (w/v) = Paraquate (w/w) x Density of Paraquat Liquid

Where

A_1 = Average peak area of the paraquat in the standard solution

A_2 = Average peak area of the paraquat in the sample solution

m_1 = mass of paraquat standard (mg)

m_2 = mass of paraquat sample (mg)

P = Purity of paraquat analytical standard

Results and Discussion

Development and Optimization of Method

HPLC chromatogram

In this work, various conditions have been optimized to develop an analytical method for determination of paraquat contents in raw and commercial samples using HPLC-UV system. A number of parameters were optimized for accurate and precise results. Fig. 2 (a & b) show HPLC-UV chromatograms showing the retention times (a) 2.37 min and (b) 2.35 min of paraquat in standard and sample solution, respectively.

Method validation

The proposed HPLC-UV analytical method shows the retention time for the analyte to elute within 2.37 ± 0.05 min with a total run time of 5 min in which complete elution of residues in the analyte mixture is done to reproduce the smooth baseline. In method validation, the following parameters were adopted to ensure the validity of the proposed method for paraquat in accordance with the ICH guidelines. These parameters are system suitability, linearity,

precision, specificity/selectivity, accuracy, repeatability, reproducibility, LOD, LOQ, and robustness.

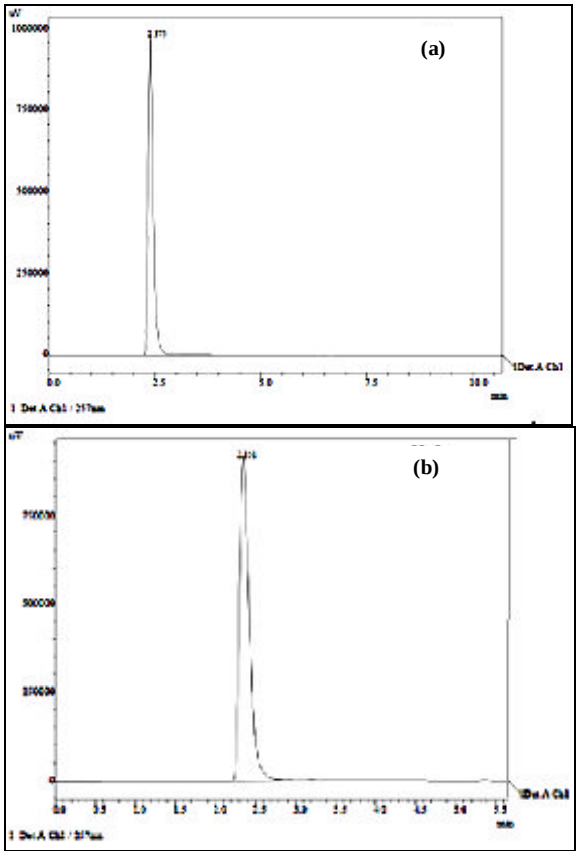

Figure 2. **HPLC Chromatogram a) paraquat standard solution b) paraquat sample solution**

The suitability of the system was tested by performing five consecutive injections of every type of formulation under optimized conditions. The system suitability test was conducted every day of validation and found within the range of accepted criteria.

Fig. 3 shows the data on the linearity of the developed method. Linearity of the developed method for paraquat was evaluated using different concentrations of 2.5 to 15 mg/L of paraquat dichloride. Correlation coefficient value (R^2) was calculated as 0.999 (Fig. 3).

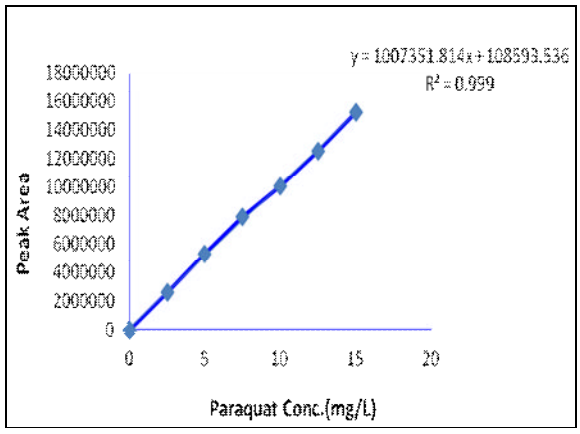

Figure 3. **Linearity plot of the developed method for paraquat**

Results on precision of the developed method for paraquat by HPLC are present in Table 1 (a). The relative standard deviation (RSD) value for paraquat was obtained as 0.32% by the five replicate readings, which have indicated that the developed method is precise.

The method is specific and selective for paraquat active ingredient contents, which were monitored separately using a blank sample and analyte standard solution. No peak was observed and detected near the peak of desired analyte (Table 1b). So, the method proved to be highly specific and selective.
<< Table # 1 >

Different standard solutions of paraquat dichloride concentrations (5.0 mg/L, 10.0 mg/L, and 15.0 mg/L) were used for the accuracy of the method developed (Table 2). Peak areas of calibration of the above said concentrations were calculated, and a calibration plot was constructed (Fig. 3) clearly indicates the slope and intercept values for paraquat using the equation y = mx + C (Y= 1007351.814x + 108593.536). The correlation (R^2) coefficient was calculated as 0.999. Table 2 (a & b) are related to the accuracy of the paraquat in terms of triplicate testing of samples A, B & C and in terms of theoretical yield, respectively.

***Table 1*. a) Precision of the developed method for paraquat determination, b) specificity of the developed method for paraquat.**

(a)

Replicate	Area of Standard Paraquat
1	8265172
2	8309842
3	8304873
4	8339651
5	8307607
Average	8305429
Standard Deviation	216534
RSD%	± 0.32

(b)

Product	Results in Mixture	Mean Result in Sample		Recovery (80% –120%)	Remarks
		Area Under the peak of the standard solution	*Area Under the peak of the sample solution*		
Paraquat	20%	8305429	7678251	99.95%	Pass
		19.99%			

***Table 2*. Accuracy of the method for paraquat.**

a) Area under the peak of sample for the accuracy of the method developed for the Paraquat by HPLC

Conc. (mg/L)	Sample No.		Peak Area	Peak Area (Mean)
5.0	Sample (A)	A1	5248812	5271827
		A2	5256423	
		A3	5310245	
10.0	Sample (B)	B1	10088225	10088560
		B2	10089104	
		B3	10088351	
15.0	Sample (C)	C1	15267729	15262262
		C2	15256843	
		C3	15262214	

b) Accuracy of the developed method for the Paraquat by HPLC

Conc. of sample (mg/L)	Mean area under the peak of sample	Mean area under the peak of standard	Observed Yield (mg/L)	Theoretical Yield (mg/L)	Percentage Recovery (%)
5.0	5271827	5248805	5.0219	5.0	100.44
10.0	10088560	10088444	10.000	10.0	100.00
15.0	15262262	15256724	15.0054	15.0	100.04

In evaluating the repeatability parameter of the newly developed method for the paraquat it was observed that by analyzing the paraquat analyte within different intervals of time under the same conditions and instrument, the RSD% value did not deviate from the standard value (RSD% ≤ 2%). Table 3 (a) is related to the repeatability of the developed method.

While performing the reproducibility parameter on two HPLC instruments named HPLC -20AT with SPD–20A detector and HPLC -10AT with SPD–10A from Shimadzu Corporation Japan, it was observed that the developed method for the paraquat analyte did not exceed the standard value of (RSD% ≤ 2%) while performing the same paraquat analyte on another instrument HPLC LC-10AT with SPD-10AVP UV-Visible detector. Hence, the developed analytical method was found to be suitable for analyzing paraquat herbicide contents in both the raw material and pesticide formulation in quality control laboratory. Table 3(b) related to the reproducibility of the developed method while Table 4. (a) is related to the reproducibility in terms of various formulations in paraquat from different industries. The method was repeatedly tested in different laboratories of local agrochemical industries and got most satisfactory repeatable and reproducible results with less retention time and high accuracy whose detail is available in inter lab comparison (ILC) in Table 4(b).

Table 3. a) **Repeatability of the developed method** ***b)*** **Reproducibility of the developed method.**

a) Reproducibility of the method

Sr.#.	**Observations**	**Paraquate (Peak area)**
1	Reading 1	7704796
2	Reading 2	7694439
3	Reading 3	7650588
4	Reading 4	7672111
5	Reading 5	7669320
6	Average	7678251
7	SD (r)	21502
8	RSD %	± 0.28%

b) Repeatability of the method

Sr. #.	**Observations**	**Paraquate (Peak area)**	
		HPLC – 20AT	**HPLC – 10AT**
1	Reading 1	7704796	7692965
2	Reading 2	7694439	7690667
3	Reading 3	7650588	7695332
4	Reading 4	7672111	7696151
5	Reading 5	7669320	7704606
6	Average	7678251	7695944
7	S.D	21502	5295
8	RSD (%)	0.28%	0.07%

Table 4. a) **Reproducibility of the developed method,** *b)* **Inter laboratory comparison.**

Formulation SL (Soluble Liquid)	Company	Proposed Method		Reference Method	
		Recovery %age [a]	RSD % [a]	Recovery % age [a]	RSD % [a]
Paraquat 20% SL	C-Crop Pesticide	102.40%	0.33%	100.22%	0.35%
Paraquat 20% SL	Standard Crop	102.15%	0.41%	104.15%	0.53%
Pointer 20% SL	Solex Chemicals	102.45%	0.14%	103.32%	0.34%
Paraquat 20% SL	Star Group	100.60%	0.61%	100.00%	0.16%
Paraquat 20% SL	Arab Fertilizer	103.20%	0.46%	100.05%	0.09%

[a]**Average of five independent analyses**

Laboratory[#]	Formulation Type			
	Paraquat 20% SL		Paraquat Tech 92% TECH	
	**Results*	*%RSD*	**Results*	*%RSD*
Lab 01	20.01%	0.24%	91.99%	0.10%
Lab 02	19.98%	0.11%	92.03%	0.11%
Lab 03	20.04%	0.35%	92.05%	0.14%
Lab 04	20.02%	0.18%	92.01%	0.09%
Lab 05	20.01%	0.31%	92.04%	0.13%

***Average of 5 replicates**

(#)

Lab 01: Solex Chemicals Quality Control Laboratory Industrial Estate Multan.
Lab 02: Exin Quality Assurance Laboratory Industrial Estate Multan.
Lab 03: Hexon Quality Assurance Laboratory Industrial Estate Multan.
Lab 04: Agri Force Chemicals Quality Assurance Laboratory Industrial Estate Multan.
Lab 05: Nuchem Quality Control Laboratory Industrial Estate Multan.

Table 5 shows that the value of LOD for paraquat was found to be 0.74 mg/L and that the value of LOQ was found to be 2.45 mg/L which is a clear indication of signal-to-noise ratio 3:1 for LOQ and LOQ. While Table 6 belongs to the robustness results of the developed method. The following equation is used to calculate LODs and LOQs, respectively.

$$LOD = 3\,\sigma / S$$
$$LOQ = 10\,\sigma / S$$

α = the standard deviation of the response
S = the slope of the calibration curve

Table 5. **LOD and LOQ of the proposed method for paraquat.**

No. of Readings	Paraquat (mg/L)
1	10.495
2	10.110
3	10.210
4	10.250
5	10.490
Average	10.495
SD (So)	+0.1734
Śo=SQR(2)* so	0.245
LOD=3* Śo	0.74
LOQ=10* Śo	2.45

While performing robustness of the method for paraquat, it was observed that by increasing the mobile phase flow rate from 1.0 mL/min to 1.2 mL/min, the area under the peak decreased. While the RSD% remained within the prescribed limits (RSD% ≤ 2%). While decreasing the flow rate of the mobile phase from 1.0 mL/min to 0.8 mL/min the area under the peak increased. In this case, again, the RSD% did not deviate from the standard value (RSD% ≤ 2%). Similarly robustness of the method was evaluated by changing the mobile phase compositions from (acetonitrile: methanol: water 1:1:2) to (acetonitrile:methanol:water 1:1:3). The area under the peak increased, but the RSD value did not deviate from the prescribed standard value (RSD % ≤ 2%). During the decrease of water ratio in the mobile phase (acetonitrile: methanol: water 1:1:2) to (acetonitrile: methanol: water 1:1:1.3), the area under the peak decreased but again the RSD value showed no deviation from the standard value (RSD% ≤ 2%). Table 7 shows the summary of the validation parameters of the developed method.

***Table 6*. Robustness at the change of flow rate and mobile phase of the developed method for paraquat.**

Sample No.	Change of Flow Rate			Change of Mobile Phase		
	Peak area at 0.8 mL/min	***Peak area at 1.0 mL/min***	***Peak area at1.2mL/min***	***ACN : Methanol : Water 30 : 30 : 40***	***ACN : Methanol : Water 25 : 25 : 50***	***ACN : Methanol : Water 20 : 20 : 60***
01	9845510	7704796	6504266	6313553	7704796	11298375
02	9829625	7694439	6500469	6312358	7694439	11271122
03	9843038	7650588	6493788	6311112	7650588	11243941
04	9840998	7672111	6489002	6313999	7672111	11285714
05	9844377	7669320	6493885	6313370	7669320	11314440
Mean	9840710	7678251	6496282	6312878	7678250	11282718
Std. deviation	6420	21502	6046	1156	21502	26919
% RSD	0.06%	0.28%	0.09%	0.02%	0.28%	0.24%

***Table 7*. Summary of validation parameters.**

Validation Parameters	Results (Paraquat)		Acceptance Criteria
Linearity	Correlation Coefficient = 0.999		Correlation Coefficient NLT 0.98
Precision	**0.32 % RSD**		% RSD NMT 2.0
	Concentration (mg/L)	**% Recovered**	
Accuracy	5	100.44%	
	10	100.00%	% Recovery within 80% - 120%
	15	100.04%	
Repeatability	**0.272 % RSD**		
	HPLC – 20AT	**HPLC – 10AT**	RSD ≤ 2.0%
Reproducibility	0.28% RSD	0.07% RSD	
Detection and Quantitation Limit	**LOD**	**LOQ**	-
	0.74 mg/L	2.45 mg/L	
	Change	**% RSD**	
	(Flow rate) 0.8 mL	0.065%	
	(Flow rate) 1.0 mL	0.28%	
	(Flow rate) 1.2 mL	0.093%	
	(Mobile Phase) Methanol : ACN :Water 300 : 300 : 400 pH 2.5 with H_3PO_4	0.018%	
Robustness	Methanol : ACN : Water 250 : 250 : 500 pH 2.5 withH_3PO_4	0.28%	% RSD NMT 1.5
	Methanol : ACN : Water 200 : 200 : 600 pH 2.5 with H_3PO_4	0.239%	

Summary of the validation parameters

The analytical method (on the basis of the parameters initially optimized) has been successfully validated by considering the parameters like the linearity, precision, accuracy, repeatability, reproducibility, suitability of the system, detection limit, quantification limit, specificity, and robustness. In this study, the precision range was within acceptable limits for this analyte than the methods reported earlier. The accuracy of the validated method showed excellent results. Percentage recovery of the paraquat was also calculated for every concentration by comparing the area under the peak of the standard solution and sample solution. The obtained results showed that the recovery percentage was maximum at concentrations 5 mg/L (100.44%) while at 10 mg/L (100.00%) and 15 mg/L (100.04%). So, the proposed method for the paraquat showed excellent results with excellent recoveries at different concentrations. The newly developed method for paraquat by HPLC has been found to be accurate and reproducible for different types of samples with excellent recoveries under the optimized conditions. At the end, the evaluation of the robustness was done by the change of flow rate and mobile phase ratio. Initially, the flow rate was shifted from 1 mL/min to 0.8 mL/min and than from 1 mL/min to 1.2 mL/min. The passage of the analyte through the system is very quick at a higher flow rate, showing low retention time, which results in the arising of the smaller peak area. But, the acceptable range of the RSD% values at the high flow rate does not exceed the limit. The ratio of the mobile phase from (acetonitrile: methanol: water 1:1:2) to (acetonitrile: methanol: water 1:1:3) and from (acetonitrile: methanol: water 1:1:2) to (acetonitrile: methanol: water 1:1:1.3) also showed variable areas under the peaks but still the RSD% value did not cross the standard acceptable ranges. Developed for the paraquat analyte, it is found that the method is rapid, efficient, low cost, repeatable and reproducible with excellent recoveries.

Conclusion

It may be concluded that RP-HPLC-UV method has the advantages of shorter retention time, easy and efficient. It has also shown excellent recoveries of paraquat contents in raw material and pesticide dosage forms. This method has been performed in the isocratic elution mode of RP-HPLC. The sample preparation step improves the overall performance for determination of paraquat in pesticide raw and dosage forms using a single mobile phase. The pH of the mobile phase set at 2.5 gives better results. Validation of the method was checked by the system suitability, linearity, precision, accuracy, repeatability, reproducibility, detection limit, quantification limit, specificity, and robustness analysis under optimized experimental conditions. This analytical method may be applied successfully at a commercial scale in the pesticide industry.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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