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Original Article

SPECTROPHOTOMETRIC DETERMINATION OF PARACETAMOL IN PHARMACEUTICALS BY DIAZOTIZATION AND COUPLING REACTION WITH RESORCINOL AND 1-NAPHTHOL

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ABSTRACT

A simple, accurate, and sensitive spectrophotometric method has been developed for the quantitative determination of acetaminophen (paracetamol, PAR) in pharmaceutical formulations including tablets, syrups, and injectable solutions. The method involves acid hydrolysis of PAR to yield p-aminophenol, which is subsequently subjected to diazotization to form a diazonium salt. This diazonium intermediate reacts with resorcinol and 1-naphthol to form colored azo dyes, exhibiting maximum absorbance at 480 nm and 510 nm, respectively. The method adheres to Beer's law over concentration ranges of 3–15 µg/mL for the resorcinol system and 2.5–20 µg/mL for the 1-naphthol system. The calculated molar absorptivity values were 18.5×10^3 and 9.8×10^3 $L \cdot mol^{-1} \cdot cm^{-1}$, with corresponding Sandell's sensitivities of 0.008 and 0.015 $\mu g \cdot cm^{-2}$, respectively. Method validation demonstrated satisfactory accuracy, with mean percentage recoveries ranging from 94.78% to 105.73%. Furthermore, the method exhibited good linearity, low limits of detection and quantification, and minimal relative error, underscoring its reliability and suitability for routine quality control analysis of PAR in commercial pharmaceutical preparations.

KEYWORDS: Diazotization, Coupling Reaction, Paracetamol, Pharmaceuticals, Spectrophotometer

Graphical Abstract

1. INTRODUCTION

Paracetamol (PAR) has been the most often used analgesic and antipyretic drug in medicine since its release in 1950, despite increasing concerns about medicines affecting organisms (AzEEz *et al*., 2021; Mezaal *et al*., 2024). The first preparation of PAR with the chemical formula $C_8H_9NO_2$ was made in 1878 by American scientist Harmon Northrop Morse. PAR with the structural formula given in Scheme 1, is known as a low

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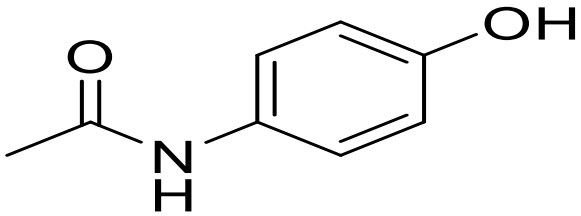
molecular-mass drug (molar mass=151.17 g/mol). N-acetyl-p-aminophenol is the chemical name for PAR, also known as acetaminophen or 4-acetamidophenol (Pasha, 2020). It is sold as a generic drug under various trade names, such as Panadol and Tylenol. Drugs must be in an aqueous solution at the absorption site to improve their bioavailability, lower their dosage, and eventually increase their effectiveness. Consequently, one of the most important physicochemical characteristics required for the successful development of any drug candidate is its water solubility. Although PAR belongs to the Biopharmaceutics Classification System (BCS) class II with a poor-moderate solubility in aqueous solutions (Arerusuoghene & Sinodukoo, 2022), its solubility can be improved in the binary aqueous mixtures with different organic solvents (Rahimpour & Jouyban, 2023). Since PAR has an acidity of just (pKa 9.7), it unionizes effectively at physiological pH levels. The partition coefficient of PAR between water and octanol is 3.2 and is likely to be in the context of passive diffusion between the membranes of a cell (Mészáros *et al*., 2022).



Scheme 1:Paracetamol (PAR)'s chemical structure with the chemical name N-acetyl-p-aminophenol.

PAR is widely used in two classes: analgesic (pain reliever) and antipyretic (fever reducer) (Arief S *et al*., 2023; Luu *et al*., 2023). It inhibits the brain's transmission of pain signals by having a very specific effect on an enzyme. Despite having a different mode of action than other analgesics, it nonetheless reduces pain all over the body (Arief S *et al*., 2023). Thus, it's advised for treating mild pain, such as headache, migraine, backache, rheumatic and muscle pain, and tooth pain. Furthermore, severe pain, such as pain following surgery or from cancer, is treated with PAR in addition to narcotic medicines (Arief S *et al*., 2023; AzEEz *et al*., 2021; Luu *et al*., 2023; Mezaal *et al*., 2024; Palakollu *et al*., 2020; Pasha, 2020; Salem, 2019; Youssef *et al*., 2019). Although PAR can also be injected, it is usually delivered orally or rectally. PAR is available in tablet, syrup, injectable, drop, and capsule. When taken as directed, PAR is generally safe. The maximum amount of 3 or 4 grams per day is advised for adults. Higher doses have the potential to be toxic and disastrous for the liver. It appears safe to breastfeed and become pregnant, yet in rare instances, severe skin rashes may occur. According to the World Health Organization, it is among the most important, safest, and most efficient drugs required in a healthcare system (Mezaal *et al*., 2024; Pasha, 2020).

Owing to the importance of the medication PAR, a variety of analytical methods for its detection, verification, and separation in various samples are documented in the literature. These techniques include electrochemical (Palakollu *et al*., 2020; Salem, 2019), thin layer chromatography (TLC) (Bober-Majnusz & Pyka-Pająk, 2024; Youssef *et al*., 2019), spectrophotometric (Ahmed *et al*., 2015; Luu *et al*., 2023; Pasha, 2020; Rahman *et al*., 2023; Selimoğlu & Pinarcik, 2023; Thanoon, 2019), liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Divya Vilas *et al*., 2020; Youssef *et al*., 2019) or liquid chromatography mass spectrometry (LC-MS) (Kam *et al*., 2018), and high-performance liquid chromatography (HPLC) (Ahmad & Omar, 2018; Arief S *et al*., 2023; Dewani & Patra, 2015; Ghazal *et al*., 2023; Youssef *et al*., 2019).

The most popular, adaptable, straightforward, and sensitive of them all is the spectrophotometric approach, which is used throughout this study. Based on p-aminophenol's acid hydrolysis of PAR, the approach produces a coloured azo dye with maximal absorbance in the visible region for both reagents by diazotizing the resulting p-aminophenol and coupling it with either resorcinol or 1-naphthol.

2. MATERIALS AND METHODS

Instruments:

All the spectral measurements were made using an ultraviolet-visible (UV-VIS) spectrophotometer (EMCLAB V-1100 DIGITAL SPECTROFOMETER), with the wavelength range between (325-1000) nm and 1cm matched glass cells. An electronic balance, model (DENVER instrument) and micropipettes 1-10µl (UNITED), 20-200µl and 200-1000µl (LAMTEK).

A. Samples and Chemicals:

Distilled water was used to prepare the solutions, and all of the compounds were of analytical reagent quality. Standard PAR, Awamedica tablet, zynova tablet, Awamedica parAzar syrup, Parahold injection. Chemicals: ethanol, (abs. 100%) a.r. (chem-Lab NV), Hydrochloric acid (35-38%) LR (SDFCL), NaOH (Scharlau), Na2CO3 (Art, -Nr.A 135.2), sulphamic acid, 1-naphthol (SDFCL), and resorcinol (SDFCL).

B. Preparation and Experimental:

Paracetamol solution, PAR (1000µg/mL): 0.25 g of paracetamol was dissolved in 10 mL ethanol; subsequently using a 250 mL volumetric flask, the solution was completed with distilled water.

Hydrochloric acid solution (4M) in a 100mL distilled water.
Resorcinol reagent solution (0.5% w/v).
1-Naphthol reagent solution (0.5% w/v).
Sodium nitrite solution (1% w/v).
Sulphamic acid solution (3% w/v).
Solutions of hydrolysed standard paracetamol, HPAR (600µg/mL): After being moved to a 250 mL round-bottomed flask with 20 mL of 4M HCl, 150 mL of 1000µg/mL PAR was refluxed for an hour. After neutralizing with a 20% sodium carbonate solution, the cold solution was diluted using distilled water in a 250 mL volumetric flask.

C. Preparation of Mixtures for the Calibration Curve:

Determination of PAR using resorcinol (480 nm):
1. Preparation of standard solutions: PAR solutions were prepared at concentrations of 0.5, 1, 2, 3, 5, 8, 10, 13, and 15 µg/mL. Each was placed in a separate 25 mL volumetric flask.
2. Diazotization reaction: to each flask, add 0.6 mL of 4 M HCl and 1.0 mL of 0.1% sodium nitrite.
3. Cooling: place the flasks in an ice bath for 3 minutes to allow the diazotization to occur under controlled conditions.
4. Removal of excess nitrite: add 1.0 mL of 1.5% sulphamic acid to each flask to destroy any extra nitrous acid.
5. Coupling reaction: add 1.0 mL of 1.5% resorcinol as the coupling agent. Shake the mixture and let it stand for 2 minutes at room temperature.
6. Volume adjustment: fill each flask to the 25 mL mark with distilled water.
7. Absorbance measurement: measure the absorbance of the orange-coloured solution at 480 nm using a UV-VIS spectrophotometer.
Determination of PAR using 1-naphthol (510 nm):

1. Preparation of standard solutions: PAR solutions were prepared at concentrations of 0.5, 1, 2, 5, 8, 15, and 20 µg/mL. Each was placed in a separate 25 mL volumetric flask. The same steps (2-4) as outlined in the previous section were then taken.
5. Coupling reaction: add 1.5 mL of 0.5% 1-naphthol as the coupling agent. Shake the mixture and let it stand for 2 minutes at room temperature.
6. Volume adjustment: fill each flask to the 25 mL mark with distilled water.
7. Absorbance measurement: measure the absorbance of the deep orange to red-coloured solution at 510 nm using a UV-VIS spectrophotometer.

D. Preparation of Pharmaceutical Samples:

Preparation of paracetamol (PAR) tablet solution (1000 µg/mL):
1.Ten tablets, each containing 0.5 g of PAR, were weighed and ground into a fine powder. A sample equivalent to 0.25 g of PAR was accurately weighed and transferred to a 250 mL volumetric flask.
2.Approximately 10 mL of ethanol was added to dissolve the sample, followed by 100–150 mL of distilled water.
3.The mixture was thoroughly mixed and filtered to remove solids. The filtrate was then diluted with distilled water up to the 250 mL mark.
Preparation of hydrolysed paracetamol (HPAR) tablet solution (600 µg/mL):
1.To a 250 mL round-bottom flask, 20 mL of 4 M HCl was added. Then, 150 mL of the previously prepared 1000 µg/mL PAR tablet solution was introduced.
2.The mixture was refluxed for one hour to achieve HPAR.
3.After cooling, the solution was neutralized using a 20% sodium carbonate solution.
4.The neutralized solution was transferred to a 250 mL volumetric flask and diluted with distilled water to the required volume.
Preparation of PAR injection solution (1000 µg/mL):
1.The content of three injections (each 5 mL with 0.5 g PAR) were combined.
2.A 2.5 mL portion (containing 0.25 g PAR) was diluted to 250 mL with distilled water.
3.Then, 150 mL of this solution was taken for hydrolysis as described above.
Preparation of PAR Syrup Solution (1000 µg/mL):
1.Five milliliters of syrup (containing 0.25 g PAR) was diluted to 250 mL with distilled water.
2.A 150 mL portion was taken and hydrolysed using the same method as the other samples.

E. Preparation of Different Samples for Paracetamol Quantification:

The quantification of PAR using resorcinol and 1-naphthol in the following pharmaceutical samples were analysed:
Awamedica/ParAzar tablets (Erbil, Iraq)
Pmol/Zynavo tablets (Oman Pharmaceutical)
Awamedica/ParAzar syrup (Erbil, Iraq)
Parahold injection (India)

For both methods, each sample was generated with the following concentrations: 4 µg/mL and 11 µg/mL (resorcinol, 480 nm) and 6 µg/mL and 12 µg/mL (1-naphthol, 510 nm). The next steps were carried out for both reagents as described in section D (steps 1–7).

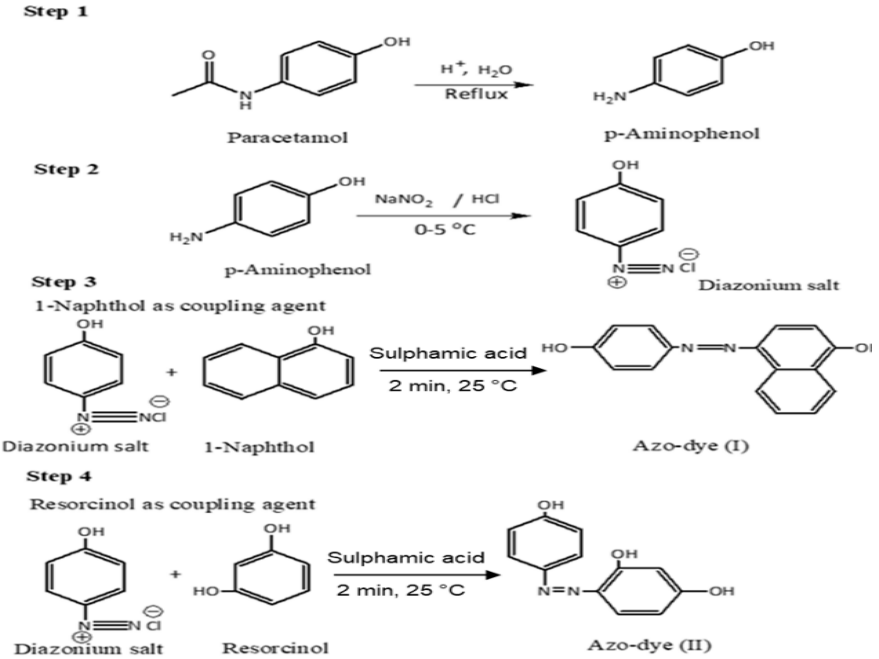
3. STATISTICAL ANALYSIS

The experiments were performed in triplicate. The results are expressed as mean values ± standard deviation (SD).

4. RESULTS AND DISCUSSIONS

Method Principle:

The Griess reaction is a widely used method to assess the quantity of nitrate in water, soil, vegetables, meat products, and other samples. It involves diazotizing aromatic amines and combining the resultant product with phenols or aromatic amines (Dixit & Patel, 2014). It was used in this study to estimate PAR in various samples. The technique involves refluxing PAR in an acidic medium to hydrolyse it into p-aminophenol (Scheme 2. step 1) and then employing $NaNO_2$ in an acidic medium to diazotize the resultant product (Scheme 2. step 2). Subsequently, the diazonium salt produced is mixed with two phenolic reagents. The first reagent, 1-naphthol, makes a deep orange-to-red colour (Scheme 2. step 3) and reaches its maximum absorption at 510 nm (Fig.1(I)). The second reagent, resorcinol, yields an orange colour (Scheme 2. step 4) and produces an azo dye, which reaches its maximum absorption at 480 nm (Fig.1(II)).



Scheme 2: Possible reaction pathway during the determination of PAR using two different coupling agents (Dixit & Patel, 2014).

Optimization of the Reaction Conditions:

Absorption spectra and assigning wavelength at maximum absorption (λ_{max}): Using the optimized reaction conditions similar to those described in the literature (Dixit & Patel, 2014), two solutions were prepared against their blank solutions as described in the earlier section (section 2,D). The solutions of the azo dye were made by mixing HPAR (p-aminophenol) with the coupling reagents, and the absorbance was scanned from 300-700 nm Figure1. The orange-red azo dye, which was made by mixing diazotized HPAR with 1-naphthol reagent, showed the maximum absorption at 510 nm in its absorption spectra Figure1(I). On the other hand, orange azo dye was formed when resorcinol was used as a coupling reagent; the maximum absorption was recorded at 480 nm Figure 1(II). One possible explanation for the variation in maximum absorption wavelength is that 1-naphthol has more aromatic conjugated double bonds than resorcinol. The wavelength of light absorbed increases with the number of conjugated pi systems because the energy gap for a π-π* transition becomes narrower.

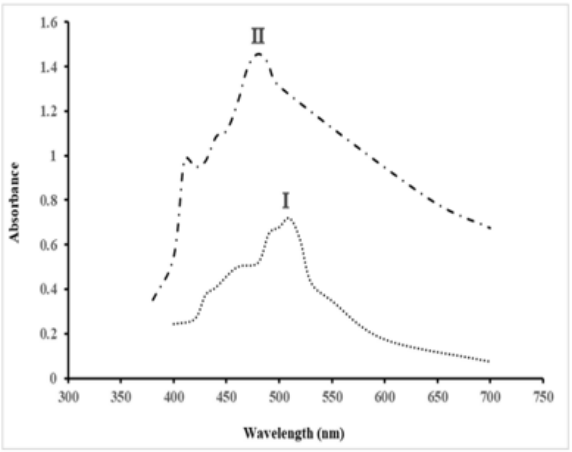


Figure 1: Absorption spectra of solutions made by mixing 20µg/mL PAR with 1-naphthol (I) and resorcinol (II) in the reaction conditions as stated in the preparation protocol.

Optimization of the Reaction Time Proceeds:

To determine the ideal amount of time needed to finish the reaction, a time scale ranging from zero to twenty-five minutes was examined, beginning with the preparation of diazonium salt and ending with the production of a coloured azo dye Figure 2. After conducting the reactions with both coupling reagents, the best duration of 5 minutes was found and used throughout the investigation. Nonetheless, it is demonstrated that the azo dye's stability holds for the duration of the study.

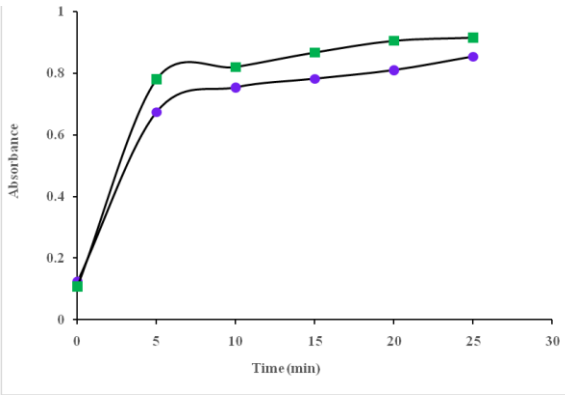


Figure 2: Time optimization of solutions made by mixing PAR with 1-naphthol (square marker, ■) and resorcinol (circle marker, ●) in the reaction conditions as stated in the preparation protocol.

5. METHOD VALIDATION

Linearity of the Method:

A standard calibration curve was plotted by mixing different concentrations of PAR after being diazotized and coupled with the two coupling reagents under optimized reaction conditions. Plotting absorbance versus PAR concentration reveals that, employing resorcinol and 1-naphthol, respectively, the generated dye follows Lambert Beer's law from (3-15) µg/mL, and (2.5-20) µg/mL of PAR respectively Figure 3. The statistical parameters were given by the regression equation Table 1, which was obtained from the calibration curve (Y= a + mX). In this case, m denotes slope, a stands for y-intercept, X represents PAR concentration in µg/mL, and Y stands for absorbance. A high determination coefficient (R^2) and a small value for the regression equation's y-intercept demonstrated the calibration graph's linearity. Both conditions are met when using resorcinol and 1-naphthol.

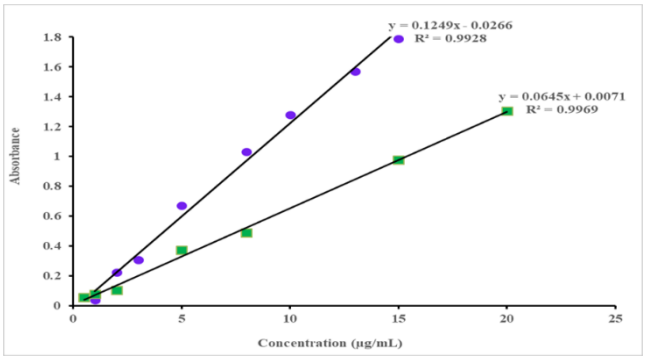


Figure 3: Lambert-Beer calibration curve for PAR employing 1-naphthol (square marker, ■) and resorcinol (circle marker, ●) at optimal experimental conditions at λ max equal to 510 nm and 480 nm, respectively.

Table 1: The analytical data obtained with the suggested method using resorcinol and 1-naphthol as coupling reagents.

Parameters	Data results	
	Resorcinol	1-Naphthol
The color of the product	Orange	Deep orange-red
Wavelength at maximum absorption (λ_{max}, nm)	480	510
Regression equation	y = 0.1249x - 0.0266	y = 0.0645x + 0.0071
Linear range (µg/mL)	3-15	2.5-20
Intercept (a)	-0.0266	0.0071
Slope (m)	0.1249	0.0645
Standard error of intercept	0.0375	0.0163

Standard error of slope (Sm)	0.0043	0.00161
Determination coefficient (R^2)	0.9928	0.9969
Limit of detection (LOD, µg/mL)	0.90	0.76
Limit of quantification (LOQ, µg/mL)	3.00	2.53
Molar absorptivity (ε, L/mol.cm)	18.5×10^3	9.8×10^3
Sandell's sensitivity (µg/cm^2)	0.0080	0.0155

Sensitivity of the Method:

Multiple criteria were used to evaluate the sensitivity of the proposed approach, including Sandell's sensitivity, molar absorptivity, LOQ, and LOD. It can be inferred that both reagents, resorcinol and 1-naphthol, provide a sensitive method based on the molar absorptivity and Sandell's sensitivity values provided in Table 1. To evaluate LOD and LOQ, the following formulas can be used:

$$LOD = \frac{3S}{m} \quad and \quad LOQ = \frac{10S}{m} \qquad (1)$$

where m = the calibration curve's slope
S = the intercept's standard error

Once more, the low value of LOD indicates strong sensitivity for the suggested method, which employs either 1-naphthol (LOD=0.76 and LOQ=2.53) µg/mL or resorcinol (LOD=0.90 and LOQ=3.00) µg/mL as a reagent. The sensitivity of the recommended method was also compared to other spectrophotometric methods suggested in the literature Table 2.

Table 2: Analytical data produced using the proposed method is compared to other methods employed in the literature.

Parameters	Proposed method		Method (I) (AzEEz *et al*., 2021)	Method (II) (Ahmed *et al*., 2015)	Method (III) (Dixit & Patel, 2014)
	Resorcinol	1-Naphthol	2-Hydroxybenzaldehyde	2,4-Dichloroaniline	8-Hydroxyquinline
Medium	− *	− *	Alkaline	Alkaline	Alkaline
Color of the product	Orange	Deep orange-red	Yellow	Red	Orange-red
Wavelength at maximum absorption (λmax, nm)	480	510	444	490	470
Linear range (µg/mL)	3-15	2.5-20	0.5-12	4-350	2-10
Determination coefficient (R^2)	0.9928	0.9969	0.9995	0.9992	-
Limit of detection (LOD, µg/mL)	0.90	0.76	0.05	-	-
Molar absorptivity (ε, L/mol.cm)	18.5×10^3	9.8×10^3	12.03×10^3	3.22×10^3	19.00×10^3

* No acid or base is used

6. APPLICATION OF THE PROPOSED METHODS TO PHARMACEUTICAL SAMPLES

An adequate amount of pharmaceutical sample solutions of PAR from various brands and forms, including tablet, syrup, and injection, was taken in the linearity range and processed in line with the preparation procedures, as per the generally recommended procedure. Furthermore, the absorbance of the resultant solution mixture in the presence of resorcinol or 1-naphthol was measured in a glass cuvette at 480 nm and 510 nm, respectively, using a spectrophotometer. Tables 3 and 4 display both proposed methods' recovery percentage and relative error (E_{rel}%,). The British Pharmacopoeia (B.P.) was used as a standard to determine the drug's amount in terms of percentages. According to B.P., the PAR concentration should range from 95.0 to 105.0% of the specified amount. For the percentage content, almost all of the samples included in the assay met the B.P., criteria.

Table 3: The level of PAR content in drug samples using resorcinol reagent.

Drugs	Amount of PAR(µg/mL)		Amount of PAR (%)		%$E_{rel.}$	%Recovery
	Taken	Found ±SD*	Taken	Found		
Awamedica/ParAzar/tablet (Erbil/Iraq)	4	3.92±0.64	0.00040	0.00039	2.00	98.00
	11	11.23±1.69	0.00110	0.00112	2.09	102.09
Pmol/Zynavo/tablet (Oman pharmaceutical)	4	3.79±0.37	0.00040	0.00038	5.22	94.78
	11	10.53±0.06	0.00110	0.00105	4.27	95.73
Parahold/Injection (India)	4	4.08±0.86	0.00040	0.00041	2.07	102.07
	11	11.62±0.24	0.00110	0.00116	5.73	105.73
Awamedica/ParAzar/ syrup (Erbil/Iraq)	4	4.02±0.87	0.00040	0.00040	0.61	100.61
	11	10.88±1.19	0.00110	0.00109	1.12	98.88

*SD, standard deviation for triplicate determinations

Table 4: The level of PAR content in drug samples using 1-naphthol reagent.

Drugs	Amount of PAR(µg/mL)		Amount of PAR (%)		%$E_{rel.}$	%Recovery
	Taken	Found ±SD*	Taken	Found		
Awamedica/ParAzar/tablet (Erbil/Iraq)	6	6.20±0.03	0.00060	0.00062	3.33	103.33
	12	11.97±1.32	0.00120	0.00120	0.23	99.77
Pmol/Zynavo/tablet (Oman pharmaceutical)	6	6.10±0.79	0.00060	0.00061	1.74	101.74
	12	11.45±0.58	0.00120	0.00115	4.58	95.42
Parahold/Injection (India)	6	6.23±0.17	0.00060	0.00062	3.89	103.89
	12	11.67±0.78	0.00120	0.00117	2.75	97.25
Awamedica/ParAzar/ syrup (Erbil/Iraq)	6	6.11±1.06	0.00060	0.00061	1.92	101.92
	12	2.03±0.99	0.00120	0.00120	0.24	100.24

*SD, standard deviation for triplicate determinations

CONCLUSIONS

Using Lambert-Beer's law and a simple UV-VIS spectrophotometer, the paracetamol (PAR) content in pharmaceutical samples was quantitatively determined through a diazotization and coupling reaction with selected coupling agents. The recovery rate ranged from 94.78% to 105.73%, indicating good accuracy. The experimental results were consistent with the labeled content, showing an error range of 0.23% to 5.73%. These findings suggest that both resorcinol and 1-naphthol are suitable reagents for determining PAR in commercial drug formulations. The proposed method is simple, accurate, and avoids the complex procedures commonly associated with other techniques such as chromatography.

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Declaration:

We hereby confirm that the document contains all of our own illustrations, tables, and diagrams.

Author Contributions:

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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