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Determination of paracetamol in pharmaceutical samples by spectrophotometric method

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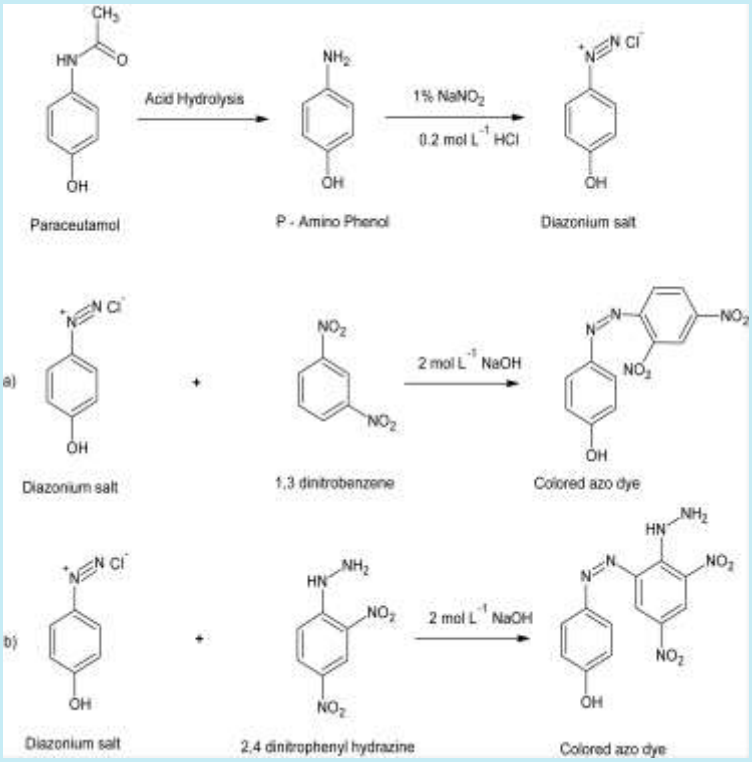
ABSTRACT: It is described the use of 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine is used as coupling agent for the spectrophotometric determination of paracetamol. This method is easy and simple based on the reaction of acid hydrolysis of paracetamol to produce p-aminophenol, which in turn reacts with nitrite in acidic standard to form diazonium ion, which is coupled with coupling agent in basic standard to produce azo dyes. The formed dyes follow Beer's law in the range of 0.8-20.5 μg mL^{-1} of paracetamol with 1, 3 dinitrobenzene or 0.5-18.4 μg mL^{-1} of paracetamol with 2,4 dinitrophenyl hydrazine with absorption maxima at 429 nm or 430 nm. The molar absorptivity and Sandell's sensitivity of paracetamol with 1,3 dinitrobenzene or paracetamol with 2,4 dinitrophenyl hydrazine azo dyes were 1.965×10^4 L mol^{-1} cm^{-1} or 2.776×10^4 L mol^{-1} cm^{-1}, and 7.692×10^{-3} μg cm^{-2} or 5.698×10^{-3} μg cm^{-3} respectively. The dyes formed are stable for more than 12 h. The optimal reaction circumstances and other analytical parameters are evaluated. Interference due to foreign organic compounds have been studied. The method has been effectively applied to the determination of paracetamol in pharmaceutical samples.



1. Introduction

Paracetamol called acetaminophen or 4-acetamidophenol, is a common pain reliever and fever reduction medicine[1]. Its chemical name is N-acetyl-p-aminophenol with a chemical formula $C_8H_9NO_2$. Paracetamol was first prepared in 1878 by Harmon Northrop Morse an American chemist[2]. It is available as a generic medication with trade names including Tylenol and Panadol, among others[3]. It is often sold in the commercial markets with a major ingredient in many cold and flu remedial combination drugs. It is usually used either by mouth or rectally, but is also available intravenously[1,4]. Paracetamol is accessible in as a tablet, drops, capsules, injection, and syrup[5].

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Paracetamol is usually safe at suggested doses[6]. The suggested maximum daily dosage for an adult is 3 or 4 grams[7,8]. Higher doses may result in toxicity, including liver disaster. Serious skin rashes may infrequently occur, and it appears to be secure during pregnancy and breastfeeding[1].

Paracetamol is also used for severe ache, such as cancer ache and ache after surgery, in combination with opioid ache medication[9]. Paracetamol has a highly targeted action in the brain, blocking an enzyme involved in the transmission of ache. Its mode of action was known to be different compared to other pain relievers, but although it produces pain relief throughout the body[10]. It is on the WHO's List of essential medicines, the most effective and safe medicines desired in a health system[11].

A lot of techniques are existing in the literature for the determination of paracetamol in various types of pharmaceutical preparations. These techniques are titrimetric[12], HPLC and RP-HPLC[13-15], HPTLC[16], Voltametric[17-20], electrochemical[21] and spectrophotometry[10]. Several spectrophotometric techniques for the determination of paracetamol are presented in the literature[10,22-41].

The reagents reported for the spectrophotometric determination of paracetamol are less selective, less sensitive and some require stringent experimental conditions and are chronic toxic in nature[27,33,36,38]. The present research work is on spectrophotometric determination of paracetamol in pharmaceutical samples. The hydrolyzed product of paracetamol is diazotized with nitrite in acidic standard at room temperature and the diazonium salt thus shaped is coupled with 1,3 dinitrobenzene and 2,4 dinitrophenyl hydrazine to give colored azo dye in alkaline standard is the source for the determination of paracetamol. The method has been successfully applied to the determination of paracetamol in pharmaceutical samples.

2. Experimental

2.1 Instruments used

A SHIMADZU Deutschland GmbH UV-2550 spectrophotometer and a pH meter- WTW pH 330 were used.

2.2 Chemicals and reagents used

Stock solution of paracetamol (Gift sample from Matrix Laboratory, Hyderabad, India): Weighed an amount 0.251 g of paracetamol and was dissolved in 10-15 mL of ethanol then the solution is transferred into a 250 mL standard flask, fulfilled to the mark with double distilled water (1000 µg mL^{-1}). Working solution was prepared as required by dilution.

Sodium nitrite solution (0.5%), hydrochloric acid solution (0.5 mol L^{-1}), 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine solution (2%), sodium hydroxide solution (2 mol L^{-1}).

2.3 Hydrolyzed paracetamol solution (100 µg mL^{-1})

A 150 mL of 1000 µg mL^{-1} paracetamol solution was transferred to 250 mL round bottomed flask provided with 20 mL of 4 mol L^{-1} of hydrochloric acid, then refluxed for 1 h, kept aside to cool the solution, then neutralized with 20% of sodium carbonate solution, then diluted with distilled water using a 250 mL volumetric flask. A 16.6 mL of the above solution was diluted with distilled water in a 100 mL volumetric flask to prepare 100 µg mL^{-1} paracetamol[40].

2.4 Paracetamol tablets solution (1000 µg mL^{-1})

Paracetamol tablets of different trademarks were purchased from local pharmacy and were finely powdered. An accurately weighed amount of powder equivalent to 0.25 g paracetamol was dissolved in 10-12 mL ethanol, then 90-100 mL distilled water was added, mixed well to increase the solubility, filtered into 250 mL calibrated flask. Then the solution was completed to the mark with distilled water, and progress as mentioned above in preparation of hydrolyzed paracetamol solution[40].

2.5 Paracetamol tablets of different trademarks used

P-750: 750 mg. Apex Laboratories Pvt. Ltd. Chennai, TamilNadu, INDIA, Dolopar: 650 mg. Micro LabsLtd. Bangalore, INDIA, Disprin Paracetamol: 500 mg. Reckitt & Benckiser Ltd. Gurgaon, Haryana, INDIA, Crocin Quik: 500 mg. Glaxo Smithkline, Mumbai, Maharashtra, INDIA, Paramet: 500 mg. Wallace Pharmaceuticals Ltd. Goa, INDIA, Nicetamol: 125 mg. Dr. Reddy's Laboratories Ltd, Hyderabad, Andra Pradesh,

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INDIA, Paracip 500 mg. Cipla Limited, Mumbai, Maharashtra, INDIA.

2.6 Procedure for the determination of paracetamol

An aliquot of the solution containing paracetamol (μg mL^{-1}) was transferred into a string of 10 mL calibrated flasks. Add 1 mL of 0.5% solution of $NaNO_2$ and 0.5 mL of 0.5 mol L^{-1} HCl and then the solution was mixed thoroughly and kept away for accomplishment of diazotization reaction. Then, add 1 mL of 2% 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine and 1.5 mL of 2 mol L^{-1} NaOH solutions and then diluted to 10 mL, using distilled water, and mixed thoroughly. Later the absorbance of the colored azo dye formed was measured at 429 nm or 430 nm beside the reagent blank.

3. Results and Discussion

The diazotization of paracetamol with nitrite, followed by the coupling of 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine in alkaline standard. The absorption spectra of the azo dye produced between paracetamol-1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine is presented in Fig. 1 having absorption maximum at 429 nm or 430 nm, respectively. The plot of absorbance against concentration of paracetamol coupled with 1, 3-dinitrobenzene or 2,4 dinitrophenyl hydrazine is presented in Fig. 2. The formed dyes obeys Beer's law in the range of 0.8-20.5 μg mL^{-1} of paracetamol with 1,3 dinitrobenzene or 0.5-18.4 μg mL^{-1} of paracetamol with 2,4 dinitrophenyl hydrazine and the reaction method is shown in Scheme 1.

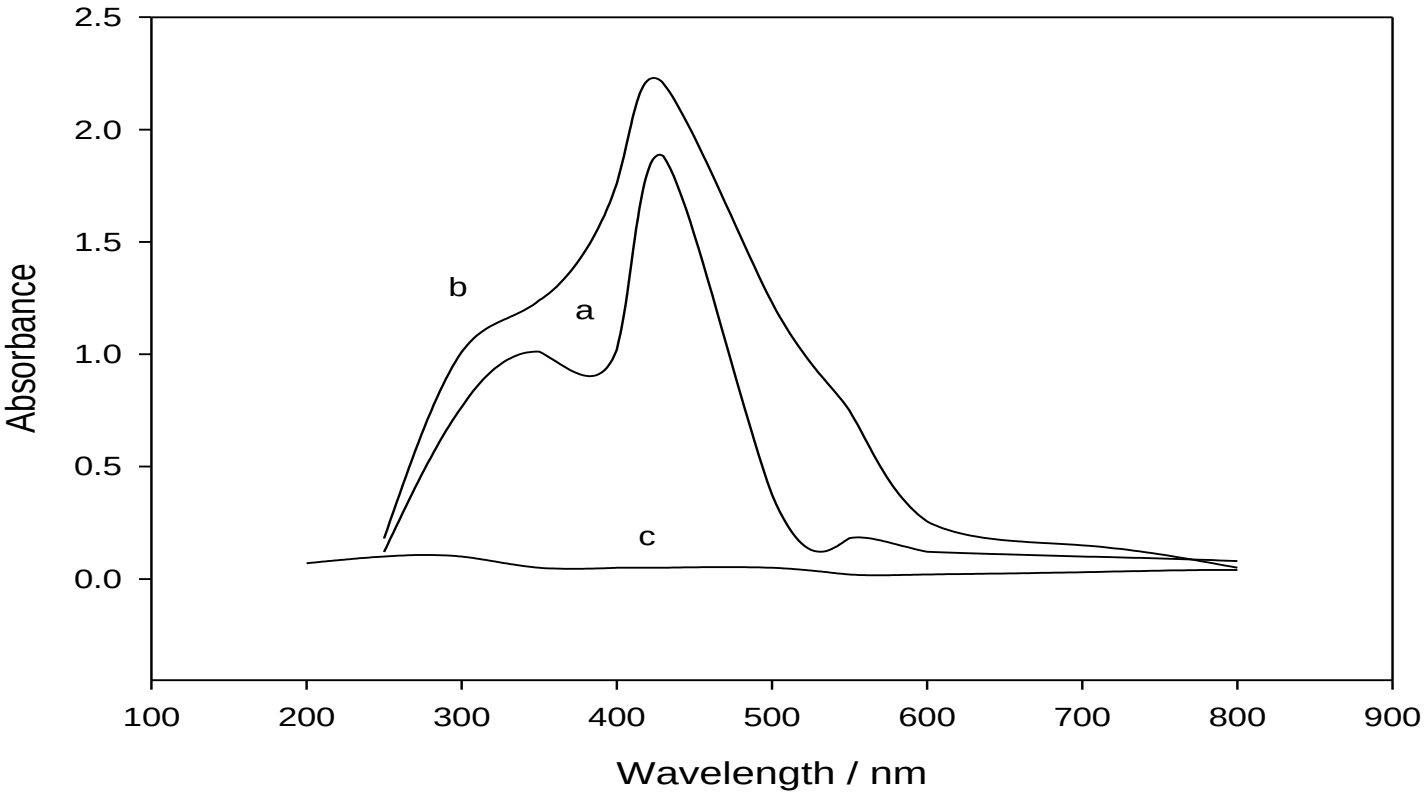

Figure 1. Absorption spectrum of the diazocouple of nitrite with 1,3 dinitrobenzene against reagent blank (a); absorption spectrum of the diazocouple of nitrite with 2,4 dinitrophenyl hydrazine against reagent blank (b) and reagent blank against distilled water (c).

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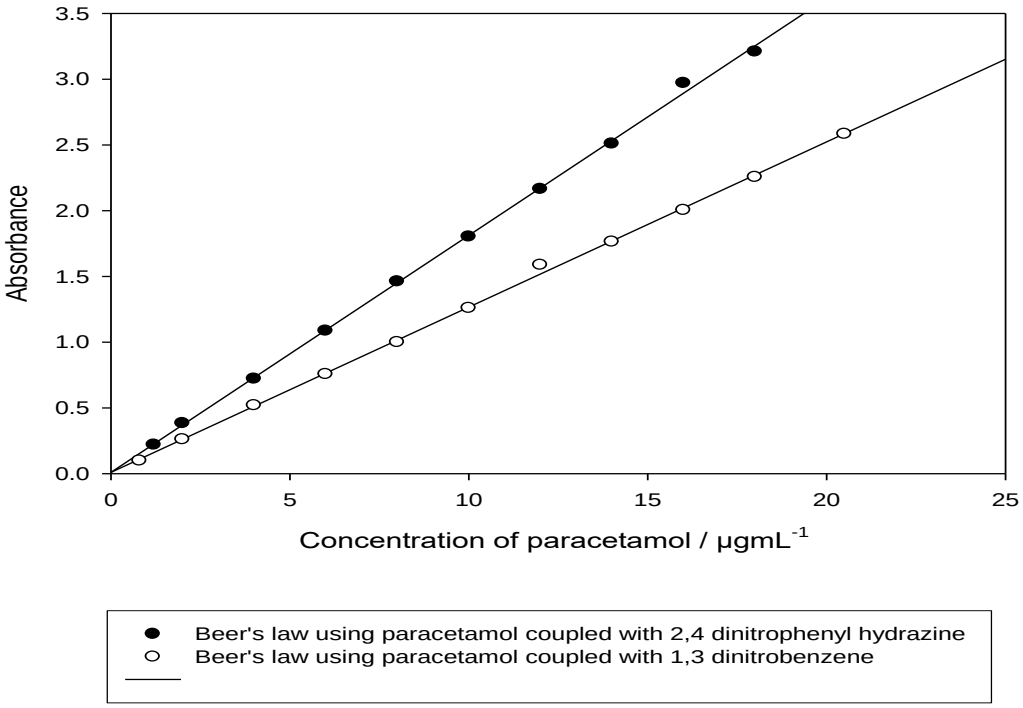
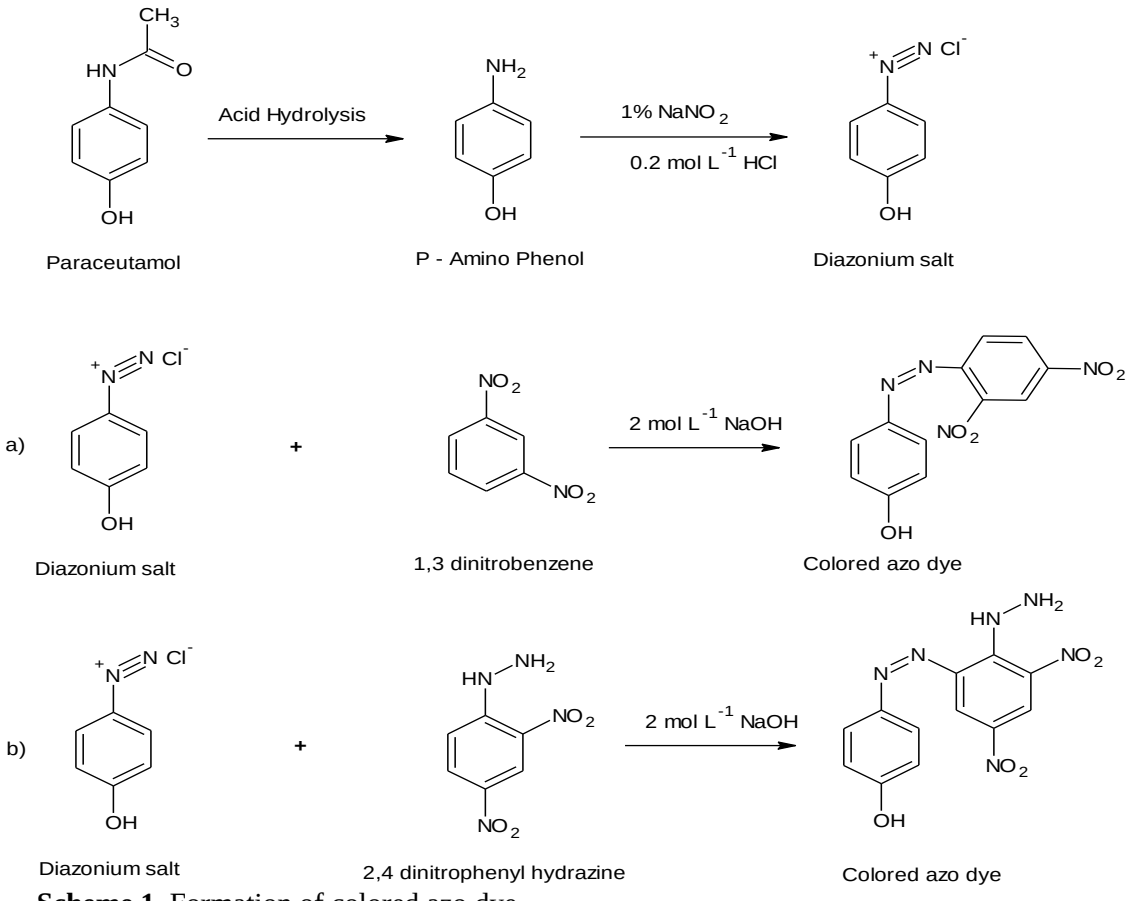


Figure 2. Adherence to Beer's law using 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine as coupling agents.



Scheme 1. Formation of colored azo dye.

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3.1 Effect of acid concentration, acids and temperature

The acidity effect on the diazotization reaction was considered with 2 µg mL^{-1} of paracetamol, in the range 0.1- 0.6 mol L^{-1} HCl. From the results, it can be observed that 0.5 mL of 0.5 mol L^{-1} HCl is the suitable concentration which gives the highest value of absorbance, for diazocouple of nitrite with 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine, beyond this range, a decrease in the absorbance was detected (Tab. 1).

Table 1. Effect of acid concentration on absorbance.

0.5 mL HCl used (mol L^{-1})	Absorbance (A)	
	1,3 dinitrobenzene	2,4 dinitrophenyl hydrazine
0.1	0.226	0.202
0.2	0.243	0.215
0.3	0.259	0.236
0.4	0.253	0.238
0.5	0.285	0.242
0.6	0.271	0.234

The effect of the amount of different acid (weak and strong) for the diazotization of paracetamol with nitrite, followed by the coupling of 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine have been investigated. The results indicated that 0.5 mL of 0.5 mol L^{-1} HCl produces the highest intensity for the dye, so it has been selected in the subsequent experiments (Tab. 2). Diazotization was conceded at room temperature (25 ± 5) ^{0}C.

Table 2. Effect of different acid concentration on absorbance.

0.5 mol L^{-1} acid concentration used	Absorbance (A) / mL of acid used			
	0.25 mL	0.5 mL	0.75 mL	1.0 mL
HCl	0.222	0.252	0.244	0.201
HNO_3	0.217	0.243	0.237	0.296
H_2SO_4	0.215	0.222	0.219	0.263
CH_3COOH	0.297	0.217	0.295	0.212

3.2. Effect of the nitrite concentration

The color is reached maximum intensity when using 1 mL of 0.5% sodium nitrite solution using paracetamol-1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine with 2 µg mL^{-1} of paracetamol and adding 1 mL of 0.1-1.0% solutions of the nitrite in hydrochloric acid (0.5 mol L^{-1}) to a series of nitrite solutions. Higher concentration did not build up the absorbance further, and at lower concentration, no good results were obtained.

3.3 Effect of coupling agent

1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine is used as a coupling agent was in the current procedure, by taking 2 µg mL^{-1} of paracetamol and adding 0.25-2.0 mL of 2% 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine to a string of nitrite solutions. It was found that utmost and firm color was obtained with 1 mL of 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine (2%) solution in an ultimate volume of 10 mL.

3.4 Effect of NaOH concentration

The experiment showed that 1.5 mL of NaOH gave utmost absorbance and 1.5 mL of 2 mol L^{-1} NaOH solutions was preferred for the diazotization of paracetamol with nitrite, followed by the coupling of 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine using 2 µg mL^{-1} of paracetamol. Other alkaline solutions were applied, but the finest results were gained by the use of NaOH solution (Tab. 3).

Table 3. Effect of NaOH on absorbance.

2 mol L^{-1} sodium hydroxide used (mL)	Absorbance(A)	
	1,3 dinitrobenzene	2,4 dinitrophenyl hydrazine
0.5	0.218	0.212
1.0	0.224	0.216
1.5	0.257	0.232
2.0	0.243	0.226

3.5 Interference of foreign compounds

The results specified that the studied foreign compounds such as 1000 µg mL^{-1} of glucose, 800 µg mL^{-1} of fructose, 500 µg mL^{-1} of lactose, 500 µg mL^{-1} of starch and 200 µg mL^{-1} of urea do not interfere in the determination of 2 µg mL^{-1} of paracetamol. An error below ±2% error in the absorbance values of paracetamol at 2 µg mL^{-1}.

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3.6 Analytical data

By plotting absorbance beside concentration of paracetamol, a straight line is obtained in the graph. Beer's law obeys in the range of 0.8-20.5 μg $mL^{-1}$of paracetamol with 1,3 dinitrobenzene or 0.5-18.4 μg mL^{-1} of paracetamol with 2,4 dinitrophenyl hydrazine. The molar absorptivity of colored system with nitrite-1,3 dinitrobenzene or nitrite-2,4 dinitrophenyl hydrazine were 1.965×10^4 L $mol^{-1}cm^{-1}$ or 2.776×10^4 L $mol^{-1}cm^{-1}$, and the Sandell's sensitivity of colored system with nitrite-1,3 dinitrobenzene or nitrite-2,4 dinitrophenyl hydrazine were found to be 7.692×10^{-3} μg cm^{-2} or 5.698×10^{-3} μg cm^{-2}.

The detection limit (D_L = 3.3 σ / S) and quantitation limit (Q_L= 10 σ / S) of paracetamol with 1,3 dinitrobenzene or paracetamol with 2,4 dinitrophenyl hydrazine were found to be 0.264 μg mL^{-1} and 0.80 μg mL^{-1} or 0.239 μg mL^{-1} and 0.724 μg mL^{-1} [where σ = Standard Deviation, (n=5) and S = Slope of the curve] and correlation coefficient of paracetamol with 1,3 dinitrobenzene or paracetamol with 2,4 dinitrophenyl hydrazine were 0.9991 or 0.9992.

3.7 Comparison of the current method with other spectrophotometric methods

A comparison of the current method with other spectrophotometric methods are reported for paracetamol determination (Tab. 4). As can be seen, the molar absorptivity, Sandell's sensitivity and color stability (more than 12 h) of the proposed method are comparable or better than other reported methods. The proposed method exhibited excellent selectivity, repeatability, and ease of operation. Thus, the presented method could be of great interest especially for determination of paracetamol in routine analytical laboratories.

Table 4. Comparison of the proposed method with other spectrophotometric methods.

Reagent used	λ_{max} / nm	ε × 10^4 / L mol^{-1} cm^{-1}	Beer's law limits / μg mL^{-1}	Sandell's sensitivity / μg cm^{-2}	Remarks	Ref. No
8-hydroxyquinoline or 2-naphthol	470 or 490	1.9 or 2.46	2-10	7.9×10^{-3} or 5.9×10^{-3}	---	[10]
1-napthol or resorcinol	505 or 485	1.68 or 2.86	0-10	9.0 ng mL^{-1} cm^{-2} or 5.3 ng mL^{-1} cm^{-2}	Color stability is < than 1 hour	[27]
sodium bismuthate	550 or 560	77.27 or 100.0	100-300 in HCl or 300-800 in CH_3COOH	---	Lack of Sandell's sensitivity	[33]
2,4-dichloroaniline	490	3219.69	4-350	---	Lack of application	[36]
Different solvents	243	---	1-30 mg L^{-1}	---	Less sensitive	[38]
Histidine	430	1.118	10-500 μg mL^{-1}	0.0135	Less selective	[41]
2,7-dihydroxy naphthalene	481	1.058	1-14	0.0142	---	[38]
Proposed method 1, 3 dinitrobenzene or 2, 4 dinitrophenyl hydrazine	429 or 430	1.965 or 2.776	0.8-20.5 or 0.5-18.4	7.692×10^{-3} or 5.698×10^{-3}	---	

3.8 Applications

The current scheme was useful for the determination of paracetamol in pharmaceuticals samples. The relative standard deviation for all five samples ranged from 0.53-1.83% at 95% confidence. The percentage recoveries were found to the range from 98.20 – 100.40. The outcomes were compared with the reference method[36,41] (Tab. 5). The additional ingredients present in pharmaceutical sample appearances did not form hinder.

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Table 5. Determination of paracetamol in different pharmaceutical samples using 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine as coupling agent.

Pharmaceutical Samples	Sample taken / $\mu g mL^{-1}$	Proposed method		Relative Standard Deviation / %		Recovery / % of	
		1,3 dinitrobenzene **Sample found ±SD[a] / µg mL^{-1}**	2,4 dinitrophenyl hydrazine **Sample found ±SD[a] / µg mL^{-1}**	1,3 dinitrobenzene	2,4 dinitropheny lhydrazine	1,3 dinitrobenzene	2,4 dinitrophenyl hydrazine
P-750 (750 mg/tab)	5.0 10.0 15.0	5.00 ± 0.04 9.98 ± 0.06 14.96 ±0.08	4.96 ± 0.05 9.94 ± 0.07 14.92 ±0.09	0.80 0.60 0.53	1.00 0.70 0.60	100.00 99.80 99.73	99.20 99.40 99.46
Dolopar (650 mg/tab)	5.0 10.0 15.0	5.01 ± 0.05 9.95 ± 0.08 14.94 ±0.09	5.00 ± 0.08 9.91 ± 0.08 14.90±0.10	0.99 0.80 0.60	1.60 0.81 0.67	100.20 99.50 99.60	100.00 99.10 99.33
Disprin Paracetamol (500 mg/tab)	5.0 10.0 15.0	4.97 ± 0.06 9.97 ± 0.08 14.98 ±0.09	4.92 ± 0.09 9.90± 0.10 14.93±0.10	1.21 0.80 0.60	1.83 1.01 0.67	99.40 99.70 99.87	98.40 98.60 99.53
CrocinQuik (500 mg/tab)	5.0 10.0 15.0	5.01 ± 0.06 9.99 ± 0.09 14.98 ±0.10	4.91 ± 0.07 9.89 ± 0.11 14.92 ±0.12	1.19 0.90 0.67	1.42 1.11 0.80	100.20 99.90 99.86	98.20 98.90 99.46
Paramet (500 mg/tab)	5.0 10.0 15.0	4.99 ± 0.08 10.00± 0.08 14.96 ±0.09	4.94 ± 0.04 9.88± 0.07 14.87 ±0.10	1.60 0.80 0.60	0.81 0.71 0.67	99.80 100.00 99.73	98.80 98.80 99.13
Nicetamol (125 mg/tab)	5.0 10.0 15.0	5.02 ± 0.08 9.92± 0.08 14.99±0.09	4.97 ± 0.08 9.96 ± 0.09 14.83±0.09	1.59 0.81 0.60	1.61 0.90 0.61	100.40 99.20 99.93	99.40 99.60 98.87
Paracip (500 mg/tab)	5.0 10.0 15.0	4.97 ± 0.06 9.94± 0.08 14.94±0.10	4.93 ± 0.09 9.83± 0.06 14.85±0.09	1.21 0.80 0.66	1.82 0.61 0.60	99.40 99.40 99.60	98.60 98.30 99.00

a. Mean (n=5) ± SD {standard deviation}.

4. Conclusions

This study demonstrated that spectrophotometric analysis is a very powerful methodology for the determination of paracetamol. For the first time 1,3 dinitrobenzene or 2,4 dinitrophenyl hydrazine is used as coupling agent for the determination of paracetamol in pharmaceutical dosage samples using an easy and simple spectrophotometric method. The proposed method has an ample range of applications with no need of heating, cooling, extraction and has high color stability (12 h). The percentage recoveries were found in the range from 98.20 – 100.40 which complete the legitimacy of the method for the analysis of paracetamol in pharmaceutical formulations. Moreover, the current method is more effective than the methods reported in the literature and has been effectively applied to the spectrophotometric analysis of determination of paracetamol in several pharmaceutical dosage samples.

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