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KINETIC SPECTROPHOTOMETRIC DETERMINATION OF TAPENTADOL

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Abstract

A simple, inexpensive, accurate and sensitive spectrophotometric method and kinetic assay have been established to determine tapentadol in pure form, tablets and urine samples. The method is based on the reaction of tapentadol with ferric ions in an acidic solution in the presence of ferricyanide to give water-soluble Prussian blue dye with a maximum absorption wavelength of 735 nm, with a maximum reaction time of 40 minutes. Several experimental factors affect the colour intensity and stability time approaches. The reaction was identified as a first-order pseudo-reaction by calculating the initial rate, and the results of the fixed-time method (at 30 min) are more suitable for quantification and used to construct the calibration curves. The correlation between concentration and absorbance was linear.
Moreover, varies from 2 to 12 µg/mL and has a detection limit of 0.1737 µg/mL and a quantification limit of 0.5264 µg/mL. The molar absorption coefficient and Sandel sensitivity were 1.5484 x 10 4 L.mol-1.cm-1 and 0.01430 µg.cm-2, respectively. A comparison of spectrophotometric data with a well-established fixed time kinetic demonstrated that the fixed time technique offers good accuracy, precision, low detection and quantification limitations, and is time efficient. These procedures were effectively used to analyze tapentadol in its pure form, tablet form, and urine sample, which were not observed in literature before.

Keywords: *Kinetic Spectrophotometric; Tapentadol: Ferric Chloride: Potassium- Ferricyanide.*

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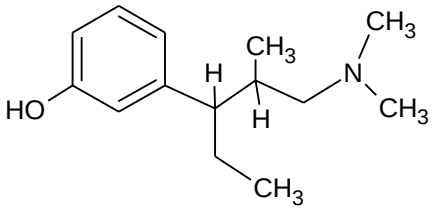
Introduction

Tapentadol (1,2) (Tap) is 3-[(1R,2R)-3-(Dimethylamino)-1-ethyl-2-methylpropyl] phenol Hydrochloride, Light brown solid. Molecular Formula: $C_{14}H_{23}NO$. Molecular Weight: 221.3385. Tap has four stereoisomers, RR, SS, RS, and SR, resulting from its two chiral centres, and the RR type is an analgesic. Tap's n-octanol: water partition coefficient has a log P value of 2.87, and the pKa values of Tap are 9.34 and 10.45, respectively [1,2]. Tap and morphine and its analogues have a 3-(3-hydroxyphenyl) propyl-amino structural component. It is extracted as the hydrochloride salt; the Tap structure is shown in (Fig 1).



Sketch 1:the chemical structure of tapentadol.

Tap activates μ-opioid receptors and inhibits the reuptake of norepinephrine, which gives it analgesic properties. It has both mechanisms of action and is effective for acute and chronic pain from various causes [3]. In November 2008, the US Food and Drug Administration approved Tap for treating moderate to severe acute pain. It was initially produced in the United States and marketed as Nucynta by Ortho-McNeil- Janssen Pharmaceuticals. Tap is now available in immediate-release oral tablets in doses of 50, 75, and 100 mg [4]. A review of the analytical techniques described in the literature for evaluating Tap includes spectrophotometric methods such as first-order (228 nm) and second-order (235 nm) derivative methods [5], UV and visible (Folin-ciocalteu reagent) analysis methods [6], zero crossing at 242nm and 272nm [7], UV at 271nm [8,9]. In the study [10], several methods were used, including UV light at 273.3 nm, Folin-Ciocalteu light at 494.6 nm, Orange-Red diazotize complex light at 414.6 nm, and ion pair with bromothymol Blue in Chloroform at 773.3 nm were all used. In addition, several chromatographic methods and techniques have been used to determine Tap in its pure form and for pharmaceutical doses, including HPLC with photodiode array detector [11], HPLC with electrochemical detection [12], RP-HPLC method [13, 14], HPTLC analysis [15], LC-MS/MS technique [16] and RP-UFLC method [17]. In addition, the simultaneous determination of Tap includes Tap with aripiprazole [18], Tap with paracetamol using two different first-order derivative methods [19] and a Q-spectrophotometric approach [20] and a nanographene-modified electrode as an electrochemical sensor. [21], Tap and its carbamate prodrug in rat plasma by UPLC - MS/MS [22]. This review indicates that the determination of Tap does not involve spectrophotometry or kinetic research based on a redox reaction with ferric. With the help of inexpensive, readily available $FeCl_3/K_3$ [Fe(CN)6] reagents[23], the current study develops a new simple, rapid, accurate, precise, sensitive and selective spectrophotometric, and kinetic method for determining Tap in pure, pharmaceutical formulations, and urine samples.

Experimental

Apparatus

The spectral runs were carried out using a Perkin Elmer Lambda-25 (USA) double-beam UV-visible spectrophotometer. HANNA (Portugal) pH meter was used for rapid and stable pH measurements.

Materials and reagents

All the chemicals and reagents used in the current study were pure analytical grade , and the pharmaceutical products were obtained from local drug stores.

- Tap drug: (100 µg mL−1) stock solution was prepared by dissolving 0.01 gm of Tap in 2mL ethanol and diluting with distilled H_2O to 100 mL. The stock solution was kept at 5^0C in the dark.
- Potassium ferricyanide (1.3 x10^{-3} M) solution was prepared by dissolving 0.05 g in 100 mL of distilled water.
- Ferric chloride (0.5M) solution was prepared from a stock solution containing 0.145 gm /mL ferric chloride in HCl by dilution.
- Interferences solutions (2000 µg mL^{-1}) were prepared by dissolving 0.2 gm of Interferences substance in 100mL distilled water.

Procedure for the tablets

Ten Tap tablets were crushed and powdered, each containing 100 milligrams of Tap. The average tablet weight was determined. The precise weighted quantity, equivalent to 0.01g, was dissolved in roughly 2 mL of ethanol and then diluted with 10 mL of pure water. Filtration was used to remove any residual remains. The filtrate was transferred to a 100 mL volumetric flask and then diluted to a volume of 100 mL with distilled water.

General Recommended Procedure

In a volumetric flask, precise quantities of Tap were mixed with 1.0 mL of each oxidizing agent, ferric chloride, and potassium ferricyanide, then diluted with distilled water and shaken. The reaction mixture was then transferred to a thermostat water bath set at 20 ± 2 °C, and the absorbance of the coloured product at 735 nm was measured for a fixed period in minutes.

Result and Discussion

Preliminary Test and Absorption spectra

The ionic Ferric in an acidic solution is a well-known oxidant that rapidly oxidizes Tap. It reduces it to Ferrous, which combines with potassium ferricyanide to produce a soluble Prussian blue dye. The absorption spectrum of the soluble Prussian blue dye was measured between 400 - 1100 nm (Fig 2b), with the highest absorbance found at 737 nm compared to the reagent blank (Fig 2a).

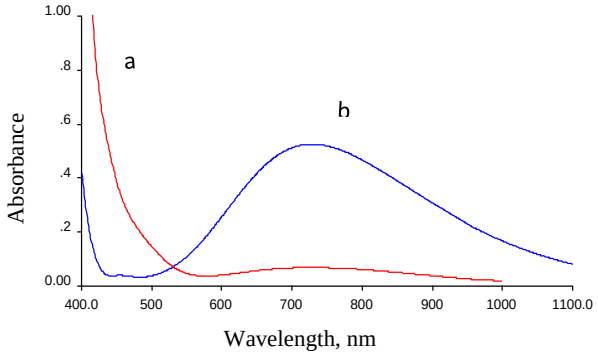


Fig. 2 Absorption spectra of (a) reagent blank and (b) Prussian blue complex produced by the reaction of Tap (4 µg/ mL) with ferric chloride(0.5 M) and potassium ferricyanide(1.3 x 10^{-3} M)

Optimization of parameters

The colour intensity of the reaction between Tap and ferric chloride/ potassium ferricyanide rises with time. Several research experiments have been conducted to determine the effects of various factors on the formation and stability of reaction products. Factors considered are the concentration of the reagents (ferric chloride and potassium ferricyanide), the sequence in which the reagents are added, the temperature, and the time.

Effect of potassium ferricyanide and ferric chloride concentration

The volumes of potassium ferricyanide (1.3 x 10^{-3} M) and ferric chloride (0.5 M) were studied from 0 to 2 ml. The maximum absorbance was observed at 1.4 mL potassium ferricyanide and 1 mL ferric chloride (Fig 3).

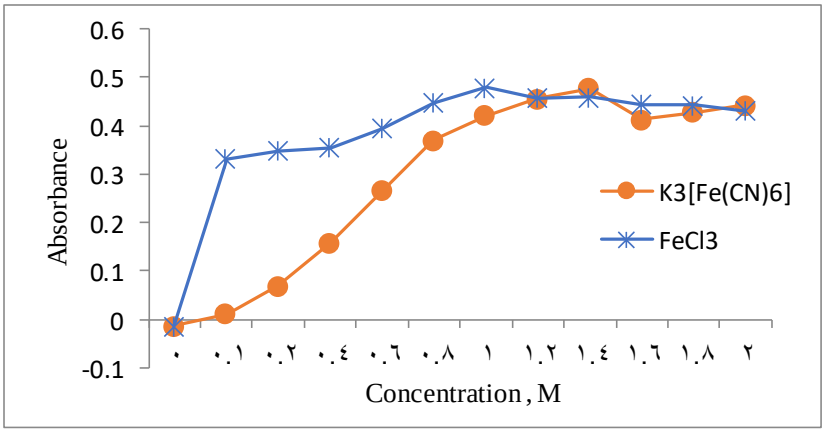


Fig. 3 The effect of the volume of potassium ferricyanide (1.3 x 10-3 M) and ferric chloride (0.5 M) on the reaction with Tap (4 µg/ mL)

Effect of time

To investigate the effect of time, 1 mL of ferric chloride and 1.4 mL of potassium ferricyanide were mixed with a fixed quantity of Tap (4 µg/ mL). The absorbance measurements were taken at various times ranging from 1.0 to 30 minutes. The oxidation reaction was finished in 30- 40 minutes and remained constant for up to 100 minutes Figure 4.

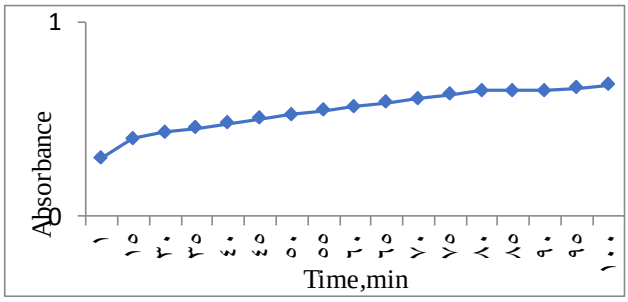


Fig. 4 Effect of time on the stability of the colour product produced by the reaction of Tap (4µg/ mL) with potassium ferricyanide(1.3 x 10^{-3} M) and ferric chloride(0.5 M)

Effect of temperature

At various temperatures, the influence of temperature on the reaction product was investigated, and it was found that as the temperature raised, the absorbance changed and increased, resulting in a cloudy dark solution. To prevent this problem and obtain satisfying results, the optimum temperature of 20 °C was chosen in this study.

Order of addition

An important part of the experiment is the order of the addition of reagents. The experimental variables have been adjusted, and further experiments have been conducted to determine the effect of the reactant addition order. The order number I was found to result in maximum absorbance. Any other addition order, on the other hand, would result in a lower absorbance value (Table 1).

Table 1. Order of addition for the determination of Tap

Order of addition	Order Number	Absorbance Tap
Drug+ potassium ferricyanide+ ferric chloride	I	0.472
Drug + ferric chloride + potassium ferricyanide	II	0.023
Potassium ferricyanide + Drug + ferric chloride	II	0.180
Potassium ferricyanide + ferric chloride + Drug	IV	0.426
Ferric chloride + Drug + potassium ferricyanide	V	0.449
Ferric chloride + potassium ferricyanide + Drug	VI	0.355

The reaction stoichiometry

The limiting logarithmic approach (ROSE 1964) was used to calculate the stoichiometric ratio between the studied Drug and the ferric chloride ratio. Two different experiments were conducted. The concentration of the tap was changed in the first batch, and the content of ferric chloride was kept constant. The Tap concentration was kept constant, while the ferric chloride content was varied in the second series of tests. The logarithm absorbance was plotted against the logarithm of the various [Tap] or [ferric chloride] concentrations (Fig 5). The slope-to-slope ratio of two straight lines was measured with a slope ratio of 0.9274:0.2175, representing a 4:1 molar ratio. A reaction mechanism was described based on this mole ratio and the presence of conjugated double bonds in the Tap structure (Scheme 1).

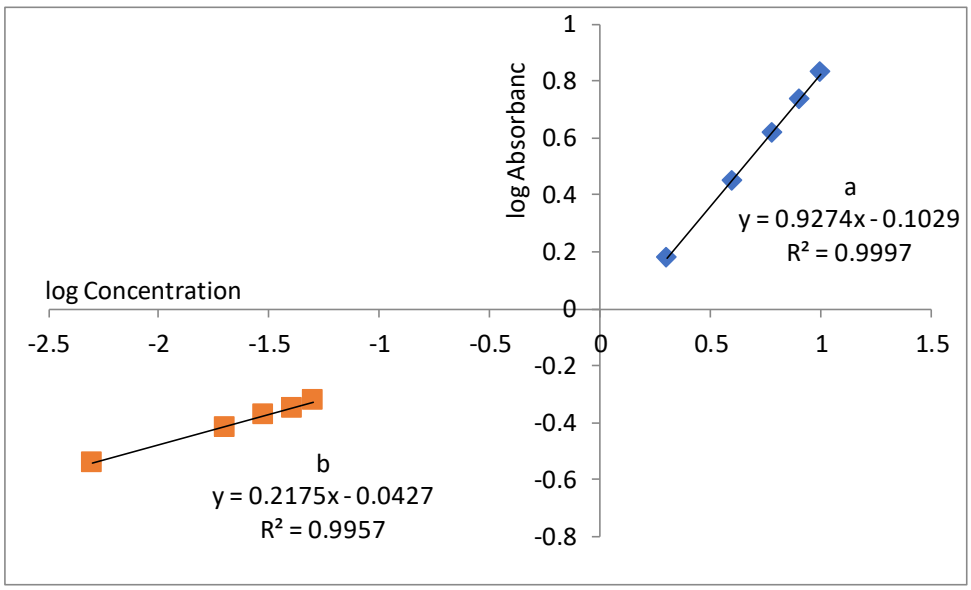
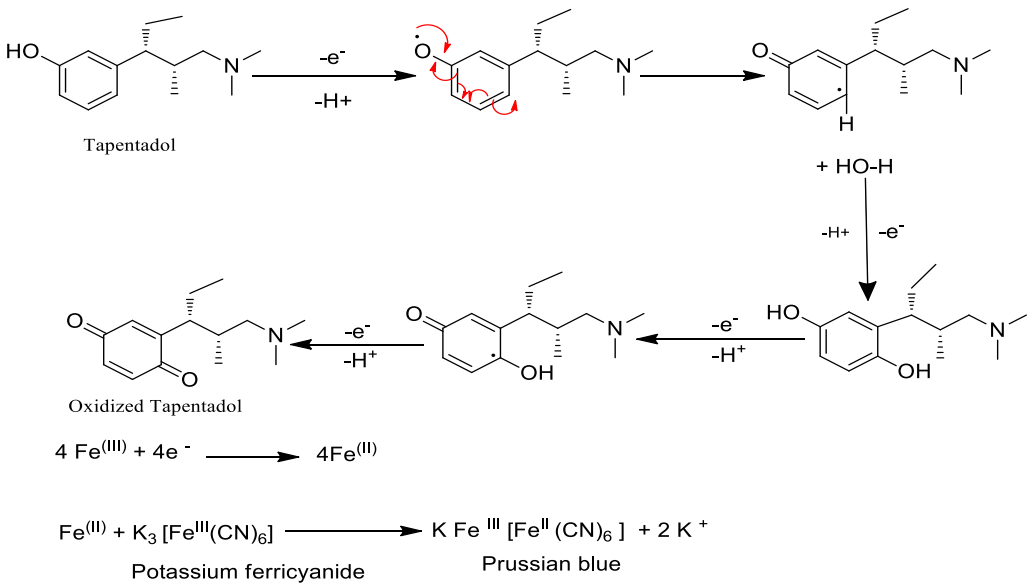


Fig. 5 Molar ratio limiting logarithmic plots: (a) log absorbance versus log [Tap], (b) log absorbance versus log [ferric chloride].



Scheme 1 Detailed mechanism of the redox reaction of Tap with iron chloride and potassium ferricyanide

3.5Spectrophotometric Quantification

From this mechanism, two-fold reasons were suggested for the generation of Prussian blue colour for the dye.

1- The generation of a double quinone system in the oxidized tapentadol, as shown in the mechanism, stated

2- The formation of a complex of formula $K\,Fe^{III}[Fe^{II}(CN)_6]$

Under optimal conditions Table 2, the concentration of tapentadol was found to be proportional to absorbance, with a linearity of 2-12 g/ml (Fig.6). Table 3 shows that the approach has good molar absorptivity, accuracy, precision LOD, and LOQ. The low intercept value indicates that the blank reading at 735nm was low. Because of the strong correlation coefficient, the approach is well-suited for quantitative Tapetadol analysis.

Table 2. Optimal conditions for the determination of Tap

Drug	***λ_{max} (nm)***	***Temp. (°C)***	***Order of addition***	***$K_3[Fe(CN)_6]^{3-}$ ($1.51x10^{-3}$ M), mL***	***$FeCl_3$ (0.5M),mL***
Tap	*735*	*20*	*Tap , $K_3[Fe(CN)_6]$, and $FeCl_3$*	*1.4*	*1.0*

(Fig.6) Calibration graphs of tapentadol (spectrophotometric study)

Table 3. Statistical data for the reaction of tapentadol with potassium ferricyanide and ferric chloride

Parameters	Tapentadol
Regression equation	y = 0.0653x + 0.208
Linearity range (µg mL^{-1})	2-12
r^2	0.9985
$S_{y/x}$, standard error of the regression	0.010641
slope (mL μg^{-1})	0.0653
Sb, a standard deviation of the slope	0.001272
Intercept	0.208
So, the standard deviation of the intercept,	0.009907
LOD (µg mL^{-1}), regression	0.45836
LOQ (µg mL^{-1}), regression	1.51715
LOD (µg mL^{-1}) , blank	0.00242
LOQ (µg mL^{-1}), blank	0.00733
Ɛ, molar absorptivity ($l.mol^{-1}.cm^{-1}$)	1.4453×10^{4}
S,Sandell's sensitivity (µg.cm-2 per 0.001 absorbance unit)	0.01530

*Average for six determinations

Kinetic methods

Under the optimal reaction conditions shown in Table 2, two kinetic methods, the initial rate and fixed time methods, were investigated, and the most effective kinetic method was chosen for the quantification of Tap. All measurements were performed at a constant temperature of 20 C°

Initial rate method

The initial rate method was used to calculate the rate constant and order for the reaction. The kinetic factors of the initial rate approach were investigated utilizing a pseudo-first-order condition established concerning the reagent concentration. The initial rate of reaction was determined using an absorbance-time plot. The kinetic equation for the reaction can be written based on experimental observations.

Rate = $k\ [Fe^{+3}]^m[drug]^n$ Since $[Fe^{+3}] >> [drug]$, as a consequence $[Fe^{+3}]$ considered as constant.

Rate = $(k\ [Fe^{+3}]^m)\ [drug]^n$

Rate = $k/\ [drug]^n$ Where $k/ = (k\ [Fe^{+3}]^m)$

k/ = The Pseudo first-order rate constant

[drug] = The concentration of the Tap

n = The order of the reaction

Take the logarithm of the rate = k/ [Drug]^n equation.

Log Rate = log ΔA /Δt = log k/ + n log [Drug].

The reaction's absorbance-time plot was constructed for 50 minutes (Figure 7), and the reaction's initial rates at each concentration were measured and summarized in Table 4. A plot of log rate versus log C (Figure 8) resulted in the following linear regression equation:

y = 0.9958x - 3.0854 (R^2 = 0.9965)

log k/ = 3.0854

k/= 1217.3067 sec^{-1}, and n = 0.9958 9 ∴The reaction is first order.

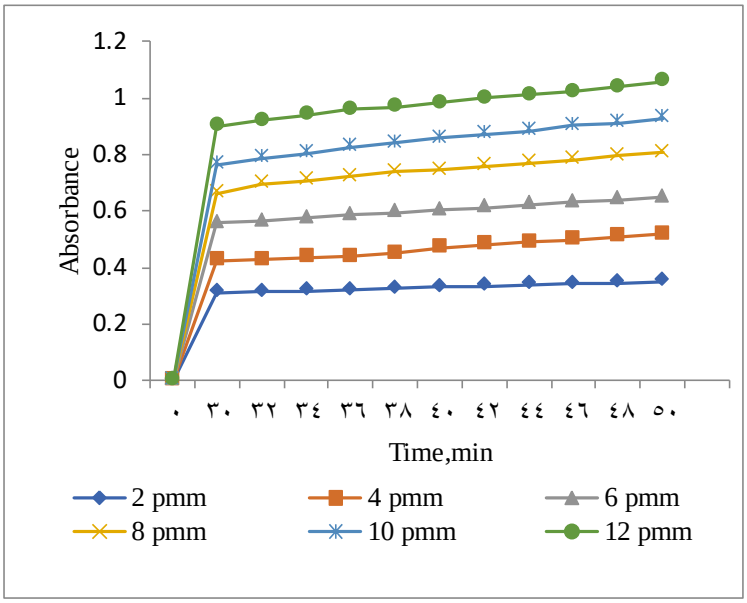


Fig.7 Absorbance-time graphs of Tap at a concentration of 2-12 µg mL^{-1}

Table 4. The logarithmic reaction rate calculation

Slop=ΔA/Δt	*LogΔA/Δt*	*[Tap] µg mL^{-1}*	*Log[Tap]*
0.0017	-2.76955	2.0	***0.30102***
0.0031	-2.50863	4.0	***0.60205***
0.0047	-2.3279	6.0	***0.77815***
0.0068	-2.16749	8.0	***0.90308***
0.0082	-2.08618	10	***1.0***
0.0098	-2.00877	12	**1.07918**

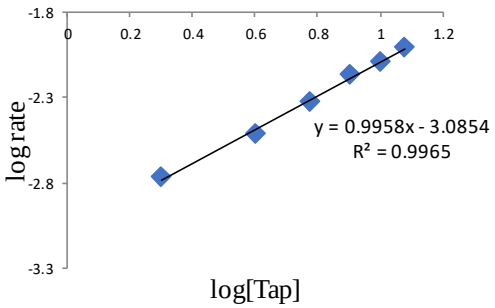


Fig.8 A plot of log rate versus log [Tap] concentration

Fixed-time method

At a certain, precisely specified time, the absorbance of the reaction solution for various Tap concentrations was measured. Calibration curves were plotted between absorbance versus initial concentrations of Tap at fixed times (20, 25, 30, 40, 50, 55, 60, 65, and 70 min) Figure 9. The initial findings supported estimating the Tap drug using the fixed time method(Table 5).

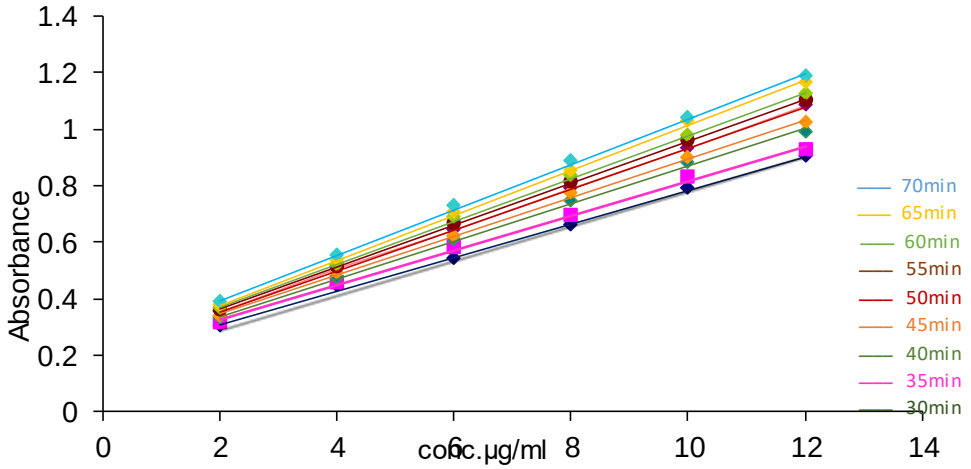


Fig. 9. Absorbance and drug concentration (Tap) calibration plots at fixed times (30,35,40,45,50,55,60,65,70).

Table 5.Regression statistics for the fixed-time calibration of 30 min

Parameters	*Values*
Regression equation	y = 0.0699x + 0.1888
Linearity range (µg mL⁻¹)	2-12
r	0.9998
slope (mL µg⁻¹)	0.0699
Intercept	0.1888
$S_{y/x}$, standard error of the regression	0.003677
So, the standard deviation of the intercept,	0.003856
Sb, a standard deviation of the slope,	0.000581
Ɛ, molar absorptivity (l.mol⁻¹.cm⁻¹)	1.5484 x 10 ⁴
S, Sandell's sensitivity (µg.cm-2 per 0.001 absorbance unit)	0.01430
LOD (µg mL⁻¹), regression	0.173716
LOQ (µg mL⁻¹), regression	0.526413
LOD (µg mL⁻¹) , blank	0.00242
LOQ (µg mL⁻¹), blank	0.00733

Accuracy and Precision

Different concentrations of Tap in six replicates were analyzed to measure the accuracy and precision of the methods. Table 6's findings demonstrate that the methods are accurate and precise, revealing agreement between spectral and fixed-time approaches.

Table 6.Comparison of the accuracy and precision of spectrophotometric and fixed time methods

Method	**Regression equation**	**Amount taken (µg/mL)**	**The amount found (µg/mL)**	**Correlation coefficient (R^2)**	**Recovery %**	**Average recovery**
Spectrophotometric method	Y=0.0653x+0.208	2 4 6 8 10 12	2.012 4.022 6.047 8.246 9.944 11.859	0.9985	100.6 100.55 100.78 103.07 99.44 98.82	100.54
Fixed time method 30 min	y = 0.0699x + 0.1888	2 4 6 8 10 12	1.912 4.074 6.032 8.011 10.11 11.962	0.9998	95.25 101.95 98.45 99.07 101.10 99.63	99.82

35min	Y=0.0613+0.2023	2 4 6 8 10 12	1.954 4.079 6.176 8.091 10.212 11.743	0.9972	97.70 101.97 102.93 101.13 102.12 97.85	100.61
40 min	Y=0.0665x+0.2031	2 4 6 8 10 12	2.036 4.013 6.0421 8.130 10.138 11.795	0.9987	101.80 100.32 100.70 101.62 101.38 98.29	100.685
45 min	Y=0.0684x+0.2099	2 4 6 8 10 12	2.010 4.09 5.980 8.184 10.040 11.858	0.9988	100.5 102.25 99.66 102.30 100.40 98.81	100.65
50 min	Y=0.072x+0.2083	2 4 6 8 10 12	1.966 4.120 5.995 8.026 9.997 12.106	0.9997	98.30 103 99.91 100.32 99.97 100.88	100.39
55 min	Y=0.0742x+0.214	2 4 6 8 10 12	1.951 3.981 6.067 8.035 9.998 11.939	0.9998	97.55 99.52 101.11 100.4399 .99.98 99.49	99.68
60 min	Y= 0.076x+0.2187	2 4 6 8 10 12	1.922 3.923 6.151 8.125 9.952 11.596	0.9991	96.10 98.07 102.51 101.56 99.52 96.63	99.065
65 min	Y=0.0795x+0.2185	2 4 6	1.963 3.947 6.118	0.9993	98.15 98.67 101.96	99.74

		8 10 12	7.947 10.133 11.885		99.33 101.33 99.04	
70 min	Y=0.0802x+0.2338	2 4 6 8 10 12	1.912 3.94 6.120 8.137 9.996 11.880	0.9992	95.60 98.50 102.00 101.71 99.96 99.00	99.46

* For six repeated measurements.

Interferences

A systematic study was conducted under ideal experimental conditions to determine the impact of additives and excipients commonly found in formulation forms, such as sucrose, lactose, fructose, starch, cellulose and aphasia, to determine the selectivity of the proposed analytical spectrophotometric method for the current Drug. An absorbance error of less than 1% was used as an interference criterion. In this study, a wide range of interference concentrations was used to determine the 3 µg /mL level of the Drug. Experimental showed no interference from additives or excipients up to a 10-fold increase in the test method, as shown in (Table 7).

Table 7. The effect of interferences on the determination of Tap

Interferences	***Recovery* % of 3µg/mL of Tap per µg mL^{-1} foreign added***			
	10	***25***	***50***	***75***
Sucrose	101.66	101.96	100.86	***98.90***
Lactose	102.32	102.82	98.86	***105.14***
Fructose	101.04	100.84	104.56	-
Starch	99.20	99.60	100.24	-
cellulose	-	-	-	-
Aghasha	98.90	98.56	100.60	

*Mean value of three repeated measurements.

Pharmaceutical Applications

Tap determination on a tablet

The spectrophotometric and fixed-time approaches were used to determine the Tap in tablets by measuring three different concentrations of Tap. These findings are summarized in (Table 8). The procedures were implemented effectively and with high accuracy and precision.

Table8. Tap determination in tablet using spectrophotometric and fixed time methods

Method	Tap amount (µg/mL)		Recovery* (%)	Average recovery (%)	RSD*
	Added	Found			
Spectrophotometric method	2.0	1.909	95.45	98.37	1.707
	6.0	6.033	100.55		1.274
	10	9.811	98.11		3.039
Fixed time method	4.0	3.819	95.47	98.66	0.686
	8.0	8.191	102.38		1.347
	12.0	11.777	98.14		0.934

*Average of six determinations

Tap determination in a spiked urine sample.

The proposed fixed-time procedure was also used to estimate Tap in urine samples under optimal conditions following the deproteinization process. The percentage recovery was computed for urine samples and revealed values of 98.95%, 100.3%, and 100.5 for each 2.0 g/ml, 3.0, and 4.0 g/ml concentration of tapentadol (Table 9), implying that the standard addition approach improved accuracy.

Table 9. Accuracy and precision values

Tabetadol add µg /ml	Found± SD n =6	% Recovery	%Error	%RSD
2.0	1.979 ± 0.0143	98.95	1.05	0.78
3.0	3.009 ± 0.0092	100.3	0.3	0.34
4.0	4.02 ± 0.0286	100.5	0.5	0.79

Comparison with other spectrophotometric methods

A previously described method with similar procedures was compared to the suggested method. Compared to the other approach (Table 10), the current spectrophotometric and kinetic methods had greater sensitivity (low detection limits). The technique was straightforward, sensitive, and low-cost, and it did not require an organic solvent, heating, or pH control.

Table 10. Comparison of the proposed kinetic method with some available spectrophotometric methods

Method	***λ max (nm)***	***Linear range (µg /mL)***	***Correlation coefficient***	***LOD (µg /mL)***	***Remarks***	***Ref.***
Determination of Tap in tablets by three newly validated spectrophotometric methods	242 & 272	10-50	0.9990	-	linear regression equation, standard absorptivity, and first-order derivative	*[7]*
Development of new spectrophotometric methods for quantitative analysis of Tap in pharmaceutical dosage forms	1: 273.3 2: 494.6 3: 414.6 4: 773.3	5-25 for all methods	-	-	1st. a method is Uv, second. method is Folin-Ciocalteu ,3rd. method is the orange-red diazotization complex, and fourth.method is Bromothymol blue in chloroform: 773.3nm	*[10]*
Method development for quantification of Tap and aripiprazole by visible spectrophotometry	540	200-1000	0.9998	82.5	Tap + 1.5mlchloranilic acid (0.1%) + chloroform	*[12]*
Spectrophotometric and kinetic Determination of Tap	737	2-12	0.9998	0.00242 0.1737	Tap , $K_3[Fe(CN)_6]$, and $FeCl_3$	*present study*

Conclusions

Tap was assessed utilizing a simple, accurate, inexpensive spectrophotometric method in which the Drug was oxidized with ferric chloride in the presence of potassium ferricyanide. The proposed approaches have high sensitivity and a low detection limit. Furthermore, the suggested approaches exhibit important selectivity because measurements were based on absorbance with reaction time. The results illustrate the successful utilization of ferric chloride and potassium ferricyanide in constructing a fixed-time kinetic spectrophotometric technique to select Tap at room temperature. A comparison of the results with the reference methodologies revealed that the current methods outperform the reference approaches in terms of LOD, accuracy and precision.

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