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Kinetic Spectrophotometric Analysis of Naftidrofuryl Oxalate and Vincamine in Pharmaceutical Preparations Using Alkaline Potassium Permanganate

TAREK SAIED BELAL[1*], MAGDA HAMDY BARARY, SUZY MOHAMMED SABRY AND MOHAMMED ELSAYED ABDEL-LATIF IBRAHIM

Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, University of Alexandria, Elmessalah 21521, Alexandria, Egypt

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ABSTRACT

A simple, rapid and sensitive kinetic spectrophotometric method is described for the analysis of naftidrofuryl oxalate (NF) and vincamine (VN) in pure form and in their pharmaceutical preparations. The procedure was based on the kinetic investigation of the oxidation of the studied drugs with alkaline potassium permanganate and the absorbance of the produced manganate species was measured at 610 nm. Variables affecting the color development were investigated and the conditions were optimized. The concentration of the studied drugs was calculated using the regression equations for the fixed-time method. The determination of the two drugs by fixed absorbance and rate constant methods was possible but the fixed time method was more applicable. The reliability and analytical performance of the proposed method including linearity, ranges, precision, accuracy, detection and quantification limits were statistically validated. Calibration graphs are linear over the concentration ranges of 3-15 μg/mL and 4-14 μg/mL for NF and VN, respectively. The proposed method was satisfactorily applied for analysis of pharmaceutical preparations containing the studied drugs. A proposal of the reaction pathway was postulated.

Key words: naftidrofuryl oxalate, vincamine, potassium permanganate, kinetic spectrophotometry, pharmaceutical preparations

INTRODUCTION

Naftidrofuryl oxalate (NF), 2-(diethylamino)ethyl 2-[(naphthalen-1-yl)methyl]-3-(tetrahydrofuran-2-yl) propanoate hydrogen oxalate, is a vasodilator drug used in the treatment of peripheral and cerebral vascular disorders. It is claimed to enhance the cellular oxidative capacity thereby protecting cells against ischemia[1]. NF is an official drug in the British Pharmacopoeia[2] where a nonaqueous potentiometric titration and HPLC procedures were described for the assay of NF bulk powder and capsules, respectively. Few analytical methods have been reported for the determination of NF in biological fluids and/or pharmaceutical preparations. Most of these studies focused on HPLC-UV detection[3,4], HPLC-fluorescence detection[5-8] and phosphorimetric analysis[9-12]. Others included potentiometric method using NF ion-selective electrodes[13], flow injection analysis with fluorescence optosensor[14] and spectrophotometry[15].

Vincamine (VN), methyl (3α, 16α)-14, 15-dihydro-14ß-hydroxy eburnamenine-14-carboxylate, is an alkaloid obtained from *Vinca minor* (Apocyanaceae). It is claimed to increase cerebral circulation and utilization of oxygen and has been used in a variety of cerebral disorders[1]. Several methods have been reported for the determination of VN in different matrices. VN has been determined in biological fluids by HPLC[16-19] and GC[20-23] methods. A fluorimetric method was described for the estimation of VN in biological fluids obtained from rats[24]. In pharmaceutical preparations, VN has been determined by derivative and chemometric spectrophotometry[25-28], HPLC[19,25,27-29], TLC[28] and PMR[30] procedures. Gravimetric, titrimetric and spectrometric analyses of VN were carried out based on its complexation with thiocyanate ion[31,32]. VN has been also determined in plant tissue cultures of *Vinca minor* by TLC[33] and HPLC[34] methods.

Analytical procedures based on kinetic

* Author for correspondence. Tel: +20-3-4871317; Fax: +20-3-4871351; E-mail: tbelaleg@yahoo.com

spectrophotometry are still lacking in the literature for the determination of NF or VN in pharmaceutical formulations. Kinetic methods are considered of great interest in chemical and pharmaceutical analysis[35]. Potassium permanganate in alkaline medium easily reacts with compounds susceptible to oxidation with the formation of manganate species which can be followed up spectrophotometrically. Several pharmaceutical compounds were determined through this approach[36-40]. In this work, a kinetics-based spectrophotometric method was developed for the assay of NF and VN. The method is based on oxidizing the two drugs with alkaline $KMnO_4$ at room temperature, and subsequently the rate of appearance of the green colored product was monitored at 610 nm. The proposed method is simple, rapid, cost-effective and readily adaptable to both bulk powders and dosage forms, hence more suitable for the application in quality control laboratories in developing countries.

MATERIALS AND METHODS

I. *Apparatus*

Spectrophotometric measurements were performed on a Perkin-Elmer Lambda EZ201 UV-visible spectrophotometer (PerkinElmer, Waltham, Massachusetts, USA) with matched 1-cm quartz cells.

II. *Drugs and Chemicals*

All chemicals and solvents used were of analytical reagent grade. Naftidrofuryl oxalate was kindly donated by Minapharm Pharmaceuticals and Chemical Industries, Cairo, Egypt. Vincamine was kindly provided by GlaxoSmithKline S.A.E., El-Salam city, Cairo, Egypt. Pharmaceutical preparations examined in this study were purchased from the local market and they included Praxilene® tablets (Minapharm Pharmaceuticals and Chemical Industries, Cairo, Egypt, under license of Merck Serono, BN. 5AE0028) labeled to contain 200 mg NF per tablet, Oxybral® capsules (GlaxoSmithKline S.A.E., El-Salam city, Cairo, Egypt, BN. 071058A) labeled to contain 30 mg VN per capsule and Oxybral® ampoules (GlaxoSmithKline S.A.E., El-Salam city, Cairo, Egypt, BN. 074983A) labeled to contain 15 mg VN per 2 mL.

III. *General Procedure*

Potassium permanganate solution, 12 mg/mL (0.076 M), and sodium hydroxide solution, 0.5 M, were prepared in distilled water. NF standard solution, 3 mg/mL (6.33×10^{-3} M), and VN standard solution, 0.5 mg/mL (1.41×10^{-3} M), were prepared in acetonitrile. Working

Table 1. Experimental and analytical parameters for the kinetic determination of NF and VN

Parameter	NF	VN
Temperature (°C)	25 ± 2	25 ± 2
Time (min)	35	20
Concentration range [M]	6.33×10^{-6} - 3.17×10^{-5}	1.13×10^{-5} - 3.95×10^{-5}
Molar absorptivity (ε) ($L\ mole^{-1}\ cm^{-1}$)	25795	20593
Regression equation $A = a + b \times C$	A = 0.0395 + 25794.84 C	A = -0.0099 + 20592.51 C
Correlation coefficient (r)	0.9974	0.9986
S_a[a]	0.0067	0.0054
S_b[b]	388.65	200.24
S_b%[c]	1.51	0.97
$S_{y/x}$[d]	0.0055	0.0047
LOD[e] [M]	8.01×10^{-7}	1.19×10^{-6}
LOQ[f] [M]	2.67×10^{-6}	3.97×10^{-6}

[a]: Standard deviation of the intercept.
[b]: Standard deviation of the slope.
[c]: Percentage relative standard deviation of the slope
[d]: Standard deviation of residuals.
[e]: Limit of detection.
[f]: Limit of quantification.

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solutions, 300 µg/mL NF (6.33×10^{-4} M) and 100 µg/mL VN (2.82×10^{-4} M), were prepared by dilution of standard solutions with acetonitrile. These solutions were found stable for at least 4 days and were stored refrigerated at 4°C during this study.

Accurate volumes of NF or VN working solutions with the concentration ranges shown in Table 1 were transferred into 10-mL volumetric flasks containing the appropriate volumes of potassium permanganate solution (1 mL) and sodium hydroxide solution (3 mL). The solutions were diluted to the volume with distilled water, mixed well and left at room temperature (25 ± 2°C) for a fixed time of 35 min for NF and 20 min for VN. The absorbance of solutions was measured at 610 nm against similarly treated blanks. The drug concentrations were then computed from the corresponding regression equations of the calibration graphs for the fixed time method.

IV. *Assay of Pharmaceutical Preparations*

(I) *For NF Tablets*

A total of 20 tablets ("Praxilene®" tablets) were weighed and finely powdered. To an accurately weighed quantity of the powder containing the equivalent of 30 mg of NF, 60 mL of acetonitrile were added, stirred for 10 min and then filtered into a 100 mL volumetric flask. The residue was washed with two 10 mL portions of acetonitrile, washings were added to the filtrate and diluted to the volume with acetonitrile and aliquots were treated as described in General Procedure.

(II) *For VN Capsules*

To an accurately weighed quantity of the powdered content of Oxybral® capsules equivalent to 10 mg of VN, 60 mL of acetonitrile were added and stirred for 10 min and then filtered into a 100 mL volumetric flask. The residue was washed with two 10 mL portions of acetonitrile, washings were added to the filtrate and diluted to volume with acetonitrile and aliquots were treated as described in General Procedure.

(III) *For VN Ampoules*

An accurate volume of the mixed contents of five Oxybral® ampoules equivalent to 10 mg of VN was transferred into a separating funnel and alkalinized with 10 mL of 0.5 M NaOH. VN was extracted by shaking the aqueous layer with 3 portions of chloroform (10 mL each). The organic layer was then collected and evaporated to dryness under vacuum. The residue was dissolved in acetonitrile by sonication for 10 min. It was then transferred quantitatively into a 100 mL volumetric flask, diluted to the volume with acetonitrile and aliquots were treated as described in General Procedure.

RESULTS AND DISCUSSION

NF and VN react with alkaline potassium permanganate to give the green colored manganate species that absorbs maximally at 610 nm (Figure 1). The extent of formation of this species depends on the concentration of reactants, alkalinity of solution and temperature. Therefore, various experimental parameters affecting the development and the stability of the reaction product were optimized by changing each variable in turn while keeping all others constant.

I. *Kinetics and Optimization of the Reaction Conditions*

The effect of potassium permanganate concentration on the reaction was studied over the range of 3.04×10^{-3} to 9.12×10^{-3} M for NF and 3.8×10^{-3} to 1.52×10^{-2} M for VN. The maximum absorbance was obtained at the concentration 7.6×10^{-3} M (1 mL of 0.076 M $KMnO_4$ diluted to final reaction volume 10 mL) for both NF and VN. Higher concentrations of potassium permanganate yielded lower absorbance values, probably due to decomposition of the product (Figure 2). Complete reaction between the investigated drugs and potassium

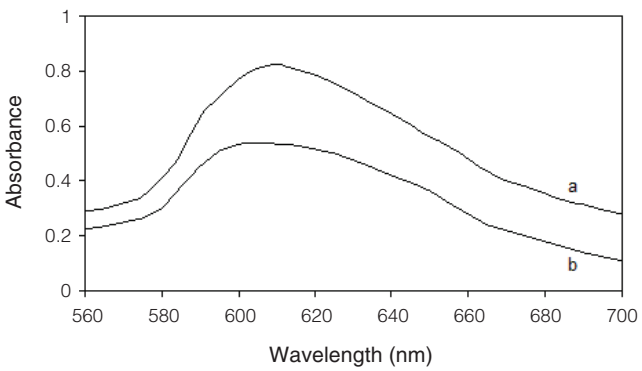


Figure 1. Absorption spectra of the reaction product of (a) 2.53×10^{-5} M NF and (b) 2.82×10^{-5} M VN.

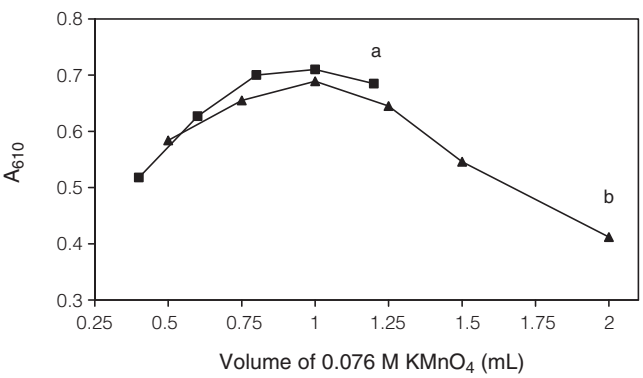
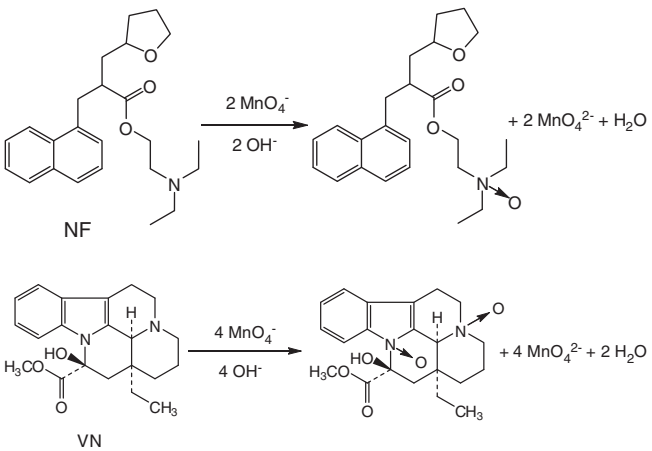


Figure 2. Effect of $KMnO_4$ concentration on the reaction product of (a) 2.11×10^{-5} M NF and (b) 3.39×10^{-5} M VN using optimum conditions for each compound.

permanganate took place only in alkaline medium. The influence of alkalinity was investigated in the range of 0.025 to 0.175 M NaOH for NF and 0.025 to 0.2 M NaOH for VN. The maximum absorbance values were obtained at concentration 0.15 M (3 mL 0.5 M NaOH) for both drugs (Figure 3). The effect of temperature was studied in the range of 25-60°C. The rate of reaction increased with increasing temperature; however, 25 ± 2°C was selected as the optimum temperature due to low reproducibility of absorbance values at higher temperature. In order to ascertain the stoichiometry of the studied reactions, Job's method of continuous variation[41] was applied. For both drugs, Job's method plot (Figure 4) reached a maximum value at a mole fraction of 0.3 for NF and 0.2 for VN which indicated a reaction ratio of 1: 2 and 1: 4 (drug : $KMnO_4$) for NF and VN, respectively. The reaction pathway can be explained by the oxidation of the tertiary amine groups into *N*-oxide. It has been reported that compounds possessing tertiary amine groups are liable to oxidation by alkaline potassium permanganate[39,40]. The following schemes represent the proposed pathways for the reaction between the investigated drugs and $KMnO_4$ in alkaline medium.



The rate of reaction was found to be drug dependant. The rates were followed at room temperature with various concentrations of the investigated drugs in the range of 6.33×10^{-6} to 3.17×10^{-5} M (3-15 µg/mL) for NF and 1.13×10^{-5} to 3.95×10^{-5} M (4-14 µg/mL) for VN, keeping $KMnO_4$ and NaOH constant at high concentrations as above. The graphs shown in Figures 5 and 6, clearly demonstrated that the reaction rates obey the following equation:

$$\text{Rate} = K` \times [C]^n \quad \text{..... (1)}$$

Where K` is the pseudo-order rate constant and n is the order of reaction. The rate of reactions could be estimated as $\Delta A/\Delta t$, where A is the absorbance and t is the time in seconds. Taking logarithms of rates and concentrations (Table 2), equation (1) is transformed into:

$$\log (\text{rate}) = \log (\Delta A/\Delta t) = \log K` + n \log [C] \quad \text{..... (2)}$$

Regression of log (rate) versus log [C] gave the following regression equations:

log (rate) = 0.872603 + 0.89630 log [NF], r = 0.998338

log (rate) = 1.382608 + 1.03817 log [VN], r = 0.998847

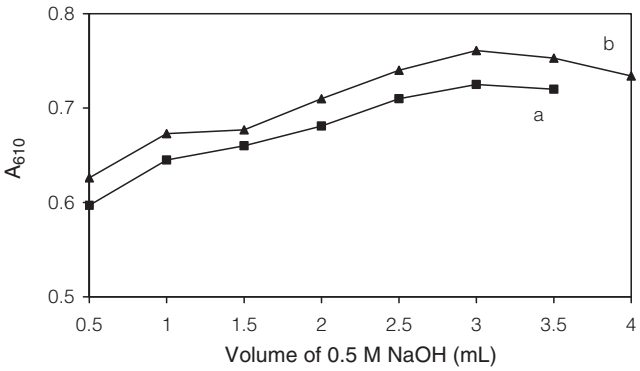


Figure 3. Effect of NaOH concentration on the reaction product of (a) 2.11×10^{-5} M NF and (b) 3.39×10^{-5} M VN using optimum conditions for each compound.

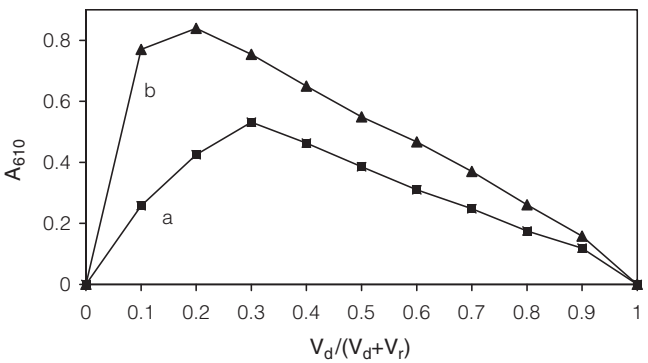


Figure 4. Continuous variation plot for (a) NF and (b) VN. Concentration of solutions of both drugs and the reagent ($KMnO_4$) was 1×10^{-2} M.

Table 2. Values of logarithms of rates and concentrations for NF and VN with alkaline KMnO4 using optimum conditions for each compound

Compound	log C[M]	log ΔA/Δt
NF	-5.198	-3.799
	-4.896	-3.500
	-4.720	-3.343
	-4.597	-3.259
	-4.499	-3.167
VN	-4.974	-3.741
	-4.772	-3.582
	-4.646	-3.448
	-4.549	-3.348
	-4.469	-3.255
	-4.403	-3.177

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Hence, K`= 7.46 sec^{-1} for NF and 24.13 sec^{-1} for VN and the reaction is pseudo-first order (n = 1) with respect to NF and VN.

II. *Appraisal of Kinetic Methods*

The determination of NF and VN under the optimized experimental conditions mentioned above, in which the potassium permanganate and sodium hydroxide concentrations were several hundreds times that of either drug, would result in pseudo-zero conditions with respect to their concentrations and the rate of reaction will be directly proportional to the concentration of NF or VN in a pseudo-first-order rate equation as follows:

$$Rate = K` \times [C] \quad (3)$$

where K` is the pseudo-first-order rate constant.

Equation (3) was the basis for several experiments, which were run to obtain concentrations of the investigated drugs using the rate data. Rate constant, fixed-concentration and fixed-time methods[42] were tested and the most suitable analytical method was selected taking into account the applicability, sensitivity (i,e. the slope of the calibration graph), correlation coefficient (r) and intercept (a).

(I) *Rate-constant Method*

Graphs of log (absorbance) versus time for NF concentrations in the range of 6.33×10^{-6} - 3.17×10^{-5} M (3-15 µg/mL) and VN concentrations in the range of 2.26×10^{-5} - 3.95×10^{-5} M (8 - 14 µg/mL) were plotted and all appeared to be rectilinear. Pseudo-first-order rate constants (K`) corresponding to different concentrations of the investigated drugs [C] were calculated from the slopes multiplied by -2.303. Regression of K` values versus [C] gave the equations:

K` = 0.00205 + 18.89 [NF], r = 0.98364

K` = -0.00186 + 28.74 [VN], r = 0.49247

The method suffered from poor linearity especially for VN as indicated from its r value, therefore this method was excluded**.**

(II) *Fixed-concentration Method*

Reaction rates were determined for different concentrations of the investigated drugs. A pre-selected absorbance value was fixed (0.4 for both NF and VN) for different concentrations of the studied drugs, in the range of 1.27×10^{-5} - 3.17×10^{-5} M (6-15 µg/mL) for NF and 2.26×10^{-5} - 3.95×10^{-5} M (8-14 µg/mL) for VN and the time required for each concentration to reach the pre-selected absorbance value was measured in seconds. The reciprocal of time (1/t) versus drug concentrations was plotted and the following equations were obtained by linear regression:

$1/t = -1.5 \times 10^{-2} + 164.25$ [NF], r = 0.98747

$1/t = -2.6 \times 10^{-2} + 1113.62$ [VN], r = 0.96103

The concentration ranges giving the most satisfactory calibration graphs were limited (6-15 µg/mL for NF and 8-14 µg/mL for VN) with poor linearity and therefore the method is excluded.

(III) *Fixed-time Method*

Reaction rates were determined for different concentrations of the investigated drugs. At a pre-selected fixed time, which was accurately determined, the absorbance was measured. Calibration graphs of the absorbance (A) versus initial concentration [C] were established at different fixed-time intervals of 2-40 min for NF and 1-40 min for VN (Figures 5 and 6) with the regression equations assembled in Table 3. It was found that the slopes increase with time and the most acceptable values for the intercept and the correlation coefficient(r) were obtained at a fixed-time of 35 min for NF and 20 min for VN therefore they were chosen as

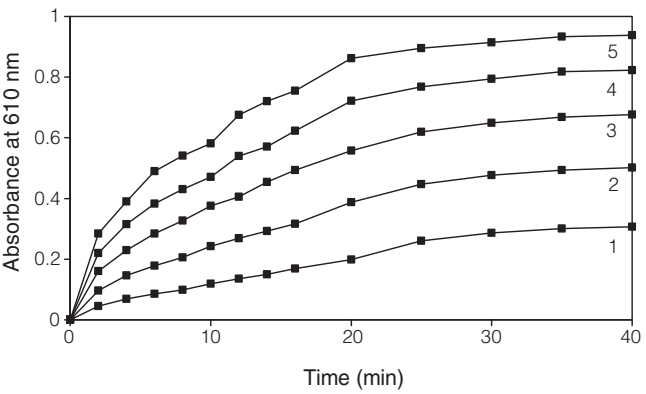

Figure 5. Absorbance versus time graphs for the reaction of NF and alkaline potassium permanganate. Concentrations of NF: (1) 6.33×10^{-6}, (2) 1.27×10^{-5}, (3) 1.90×10^{-5}, (4) 2.53×10^{-5}, (5) 3.17×10^{-5} M.

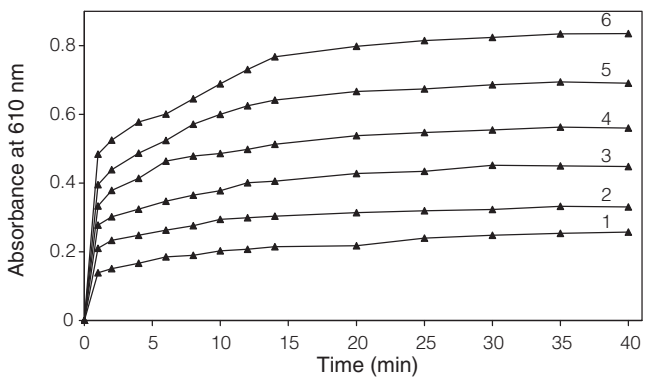

Figure 6. Absorbance versus time graphs for the reaction of VN and alkaline potassium permanganate. Concentrations of VN: (1) 1.13×10^{-5}, (2) 1.69×10^{-5}, (3) 2.26×10^{-5}, (4) 2.82×10^{-5}, (5) 3.39×10^{-5}, (6) 3.95×10^{-5} M.

Table 3. Regression equations at different fixed-times for NF in the range 6.33×10^{-6} - 3.17×10^{-5} M and VN in the range 1.13×10^{-5} - 3.95×10^{-5} M with alkaline $KMnO_4$ using optimum conditions for each compound

Compound	Time	Regression equation	(r)
NF	2	A = -0.01943 + 9504.05 C	0.99929
	4	A = -0.01354 + 12803.07 C	0.99971
	6	A = -0.01976 + 15992.96 C	0.99971
	8	A = -0.01196 + 17508.15 C	0.99974
	10	A = 0.01194 + 18218.71 C	0.99832
	12	A = 0.00022 + 21297.50 C	0.99998
	14	A = 0.01161 + 22403.06 C	0.99909
	16	A = 0.02745 + 23348.12 C	0.99825
	20	A = 0.03274 + 24994.74 C	0.99844
	25	A = 0.10503 + 25716.40 C	0.99769
	30	A = 0.13035 + 25605.02 C	0.99757
	35	A = 0.03954 + 25794.84 C	0.99741
	40	A = 0.14524 + 25842.15 C	0.99734
VN	1	A = 0.00637 + 11816.06 C	0.99781
	2	A = 0.00849 + 12979.56 C	0.99910
	4	A = 0.00180 + 14482.97 C	0.99959
	6	A = 0.01430 + 15080.14 C	0.99693
	8	A = 0.00015 + 16569.02 C	0.99861
	10	A = -0.00258 + 17490.14 C	0.99884
	12	A = -0.01482 + 18700.25 C	0.99883
	14	A = -0.02486 + 19666.37 C	0.99759
	20	A = -0.00989 + 20592.51 C	0.99857
	25	A = -0.01616 + 20511.65 C	0.99660
	30	A = -0.00879 + 20608.64 C	0.99677
	35	A = -0.00575 + 20744.71 C	0.99655
	40	A = -0.00440 + 20658.66 C	0.99561

the most suitable time intervals for measurements. The calibration graphs were linear over the concentration ranges of 6.33×10^{-6} - 3.17×10^{-5} M (3-15 μg/mL) and 1.13×10^{-5} - 3.95×10^{-5} M (4-14 μg/mL) for NF and VN, respectively.

III. *Analytical Performance of the Proposed Method*

(I) *Concentration Ranges and Calibration Graphs*

The analytical parameters, molar absorptivities, linearity ranges and regression equations calculated from calibration graphs along with the standard deviations of the slope (S_b), intercept (S_a) and the standard deviation of residuals ($S_{y/x}$) are presented in Table 1. The values of the correlation coefficients (r) of regression equations indicated good linearity and conformity to Beer's law. The linearity was also evaluated by calculation of percentage relative standard deviation of the slope (S_b %). It was found to be less than 2% for the developed analytical method. An important statistic indicating the random error in the estimated values of y is the standard error of the estimate, standard deviation about regression, or standard deviation of residuals, $S_{y/x}$. The smaller the standard error of the estimate, the closer the points are to the straight line.

Table 4. Precision and accuracy for the proposed fixed time kinetic method for the determination of NF and VN

Compound	Nominal Value (μg/mL)	% Recovery*	RSD (%)
NF	3	100.33	1.16
	6	100.67	1.39
	12	100.08	0.41
VN	4	101.25	1.80
	8	98.00	1.51
	12	102.08	2.65

*Mean % recovery of five determinations.

(II) *Detection and Quantification Limits*

The detection limits were 8.01×10^{-7} and 1.19×10^{-6} M (0.38 and 0.42 μg/mL) for NF and VN, respectively, while the quantification limits were 2.67×10^{-6} and 3.97×10^{-6} M (1.26 and 1.40 μg/mL) for NF and VN, respectively. These values were calculated according to the formulae provided by the USP[43].

(III) *Precision and Accuracy*

Five replicate determinations at different concentration levels were carried out to test the precision and accuracy of the proposed fixed time kinetic method. As shown in Table 4, the % recovery and RSD (%) values demonstrated the good repeatability and accuracy of the proposed method.

(IV) *Robustness*

The robustness of the method was demonstrated by the flexibility of the experimental factors that affect the absorbance values. Variation of the volumes added of the both NaOH and $KMnO_4$ solutions by ± 5% and variation of the measurement wavelength by ± 2 nm did not have significant effect on the measured absorbance values.

IV. *Assay of Pharmaceutical Preparations*

The fixed-time method was applied to the determination of NF and VN in their commercially available dosage forms. The fixed-time method gave better linearity as indicated from the (r) values. In addition it was easier in application than the rate constant method. Direct application of the method on the aqueous extract

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Table 5. Application of the proposed kinetic method for the determination of NF and VN in their pharmaceutical preparations

Praxilene® tablets	Kinetic method	Reference method[b]
%Recovery ± SD[a]	100.18 ± 1.84	99.87 ± 1.99
RSD %[b]	1.84	1.99
t	0.26	
F	1.17	
Oxybral® capsules	**Kinetic method**	**Reference method[c]**
%Recovery ± SD[a]	98.83 ± 0.74	99.52 ± 1.25
RSD %[b]	0.75	1.26
t	1.04	
F	2.88	
Oxybral® ampoules	**Kinetic method**	**Reference method[c]**
%Recovery ± SD[a]	99.32 ± 1.13	100.04 ± 0.64
RSD %[b]	1.14	0.64
t	1.25	
F	3.12	

[a]Mean % recovery ± SD for five determinations.
[b]Measurement of A_{max} in saline at 283 nm[15].
[c]Measurement of the first derivative of the ratio spectra ($^1DD_{293}$) of VN over 20 μg ml^{-1} standard VA[28].
Theoretical values for t and F at P = 0.05 are 2.31 and 6.39, respectively.

of Praxilene® tablets resulted in a positive error in recovery. This error can be attributed to the oxidation of the common excipients usually present in the tablet dosage form (e.g. lactose, starch, etc), therefore, acetonitrile was chosen as a dissolution medium and the reaction was applied on the acetonitrile aliquots. On the other hand, because VN has a limited solubility in water, acetonitrile was also chosen as a solvent for VN. For Oxybral® ampoules, an extraction procedure with chloroform has been followed in order to eliminate the interference caused by the antioxidant present in the ampoules which is easily oxidized by $KMnO_4$ yielding a positive error in recovery values. The results obtained show good precision and accuracy (Table 5) and they were statistically compared with those obtained by the reference methods[15,28]. The student's t-test and the variance-ratio F-test values at 95 % confidence level did not exceed the theoretical values, indicating no significant difference between the proposed and the reference method (Table 5).

Table 6. Effect of various foreign species on the determination of NF and VN at the optimum conditions

Species	Tolerance Limit (μg/mL)	
	NF (10 μg/mL)	VN (10 μg/mL)
Glucose	12.35	12.77
Lactose	14.02	12.35
Sucrose	20.98	29.76
Starch	13.10	16.22
Ascorbic acid	23.44	25.42
Riboflavin	21.43	32.70
Carboxymethylcellulose	16.67	17.24
Hydroxypropylmethylcellulose	12.35	11.49
Piracetam	—	5.45

V. *Interferences*

Interferences due to common excipients and related co-formulated compounds were studied using glucose, lactose, sucrose, starch, ascorbic acid, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, riboflavin and piracetam. Different aliquots of the interfering substance solutions in acetonitrile were added to standard NF and VN solutions, treated and measured at the optimum conditions for each compound. The tolerance limit[37] for each of these substances (Concentration of interfering substance causing 3% relative error) was calculated and listed in Table 6.

CONCLUSIONS

In this study, a simple and sensitive kinetic fixed-time spectrophotometric procedure was developed for the analysis of the two vasodilators: NF and VN. Reviewing the literature exposed that there were no reports for the kinetic spectrophotometic determination of the two drugs. Moreover, nothing was reported concerning the use of colorimetry in the assay of NF, and only single previous report for the UV spectrophotometric estimation of NF[15]. On the other hand, very few previous studies were concerned with the spectrophotometric or colorimetric analysis of VN. The simplicity, convenience at low cost and sensitivity of the proposed method are superior or comparable to those of the official non-aqueous titration method[2] and several previously published spectrophotometric methods[15,25-28,31,32]. Furthermore, the proposed method does not require elaborate treatment or sophisticated experimental setup usually associated with HPLC methods of analysis. The developed method used only a spectrophotometer, which is available in all quality control laboratories, and it involved very simple procedure with readily available chemicals ($KMnO_4$ and NaOH). The applicability of the developed method was evaluated through the determination of the two drugs in bulk form and in pharmaceutical formulations with good accuracy and precision, therefore it can be considered useful and convenient for the routine and quality control assay of the two drugs.

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