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Kinetic spectrophotometric determination of simvastatin using alkaline potassium permanganate

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ABSTRACT

Two simple and sensitive kinetic spectrophotometric methods were established for the determination of simvastatin (SIM) in pure and dosage forms using alkaline potassium permanganate as an oxidant. The investigated methods involve the determination of SIM by kinetic study of its oxidation reaction at room temperature for a fixed time of 20 minutes and 10 minutes for the first and second methods, respectively. In the first method, the absorbance of the produced manganate was measured at 610 nm, while in the second method the reduction in the absorbance of permanganate was measured at 525 nm. The absorbance-concentration plots were rectilinear over the concentration range of 3.0-30.0 μg/mL in the first method and 3.0-25.0 μg/mL in the second method with detection limits of 1.0 μg/mL in both methods. The proposed methods were applied successfully for determination of SIM in pure and dosage forms. The proposed methods were statistically compared with a reference one showing no significant differences regarding accuracy and precision. In addition, the activation parameters such as E_a, ΔH, ΔS and ΔG were also evaluated for the reaction and found to be 43.03 KJ mol^{-1}, 45.78 KJ mol^{-1}, 33.06 JK^{-1} mol^{-1} and -9.85 KJ mol^{-1}, respectively.

KEYWORDS

Simvastatin;
Kinetic spectrophotometric determination;
Potassium permanganate;
Activation parameters.

INTRODUCTION

Simvastatin (SIM) is an official lipid-lowering agent that is derived synthetically from fermentation products of *Aspergillus terreus*. After oral ingestion of Simvastatin (Figure 1), an inactive lactone, is hydrolyzed to corresponding ortho-hydroxy acid leading to the inhibition of 3-hydroxy 3-methyl glutaryl-coenzyme A (HMG-Co A) reductase, responsible for catalysing the conversion of HMG-Co A to mevalonate, which is an early and rate limiting step in cholesterol biosynthesis[1,2].

Many techniques like UV-Visible spectrophotometry[3-5], HPLC[6-12] and LC/MS/MS[13-16] have been reported for the determination of SIM alone, in presence of its metabolites or in combination with other drugs either in pharmaceuticals or in biological fluids.

Although the reaction between SIM and permanganate was used for the quantification of SIM[17] but the reported method did not introduce a kinetic study for this reaction.

The goal of the present work is to introduce a kinetic study for the reaction between SIM and permanganate and also use this study to develop simple, accu-

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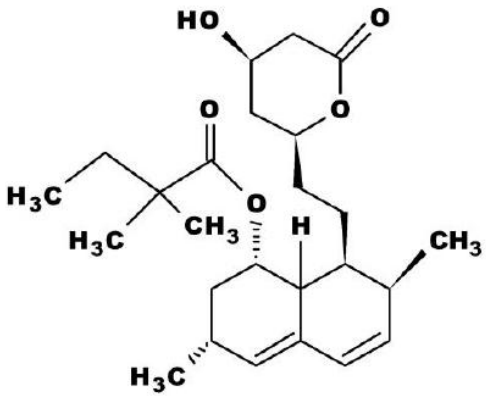
rate, reproducible and economic methods for determination of SIM either in pure or dosage forms.



Butanoic acid, 2, 2- dimethyl-, 1, 2,3, 7, 8, 8a-hexahydro-3, 7-dimethyl-8-[2(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1- naphthalenylester ($C_{25}H_{38}O_5$) (418.57 g / mol)[1]

Figure 1 : Structure of SIM.

EXPERIMENTAL

Apparatus

JASCO V-630 BIO spectrophotometer (S/N B206561148) equipped with kinetic accessory provided with temperature controlled cell (EHCS - 760) thermo-electric temperature. Recording range, 0-2; wavelengths 610 nm, 525 nm; factor 1; number of cell, 1; reaction time 30 min.; cycle time, 0.2 minutes.

Reagents and materials

All used chemicals were of analytical reagent grade and all solvents were of spectroscopic grade.

- Potassium permanganate (Merck, Darmstadt, Germany): $5x10^{-3}$M and 7.6×10^{-3} M aqueous solutions, freshly prepared.
- Sodium hydroxide (BDH, UK): 0.5M aqueous solution is prepared.
- Acetonitrile (Merck, Darmstadt, Germany).
- Distilled water from "Aquatron" Automotive water Still A 4000 (bibby Sterillin Ltd., Staffordshire-UK).
- Pure simvastatin (Batch no. EA-B10-02-001076/ 02676) was kindly supplied by EVA-Pharmaceuticals, Cairo-Egypt. Its purity was assessed to be 99.81% according to a reported UV-spectrophotometric method[4].
- Zocor® tablets, labeled to contain 40 mg simvastatin per tablet (Batch No. 510304), manufactured by Global Napi Pharmaceuticals (Cairo-Egypt) under license from Merk Sharp & Dohme International, USA.

Standard solutions

Stock standard solution of SIM was prepared by dissolving 10.0 mg of SIM in 30 mL acetonitrile into 100-mL measuring flask with continuous shaking for about 10 minutes. The volume was completed to the mark with the corresponding solvent to reach concentration of 0.1 mg/mL. Other concentrations were prepared by further dilution with acetonitrile. The prepared solutions were stable for up to five days, on keeping in refrigerator (4^0C).

Procedures

(a) Construction of kinetic calibration graph (first method)

Aliquots of SIM standard solution (0.1mg/mL) equivalent to 30.0-300.0 µg were accurately transferred into a series of 10-mL measuring flasks, 1.5 mL of 0.5 M NaOH was added followed by 4 mL of 5×10^{-3} M $KMnO_4$. Mixtures were shaken well and completed to the volume with distilled water. The absorbance was measured during 20 minutes at room temperature at 610 nm against similar reagent blank prepared simultaneously. The reaction order was estimated by plotting log reaction rate ($\Delta A/\Delta t$) over the specified time period *versus* log concentration of the drug. The calibration graphs and the regression equations were constructed by plotting absorbance (A) at specified time *versus* concentration of the drug in µg/mL.

(b) Construction of kinetic calibration graph (second method)

Aliquots of SIM standard solution (0.1mg/mL) equivalent to 30.0-250.0 µg were accurately transferred into a series of 10-mL measuring flasks, 1mL of 0.5 M NaOH was added followed by 0.5 mL of 7.6×10^{-3} M $KMnO_4$. Mixtures were shaken well and completed to the volume with distilled water. The reduction in absorbance was measured during 10 minutes at room temperature at 525 nm against a similar blank prepared simultaneously.

(c) Accuracy

Accuracy was assured by carrying out the previ-

ously mentioned procedures under linearity for the determination of different concentrations of pure SIM. The concentrations were calculated from the corresponding regression equations.

(d) Precision

(A) Intraday precision (Repeatability)

Two concentrations of pure SIM were analyzed three times intraday using the previously mentioned procedures. The percentage recoveries and its relative standard deviation were calculated using the suggested methods.

(B) Intermediate precision

Two concentrations of pure SIM were analyzed on three successive days using the procedure stated under linearity. The percentage recoveries and its relative standard deviation were calculated using the suggested methods.

(e) Application to pharmaceutical formulation

Ten tablets (Zocor® tablets) were weighed to calculate the average weight of a tablet then crushed, finely powdered and mixed well.

An accurately weighed quantity of the powdered tablets equivalent to 10.0 mg of the drug was transferred into a 100-mL measuring flask. The content of the flask was completed to 100 mL with acetonitrile then sonicated for 15 minutes and filtered. An aliquot of the cited solution was taken and the above procedure was applied. The nominal content was calculated either from a previously plotted calibration graph or using the regression equation.

RESULTS AND DISCUSSION

The reaction between SIM and $KMnO_4$ in alkaline medium yields a green color due to the production of manganate ions, which absorb maximally at 610 nm (Figure 2). As the intensity of the color increases with time, this was used as a useful method for the determination of SIM in bulk as well as in dosage forms (first method). At the same time, owing to the consumption of $KMnO_4$ in the reaction, the absorbance of $KMnO_4$ at 525 nm decreases with time. This was also used as a useful method for the determination of SIM (second method). The various experimental parameters affecting the development and stability of the reaction product in both methods were optimized by changing each variable in turn while keeping all others constant.

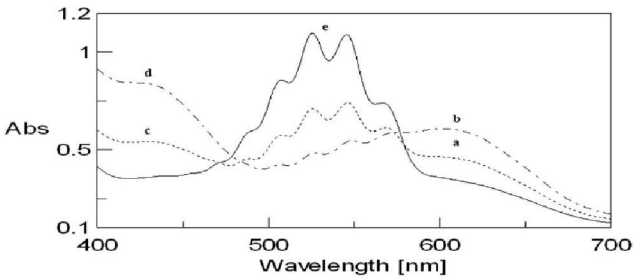


Figure 2 : Absorption spectra of the simvastatin after reaction with $KMnO_4$/ NaOH system. (a,b) The produced manganate ions after the reaction of $KMnO_4$ with SIM (3µg/mL) or (10µg/mL); (c,d) Oxidation products of SIM, respectively; (e) $KMnO_4$ ($7.6x10^{-3}$M).

Study of experimental parameters

(a) Effect of diluting solvent

For both methods, the effect of diluting solvent was tried and the most suitable and economic one is distilled water.

(b) Effect of $KMnO_4$ concentration

In the first method, the reaction rate and maximum absorbance increased with increasing $KMnO_4$ concentration. It was found that 4 mL of 5×10^{-3} M $KMnO_4$ was adequate for the maximum absorbance (Figure 3). Higher concentrations of $KMnO_4$ yielded lower absorbance values probably due to decomposition of the product (Figure 2). While in the second method, the reaction rate and maximum absorbance reduction increased with increasing $KMnO_4$ concentration. It was found that 0.5 mL of 7.6×10^{-3} M $KMnO_4$ was adequate for the maximum absorbance reduction (Figure 4).

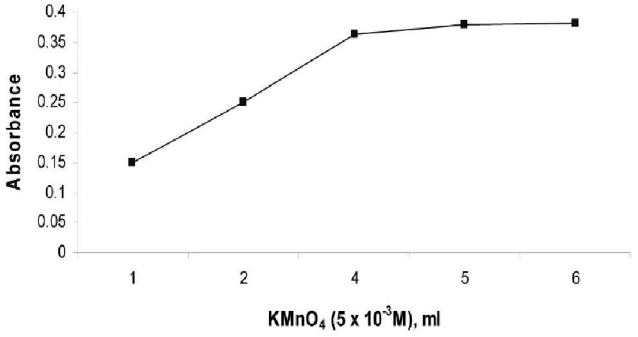


Figure 3 : Effect of $KMnO_4$ on the absorbance intensity at 610 nm.

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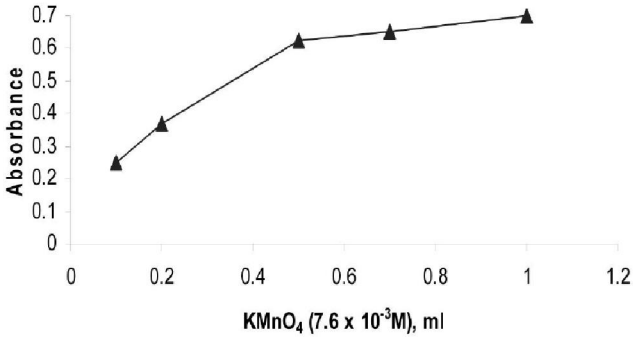

Figure 4 : Effect of $KMnO_4$ on the absorbance intensity at 525 nm.

(c) Effect of NaOH concentration

It was found that increasing the volume of 0.5 M NaOH would increase the absorbance of the reaction product up to 1.5 mL (In the first method) (Figure 5). In the second method increasing the volume of 0.5 M NaOH would increase the reduction in the absorbance of $KMnO_4$ up to 1 mL (Figure 6).

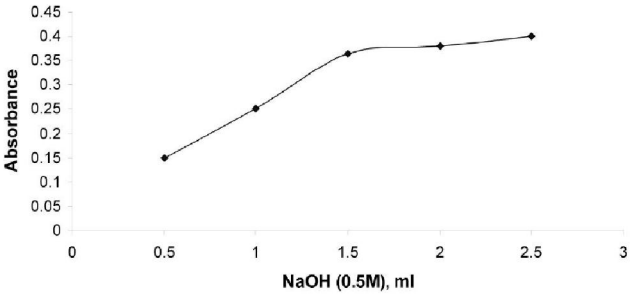

Figure 5 : Effect of NaOH on the absorbance intensity at 610 nm.

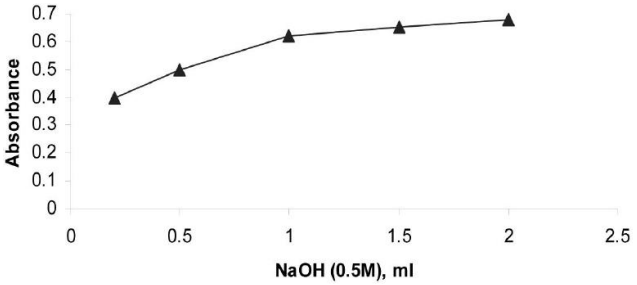

Figure 6 : Effect of NaOH on the absorbance intensity at 525 nm.

(d) Effect of temperature

The effect of temperature on the reaction rate was studied, it was found that, permanganate was reduced to manganate radical at room temperature (25°C) while at higher temperatures, manganese dioxide was produced. Therefore, room temperature was selected as the optimum temperature.

(e) Effect of time

The effect of time on the reaction between $KMnO_4$ and the studied drug was studied. The absorbance of the reaction mixture changed with time so quantification was made at fixed times of 20 minutes for SIM in the first method and at 10 minutes in the second one (Figures 7 and 8).

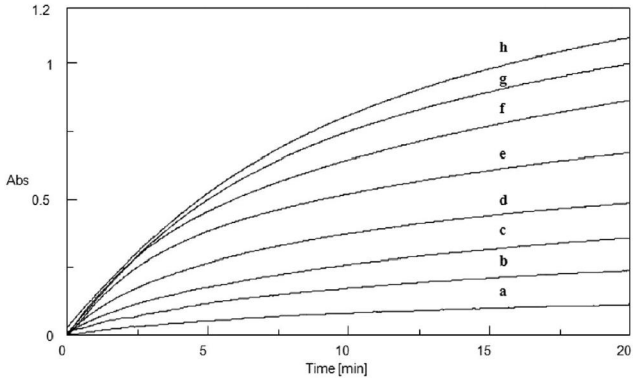

Figure 7 : Absorption versus time graphs for the reaction between SIM and $KMnO_4$ at 610 nm. a) 3 µg/mL b) 5 µg/mL c) 10 µg/mL d) 12 µg/mL e) 15 µg/mL f) 20 µg/mL g) 25 µg/mL h) 30 µg/mL.

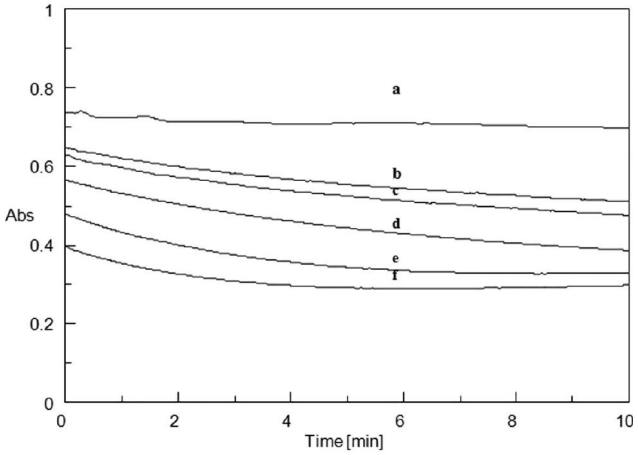

Figure 8 : Absorption versus time graphs for the reaction between SIM and $KMnO_4$ at 525 nm. a) Blank b) 3 µg/mL c) 5 µg/mL d) 10 µg/mL e) 20 µg/mL f) 25 µg/mL.

Evaluation of kinetic parameters

As mentioned above, the reaction between $KMnO_4$ and the studied drug never reach completion and a decision was made to apply a kinetic method for their determination.

Consequently, the order of the reaction and reaction rate constants were determined at 610 and 525 nm. The rate of the reaction was found to be dependent on SIM concentration. The rates were followed at

room temperature with various concentrations in the range of 3.0-30.0 μg/mL for SIM keeping $KMnO_4$ and NaOH concentrations constant at the recommended levels mentioned above. The reaction rate obeys the following equation:

$$\text{Rate of the reaction} = \frac{\Delta A}{\Delta t} = K`[\text{drug}]n \qquad (1)$$

Where K´ is the pseudo-order rate constant and n is the order of the reaction. The rate of the reaction may be estimated by the variable time method measurement[18], where A is the absorbance and t is the time in seconds. Taking logarithms of rates and drug concentrations (TABLE 1), the previous equation is transformed into:

$$\log(\text{rate}) = \log\frac{\Delta A}{\Delta t} = \log K` + n\log[\text{drug}] \qquad (2)$$

Plot of log reaction rate versus log SIM concentration at 610 nm and 525 nm gave the regression equation, correlation coefficient, pseudo-order rate constant and order of the reaction which are indicated below. These results indicate that the reaction is pseudo first order reaction in the drug concentration.

Log (rate) versus log [drug] gave the regression equation:

Log rate = 1.283 + 1.056 log C r = 0.9998
(in the first method)

Hence K´ = 19.19 S^{-1} and the reaction is first order (n = 1.05).

Log rate = 1.810 + 1.113 log C r = 0.9959
(in the second method)

Hence K´ = 64.56 S^{-1} and the reaction is first order (n = 1.11).

TABLE 1 : Logarithms of rate for different concentrations of SIM at room temperature and at 610 nm, 525 nm.

At 610 nm		At 525 nm	
$\text{Log}\frac{\Delta A}{\Delta t}$	Log[SIM]	$\text{Log}\frac{\Delta A}{\Delta t}$	Log[SIM]
- 4.155	- 5.144	- 3.939	- 5.144
- 3.910	- 4.922	- 3.633	- 4.922
- 3.600	- 4.621	- 3.330	- 4.621
- 3.273	- 4.320	- 3.053	- 4.320
- 3.100	- 4.144	- 2.853	- 4.223

Selection of the best kinetic method

Several kinetic techniques were adopted for the selection of the best method. Rate constant, fixed absorbance and fixed time methods[18] were tried and the most suitable analytical method was selected taking into account the applicability, the sensitivity, i.e. the slope of the calibration graph and the correlation coefficient (r).

(a) Rate constant method

Graphs of log absorbance versus time for SIM concentration in the range of $7.17 \times 10^{-6} - 4.78 \times 10^{-5}$ M for the first method and $2.39 \times 10^{-5} - 5.97 \times 10^{-5}$ M for the second method were plotted and all appeared to be rectilinear. Pseudo-first order rate constants (K´) corresponding to different drug concentrations (C) were calculated from the slopes multiplied by –2.303 and are presented in TABLE 2.

Regression of (C) versus K´ gave equations:

At 610 nm

K´ = - 0.001 + 11.22 C r = 0.9948

At 525 nm

K´= - 0.0004 + 4.0139 C r = 0.9792

Where C is the molar concentration of the drug.

TABLE 2 : Values of K´ calculated from slopes of log A versus time graphs at 610 nm and 525 nm.

At 610 nm		At 525 nm	
K`, S^{-1}	[SIM], M	K`, S^{-1}	[SIM], M
-9.20×10^{-4}	7.17×10^{-6}	-3.00×10^{-4}	2.39×10^{-5}
-6.90×10^{-4}	2.39×10^{-5}	-2.70×10^{-4}	3.58×10^{-5}
-4.60×10^{-4}	4.78×10^{-5}	-2.00×10^{-4}	4.78×10^{-5}
		-1.60×10^{-4}	5.97×10^{-5}

(b) Fixed absorbance method

Reaction rates were recorded for different concentrations of the drug in the range of $1.195 \times 10^{-5} - 4.78 \times 10^{-5}$ M in the first method and $7.17 \times 10^{-6} - 2.39 \times 10^{-5}$ M in the second method. Preselected values of the absorbance (0.2) in the first method and (0.55) in the second method were fixed and the time was measured in seconds. The reciprocal of times (1/t) versus the initial concentrations of drug (TABLE 3) were plotted and the following equations of the calibration graphs were obtained:

1/t = - 0.0015 + 201.33 C r = 0.9934
(first method)

1/t = - 0.0071 + 1041.3 C r = 0.9707
(second method)

Where C is the molar concentration of the drug.

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TABLE 3 : Values of reciprocal of time taken at fixed absorbance for different rates of variable concentrations of SIM at constant concentrations of NaOH and $KMnO_4$ at room temperature.

At 610 nm		At 525 nm	
1/t, S^{-1}	[SIM], M	1/t, S^{-1}	[SIM], M
1.20×10^{-3}	1.19×10^{-5}	2.16×10^{-3}	7.17×10^{-5}
2.80×10^{-3}	2.39×10^{-5}	2.87×10^{-3}	1.19×10^{-5}
8.30×10^{-3}	4.78×10^{-5}	1.85×10^{-2}	2.39×10^{-5}

(c) Fixed time method

At a preselected fixed time, which was accurately determined, the absorbance was measured. Calibration graphs of the absorbance versus initial concentrations of SIM at fixed times of 5, 10, 15, 20 min., in the first method and 2, 4, 6, 8, 10 min., in the second method, were established with the regression equations and correlation coefficients assembled in TABLE 4. It is clear that the slope increases with time and the most acceptable values of the correlation coefficient (r) was chosen as the most suitable time interval for the measurement.

As a conclusion, the fixed time method was chosen for quantification because it gave the best correlation coefficient in a reasonable time.

TABLE 4 : Regression equations for SIM at different fixed times over the range of $7.17 \times 10^{-6} - 7.17 \times 10^{-5}$ M for first method and $7.17 \times 10^{-6} - 5.97 \times 10^{-5}$ M for second method.

At 610 nm			At 525 nm		
Time, min.	Regression equation	(r)[a]	Time, min.	Regression equation	(r)[a]
5	$A = 1.53 \times 10^{-2} + 1.69 \times 10^{-2} C$	0.9981	2	$A = -6.3 \times 10^{-3} + 1.48 \times 10^{-2} C$	0.9990
10	$A = 2.67 \times 10^{-2} + 2.46 \times 10^{-2} C$	0.9982	4	$A = 3 \times 10^{-4} + 1.53 \times 10^{-2} C$	0.9995
15	$A = 3.42 \times 10^{-2} + 2.98 \times 10^{-2} C$	0.9983	6	$A = 1.1 \times 10^{-3} + 1.64 \times 10^{-2} C$	0.9998
20	$A = 1.99 \times 10^{-2} + 3.38 \times 10^{-2} C$	0.9998	8	$A = 8.8 \times 10^{-3} + 1.68 \times 10^{-2} C$	0.9998
			10	$A = 9.6 \times 10^{-3} + 1.76 \times 10^{-2} C$	0.9999

[a]correlation coefficient

Method validation

After optimizing the reaction conditions, the fixed time method was applied to the kinetic determination of pure SIM in the range of 3.0-30.0 μg/mL in the first method and 3.0-25.0 μg/mL in the second method.

Analysis of the data gave the following regression equations:

$A = 1.99 \times 10^{-2} + 3.38 \times 10^{-2} C$ (r = 0.9998) (at 610 nm)

$A = 9.6 \times 10^{-3} + 1.76 \times 10^{-2} C$ (r = 0.9999) (at 525 nm)

Where A is the absorbance and C is the concentration in μg/mL.

Validation of the proposed kinetic methods is indicated with accuracy, precision, robustness, linearity, detection limits and quantification limits as shown in TABLE 5.

The results of the proposed method is statistically compared with a UV-spectrophotometric[4] reported one not the USP-method as the pharmacopeial method is an HPLC method so for method sensitivity matching, we use the UV-spectrophotometric one for comparison. Statistical analysis revealed no significant difference regarding accuracy and precision as indicated by the Student t-test and F-test[19] (TABLE 6). The proposed methods are successfully applied for the determination of the studied drug in its tablet form and also standard addition technique is successfully applied (TABLE 7).

TABLE 5 : Validation results of the proposed kinetic methods for the determination of SIM.

Parameters	The proposed kinetic methods	
	at 610 nm	at 525 nm
Accuracy (Mean±SD)	100.19 ± 0.65	100.55± 1.20
Precision RSD:		
Repeatability*	100.98 ± 0.76	99.79 ± 1.02
Intermediate precision*	99.58 ± 0.99	101.89 ± 1.00
Robustness	101.34 ± 0.90	99.68 ± 0.75
Linearity:		
Slope	0.0338	0.0176
Intercept	0.0199	0.0096
Correlation coefficient (r)	0.9998	0.9999
Range(μg/mL)	3.0-30.0	3.0-25.0
LOD (μg/mL)	1.0	1.0
LOQ(μg/mL)	3.0	3.0

*** Intra-day and interday relative standard deviation of the average of three concentrations; LOD and LOQ are obtained experimentally.**

TABLE 6 : Statistical comparison of the proposed methods for the determination of SIM and a reference method.

Items	The proposed method		The reference method*
	at 610 nm	at 525 nm	
Mean± SD	100.19±0.65	100.55±1.20	99.81±0.59
RSD	0.65	1.19	0.59
n	5	5	5
Variance	0.42	1.44	0.35
F-value (6.39)	1.20	4.11	-
Student's t-test (2.31)	0.97	1.24	-

***D^2-method for determination of simvastatin at 243 nm[4]; Values in parenthesis are the theoretical values of t and F at P= 0.05[19].**

Mechanism of the reaction

The data used in the optimization of $KMnO_4$ concentration and the data of the calibration graphs were used to calculate the stoichiometry of the reaction adopting the limiting logarithmic method[20]. The ratio of the reaction between SIM and $KMnO_4$ in alkaline medium was calculated by dividing the slope of $KMnO_4$ curve over the slope of the drug curve (Figures. 9A & 9B). It was found that, the ratio was 4.224: 1.073 for SIM pointing out to a ratio of 4:1 ($KMnO_4$ to drug). Based on the obtained molar reactivity, the reaction pathway is proposed to proceed as in Figure 10.

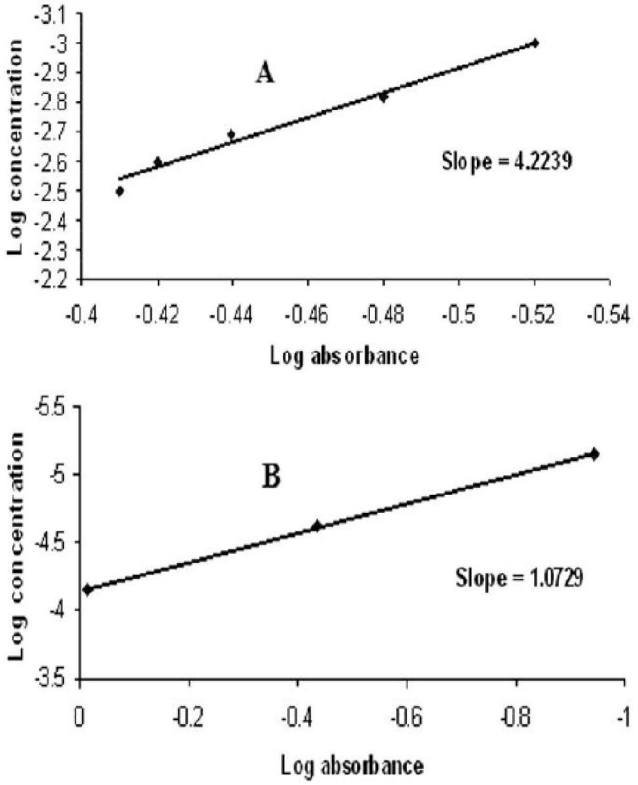

Figure 9 : Stoichiometry of the reaction between SIM and $KMnO_4$ adopting limiting logarithmic method[20]. (A) Variable concentrations of $KMnO_4$ at constant SIM concentration; (B) Variable concentrations of SIM at constant $KMnO_4$ concentration

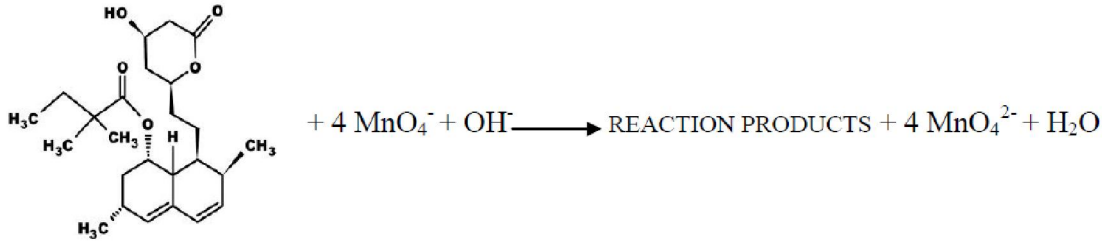

Figure 10 : The proposed pathway for the reaction between SIM and potassium permanganate in alkaline medium.

TABLE 7 : Application of standard addition technique for the determination of SIM in pharmaceutical formulation.

Pharmaceutical formulation	Taken (µg/mL)	Found%* ± SD (at 610 nm)	Found%* ± SD (at 525 nm)	Standard addition technique				
				Pure added (µg/mL)	Pure found** (µg/mL) (at 610 nm)	Pure found** (µg/mL) (at 525 nm)	Recovery % (at 610 nm)	Recovery % (at 525 nm)
Zocor® tablets claimed to contain 20 mg simvastatin/ tablet Batch No.510304	3	100.27 ± 0.63	99.55 ± 0.78	9	9.02	8.95	100.22	99.44
				12	11.89	12.11	99.08	100.92
				15	14.97	15.25	99.80	101.67
				18	18.21	17.95	101.17	99.72
				21	21.06	21.10	100.29	100.48
				Mean			100.11	100.45
				SD			0.762	0.903
				RSD			0.761	0.899

***Average of 5 determinations; **Average of 3 determinations.**

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Activation parameters

For the evaluation of apparent activation parameter[21], the reaction was studied at 298, 303, and 308 K at [SIM] = 2.39 x10^{-5} M, [$KMnO_4$] = 5x10^{-3} M and [NaOH] = 0.5 M at 610 nm. The Arrhenius plot of ln k versus 1/T was found to be linear with a correlation coefficient of 0.9997 (Figure 11). The Eyring plot of ln k/T versus 1/T was linear with a correlation coefficient of 0.9999 (Figure 12). The value of Ea was evaluated from the slope (-Ea/R) of Arrhenius plot and found to be 43.03 KJ mol^{-1}. The value of ΔH and ΔS were evaluated from the slope (-ΔH/R) and intercept [ln (k_b/h) + ΔS/R] of Eyring plot and found to be 45.78 KJ mol^{-1} and 33.06 JK^{-1} mol^{-1}, respectively. The value of Gibbs free energy (ΔG) of activation of the reaction product was found to be -9.85 KJ mol^{-1}. This value indicated that the proposed reaction is a favored reaction (spontaneous) can be occurred without external supply of energy.

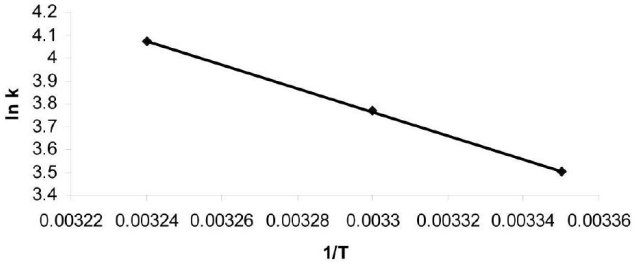

Figure 11 : Arrhenius plot of ln k versus 1/T at 298.0, 303.0, and 308.0 K for determination of activation energy at 610 nm.

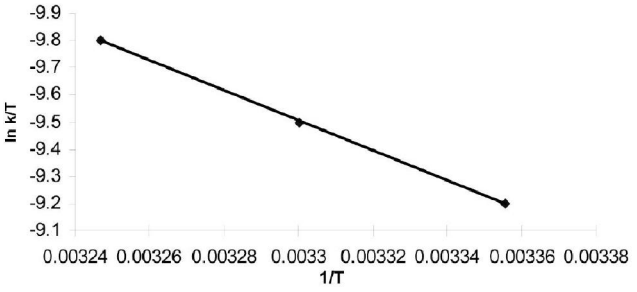

Figure 12 : Eyring plot of ln k/T versus 1/T at 298.0, 303.0, and 308.0 K for determination of ΔH and ΔS at 610 nm.

CONCLUSION

The proposed kinetic methods are appreciable with a view that the oxidation of drug can be exploited for the routine quality control analysis of SIM in its pharmaceutical formulation. The proposed methods are sensitive with a simple calibration system that does not require any laborious clean up procedure prior to analysis. Moreover the present technique has the advantage of using inexpensive and easily available reagents and therefore can be frequently used in the laboratories of research, hospitals and pharmaceutical industries. The only limitation for these method, if used in other pharmaceutical preparations containing antioxidant or any other oxidisable matter which will cause interference and this can be solved by using suitable solvent extraction.

From the above study some specific advantages in the application of kinetic methods can be expected[22]:

Selectivity due to the measurement of the evolution of the absorbance with the time of reaction instead of the measure of a concrete absorbance value.

Possibility of no interference of other absorbent active compounds present in the commercial product, if they are exhibiting stability in the chemical reaction conditions established for the proposed kinetic method.

Possibility of no interference of the colored and /or turbidity back ground of the sample.

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