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Original Article

SPECTROPHOTOMETRIC DETERMINATION OF ROSUVASTATIN CALCIUM IN PURE FORM AND PHARMACEUTICAL FORMULATIONS BY THE OXIDATION USING IODINE AND FORMATION TRIIODIDE COMPLEX IN ACETONITRILE

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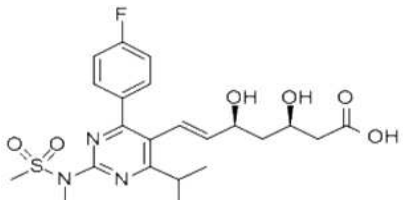
ABSTRACT

A simple, sensitive and economical spectrophotometric method is developed for the determination of rosuvastatin calcium in pure form and its pharmaceutical formulations in acetonitrile. This method is based on the oxidation of rosuvastatin calcium by iodine and formation triiodide (I_3^-) complex. The formed complex was measured at 291 and 360 nm against the reagent blank prepared in the same manner. The optimum experimental parameters are selected. Beer's law is valid within a concentration range of 2.408-48.154 µg.mL^{-1}. The developed method is applied for the determination of rosuvastatin calcium in pure and its pharmaceutical formulations without any interference from excipients with average recovery of 95.8 to 104.0%, the results obtained agree well with the contents stated on the labels.

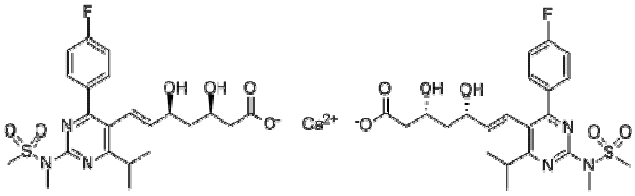
Keywords: Spectrophotometric method; Rosuvastatin; Iodine; Triiodide complex.

INTRODUCTION

Rosuvastatin calcium (RSV_{Ca}) $C_{44}H_{54}CaF_2N_6O_{12}S_2$ or $(C_{22}H_{27}FN_3O_6S)_2Ca$, a member of the class of statins, is the calcium salt of (E)-7-[4- (4-fluorophenyl) -6-isopropyl-2- [methyl (methyl sulfonyl) amino] pyrimidin-5-yl] (3R,5S)-3,5-di hydroxyhept-6-enoic acid, mol. mass 1001.14 g, while rosuvastatin (RSV) is $C_{22}H_{28}FN_3O_6S$ and its mol. mass is 481.539 g (Scheme1) [1-3].



Rosuvastatin $C_{22}H_{28}FN_3O_6S$, RSV



Rosuvastatin calcium $(C_{22}H_{27}FN_3O_6S)_2Ca$, RSV_{Ca}

Scheme1: Chemical structure of rosuvastatin and rosuvastatin calcium.

A derivative ratio spectrophotometric methods were used to determine rosuvastatin in the presence of its acid degradation products using methanol as a solvent. A linear relationship was obtained in the range 5-35µg.mL^{-1}. The proposed methods were validated for RSV in pharmaceutical formulations[4]. A simple, precise, accurate and reproducible spectrophotometric method has been developed and validated for the quantification of RSV_{Ca} and glimepiride in solid dosage form. Both the drugs followed Beer's law in concentration range of 10-22µg.mL^{-1} [5]. A specific, rapid and simple spectrophotometric method with good sensitivity was developed and validated for the simultaneous quantification of RSV_{Ca} and aspirin in standard solutions and tablets [6], in bulk and in capsule dosage form [7], in bulk and its pharmaceutical dosage form [8], in fixed dose combination products [9] and in combined dosage form [10]. A simple and highly sensitive spectrometric method is described for the estimation of RSV_{Ca} and telmisartan in bulk and in combined dosage form [11-12]. New, simple, accurate and precise UV spectrophotometric methods have been developed and validated for the simultaneous determination of rosuvastatin and ezetimibe in their combined dosage forms [13].

A sensitive and rapid extractive spectrophotometric method has been developed for the assay of RSV_{Ca} in pharmaceutical formulations. The method is based on the formation of a chloroform soluble ion-pair complex between RSV and safranin in phosphate buffer medium at pH7.2 [14]. The use of the first order derivative spectrophotometry allowed simultaneous determination of RSV_{Ca} and fenofibrate (FEN) in fixed dose combination product [15]. A method is described for the simultaneous estimation of RSV_{Ca} and FEN in binary mixture [16], in bulk and in pharmaceutical formulations [17], in synthetic mixture and its dosage form [18] and in pharmaceutical formulation [19]. A simple and economical first derivative spectrophotometric method has been developed for the simultaneous estimation of RSV and diltiazem in their combined dosage forms [20]. Simple and accurate spectrophotometric methods are presented for the determination of five statins, namely atorvastatin, fluvastatin, pitavastatin, rosuvastatin, and simvastatin, in pharmaceutical preparations. Beer's law was obeyed in the concentration ranges 4–20 µg.mL^{-1}, 4–12 µg.mL^{-1}, 0.8–2.4 µg.mL^{-1}, 4–14 µg.mL^{-1}, and 2.5–20 µg.mL^{-1} for atorvastatin, fluvastatin, pitavastatin, rosuvastatin, and simvastatin, respectively. The proposed methods were successfully applied to the pharmaceutical preparations without any interference from excipients [21]. Literature survey revealed that, in addition to the previously mentioned spectrophotometric methods, HPLC [22-24], capillary zone electrophoresis [25] and electrochemical methods [26,27] are available for rosuvastatin analysis in pharmaceuticals either single or combine with other drugs. In chemistry, **triiodide** usually refers to the triiodide ion, I_3^-, see Scheme 2. This anion, one of the polyhalogen ions, is composed of three iodine atoms. It

is formed by combining non-aqueous and aqueous solutions of iodide salts and iodine according to the following equation [28-42]

$$I^- + I_2 \rightarrow I_3^- \quad (1).$$

Scheme 2: Chemical structure of triiodide, I_3^-

In the present work, spectrophotometric determination of rosuvastatin calcium in pure form and pharmaceutical formulations by oxidized it using iodine and formation I_3^- complex in acetonitrile, the first time, was applied.

MATERIALS AND METHODS

Instruments and apparatus

Spectrophotometric measurements was made in PG Instruments Lid model UV-Visible spectrometer T190+ with 0.2 cm quartz cells. A ultrasonic processor model POWERSONIC 405 was used to sonicate the sample solutions. The solution was kept in a thermostat at 30°C. The diluter pipette model DIP-1 (Shimadzu), having 100 µL sample syringe and five continuously adjustable pipettes covering a volume range from 20 to 5000 µL (model PIPTMAN P, GILSON), centrifuge (Centurion Scientific Ltd., Model: K2080-Manufactured in the United Kingdom) were used for preparation of the experimental solutions.

Reagents

Rosuvastatin calcium (98.6%) was supplied by BDR PHARMACEUTICALS INTERNATIONAL PVT. LTD. (INDIA), its purity as rosuvastatin was 94.66%. Iodine (purity 99.8%) of analytical grade and acetonetrile for HPLC were from MERCK.

A stock standard solution of iodine($1x10^{-2}$ mol.L^{-1})

Dissolving 63.58 mg of iodine with acetonitrile into volumetric flask (25 mL) and dilute to mark by acetonitrile.

A stock standard solution of Rosuvastatin calcium

This solution was prepared by dissolving 25.38 mg from RSV_{Ca} in 50 mL acetonitrile ($1x10^{-3}$ mol.L^{-1}). The stock solution was further diluted to obtain ***working solutions*** daily just before use in the ranges of RSV: 2.408, 4.815, 7.223, 9.631, 14.446, 19.262, 24.077, 28.892, 38.523, 48.154, 60.193 and 72.223 µg.mL^{-1} (5, 10, 15, 20, 30, 40, 50, 60, 80, 100, 125 and 150 µmol.L^{-1}) by dilution of the volumes: 0.050, 0.100, 0.150, 0.200, 0.300, 0.400, 0.500, 0.600, 0.800, 1.000, 1.250 and 1.500 mL from stock standard solutions into volumetric flasks (10 mL) content each one 1 mL standard solutions iodine with acetonitrile. All solutions and reagents were prepared with acetonitrile.

Sample preparation

A commercial formulations (as tablets) were used for the analysis of RSV_{Ca} in pure form and its pharmaceutical formulations by oxidized it with iodine and formation I_3^- complex in acetonitrile. The Syrian pharmaceutical formulations were subjected to the analytical procedures:

(1) ***Rosuvastatin*** tablets, **Balsam pharma Co.**, Homs–SYRIA (Mfg. 06/2010, Exp. 06/2014), each tablet contains: 5 mg of RSV.

(2) ***Rosuva*** tablets, **Unipharma**, Damascus–SYRIA(Mfg. 11/2013, Exp. 11/2015), Each tablet contains: 5 mg of RSV.

(3) ***Rosuva*** tablets, **Unipharma**, Damascus–SYRIA(Mfg. 05/2013, Exp. 05/2016), Each tablet contains: 10 mg of RSV.

(4) ***Rosuva*** tablets, **Unipharma**, Damascus–SYRIA(Mfg. 07/2013, Exp. 07/2016), Each tablet contains: 20 mg of RSV.

(5) ***Rosuvastatin***-ElSaad tablets, **ELSaad pharma**, Aleppo–SYRIA, (Mfg. 12/2012, Exp. 12/2016), Each tablet contains: 5 mg of RSV.

(6) ***Rosuvastatin***-ElSaad tablets, **ELSaad pharma**, Aleppo–SYRIA, (Mfg. 4/2012, Exp. 4/2016), Each tablet contains: 10 mg of RSV.

(7) ***Rosuvastatin***-ElSaad tablets, **ELSaad pharma**, Aleppo–SYRIA, (Mfg. 4/2012, Exp. 4/2016), Each tablet contains: 20 mg of RSV.

Stock solutions of pharmaceutical formulations

Three tablets of each studied pharmaceutical formulations were weighted accurately, crushed to a fine powder and mixed well. Equivalent four tenth, two tenth and one tenth the weight of one tablet from pharmaceutical formulations content 5, 10 and 20 mg/tab, respectively, were solved by acetonitrile into volumetric flasks (10 mL) using ultrasonic, mixed well, and transferred to the closed centrifuge tube and centrifuged. Finally, the clear solution is ready to measure. One mL is taken and extends up to 10 ml with acetonitrile, Each of these solutions contents 200 µg.mL^{-1} of RSV.

Working standard addition solutions of pharmaceuticals

These solutions were prepared as the follows: 0.500 mL from stock solutions of pharmaceutical formulations with 0.000, 0.150, 0.300, 0.450 and 0.600 mL from stock solution of rosuvastatin with 1mL standard solutions iodine and diluting to 10 mL with acetonitrile; these solutions content (each one) 10 µg.mL^{-1} of RSV (from pharmaceuticals) plus 7.223, 14.446, 21.669 and 28.892 µg.mL^{-1} of RSV, respectively.

Procedure

A solution containing an appropriate concentrations of rosuvastatin calcium (or working standard addition solutions of pharmaceuticals) and iodine solution ($C_{I2} \geq 10C_{RSV}$, M) in acetonitrile at temperature 50±2°C within 60 min, then wait 20 minutes (until the solution is cooled to room temperature), at $\lambda_{max,1}$= 291 nm or at $\lambda_{max,2}$= 360 nm be ready for spectrophotometric measurement.

RESULTS AND DISCUSSION

The different experimental parameters affecting on the spectrophotometric determination of rosuvastatin calcium through oxidation it by iodine and formation I_3^- complex in acetonitrile were extensively studied in order to determine the optimal conditions for the determination of RSV.

Spectrophotometric results

UV-Vis spectra solutions of RSV_{Ca}, Iodine and I_3^- complex (resulting from the oxidation of RSV_{Ca} by iodine) in acetonitrile were studied. The RSV_{Ca} solutions do not absorb in range 340-600 nm, the λ_{max} at 242 nm (the molar absorptivity ε=$1.8x10^4$ L.mol^{-1}.cm^{-1}). The iodine solutions absorb at 456 nm (ε=830 L.mol^{-1}.cm^{-1}). While complexes solutions of I_3^- have absorption at $\lambda_{max,1}$ = 291 nm and $\lambda_{max,2}$=360 nm (ε_{291}=$4.97x10^4$ L.mol^{-1}.cm^{-1} and ε_{360}=$2.32x10^4$ L.mol^{-1}.cm^{-1}), see Figure 1.

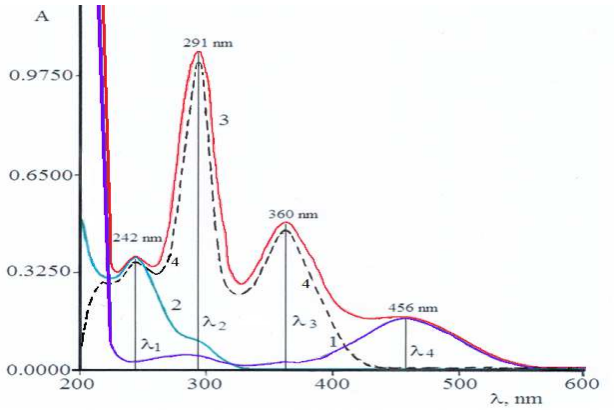
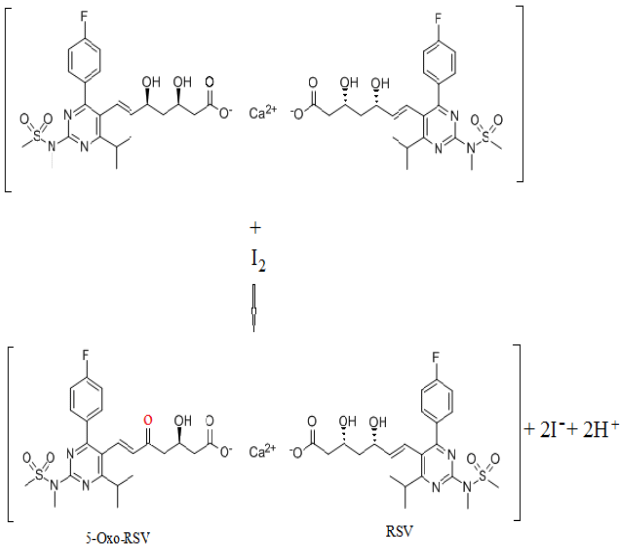


Fig. 1: UV-Vis spectra in acetonitrile of: 1- $1x10^{-3}$mol.L^{-1} of iodine; 2- $1x10^{-4}$ mol.L^{-1} of RSV; 3- $1x10^{-4}$ mol.L^{-1} of RSV with $1x10^{-3}$mol.L^{-1} of iodine, where the complex I_3^- is formed {reagent blank is acetonitrile (1-3) and iodine solution $1x10^{-3}$ mol.L^{-1} (4), ℓ =0.2 cm}.

We suggest that, the reduction of oxidation rosuvastatin calcium by iodine and formation I_3^- complex may take place according to the equations of Scheme 2, as the follows: ***i***- The first step:



(2)

ii- The second step:

$2I^- + 2I_2 \rightarrow 2I_3^-$

iii- The proceeds equation:

$[RSV]_2Ca + 3I_2 \rightarrow$ [5-Oxo-RSV Ca RSV] + $2I_3^-$ +$2H^+$ (3)

Scheme 2: Reduction of oxidation rosuvastatin calcium by iodine and formation I_3^- complex.

Calibration curve

The calibration curves for RSV in pure form through oxidation RSV_{Ca} by iodine and formation I_3^- complex showed excellent linearity over concentration ranges of $5x10^{-6}$ to $1.0x10^{-4}$ $mol.L^{-1}$ (2.408-48.154 $\mu g.mL^{-1}$), see Figures 2 and 3. The spectra characteristics of determination of RSV_{Ca} solutions as the molar absorptivity (ε), λ_{max}, Beer's law, regression equations at $\lambda_{max,1}$=291 nm was y=0.0203x+0.00048 and at $\lambda_{max,2}$=360 nm were y=0.00953x+0.0010; where y=absorbance, x=concentration of RSV in $\mu g.mL^{-1}$ and the correlation coefficient are summarized in Table 1.

Analytical results

Spectrophotometric determination of RSV through oxidation rosuvastatin calcium by iodine and formation I_3^- complex in optimal conditions using calibration curve was applied. The results, which summarized in Table 2, showed that, the determined concentration

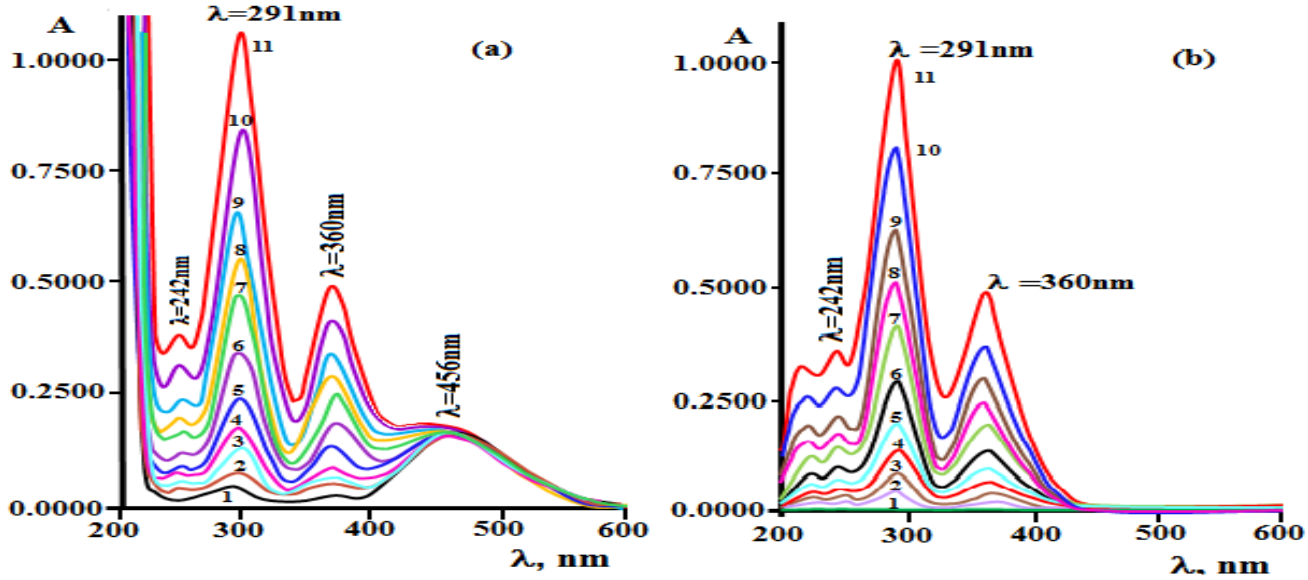


Fig. 2: UV-Vis spectra of $1.0x10^{-3}$ M iodine with RSV at concentrations as the follows: 1- 0.0, 2- $0.5x10^{-5}$; 3- $1.0x10^{-5}$; 4- $1.5x10^{-5}$; 5- $2.0x10^{-5}$; 6- $3.0x10^{-5}$; 7- $4.0x10^{-5}$; 8- $5.0x10^{-5}$; 9- $6.0x10^{-5}$; 10- $8.0x10^{-5}$ and 11- $1.0x10^{-4}$ $mol.L^{-1}$ in acetonitrile { reagent blank: (a) acetonitrile and (b) iodine solution $1.0x10^{-3}$ M in acetonitrile , ℓ =0.2cm}.

of RSV at λ= 291 nm was rectilinear over the range of 2.408 to 48.154 $\mu g.mL^{-1}$ with relative standard deviation (RSD) was not than 3.1%. The limit of detection (LOD) and limit of quantification (LOQ) was found to be 0.25$\mu g.mL^{-1}$ and 0.77$\mu g.mL^{-1}$, respectively. The proposed method was validated statistically and through recovery studies. The method was successfully applied for the determination of RSV in pure form. The results obtained from the proposed method have been compared with the official RP-HPLC method [24] and good agreement was found between them.

Applications

Many applications for the determination of rosuvastatin calcium in some Syrian pharmaceutical preparations with a spectro photometric method through oxidized it with iodine and formation I_3^- complex in acetonitrile according to the optimal conditions were proposed. Regression equations and correlation coefficients were included in Table 3. Standard addition curves for determination of rosuvastatin calcium in different pharmaceutical preparations were used. The standard addition curve of *Rosuva* tablets (Unipharma, 10 mg/tab.) was showed in Figure 4, as an example. The amount (m) of rosuvastatin calcium in one tablet calculated from the following relationship: m = h. m', where: m' is the amount of RSV in tablet calculated according to the following regression equation: y=a.x+b; when y=0; m'=x=b/a=intercept/slope ($\mu g.mL^{-1}$), h conversion factor is equal to 0.5, 1 and 2 for 5, 10 and 20 mg/tab. of RSV. The results of quantitative analysis for RSV in some pharmaceutical preparations were calculated using the standard additions method were summarized in Table 4. The proposed method was simple, economic, accurate and successfully applied to the determination of RSV in pharmaceuticals with average recovery of 95.8 to 104.0%, the results obtained agree well with the contents stated on the labels. The results obtained by this method were validated by RP-HPLC [24].

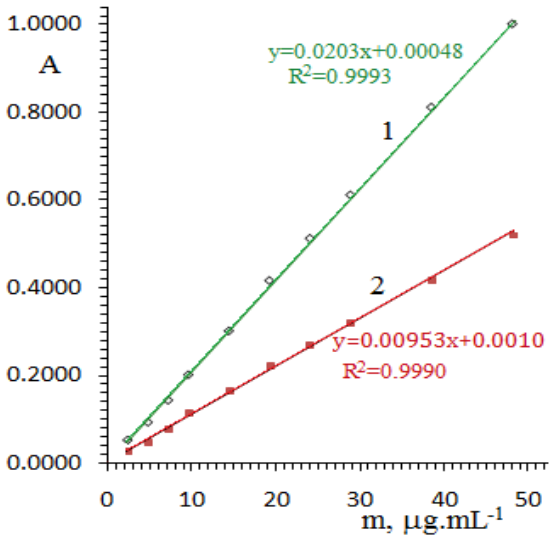


Fig. 3: Calibration curve for determination RSV through oxidation rosuvastatin calcium by iodine and formation I_3^- complex according to optimal conditions at λ_{max}: 1- 291 nm and 2- 360 nm (ℓ = 0.2 cm).

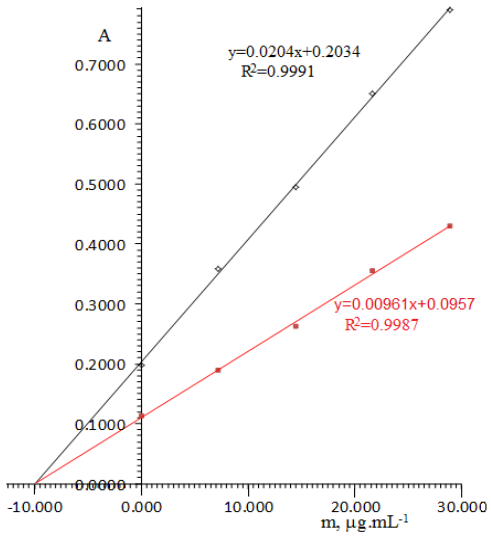


Fig. 4: The standard addition curve for determination of RSV in *Rosuva* tablets (Unipharma, 10 mg/tab.) using spectrophotometric method through oxidation rosuvastatin calcium by iodine and formation I_3^- complex in acetonitrile at $\lambda_{max,1}$=291 nm (1) and at $\lambda_{max,2}$=360 nm (2).

Table 1: The optimum parameters established for spectrophotometric determination of RSV through oxidation rosuvastatin calcium by iodine and formation I_3^- complex in pure and pharmaceuticals.

Parameters	Operating modes
Time of maximum color intensity	60 min
Temperature of solution	50±2°C
C_{I2}:C_{RSV}, M	≥10
Solvent	Acetonitrile
$\lambda_{max,1}$ of complex I_3^-	291 nm
$\lambda_{max,2}$ of complex I_3^-	360 nm
λ_{max} of rosuvastatine	242 nm
Molar absorptivity of complex I_3^- (ε_1)	$4.97x10^4$ L.mol^{-1}.cm^{-1}
Molar absorptivity of complex I_3^- (ε_2)	$2.32x10^4$ L.mol^{-1}.cm^{-1}
Molar absorptivity of RSV (ε_{Psv})	$1.8x10^4$ L.mol^{-1}.cm^{-1}
Working $\lambda_{max,1}$	291 nm
Working $\lambda_{max,2}$	360 nm
ℓ	0.2 cm
Spectra range	200 – 600 nm
Working C_{I2}, mol.L^{-1}	$1x10^{-3}$
Beer's Law Limit, µg.mL^{-1} (at $\lambda_{max,1}$=291 nm)	2.408– 48.154
LOD(3.3SD), µg.mL^{-1}(at $\lambda_{max,1}$=291 nm)	0.25
LOQ (10SD), µg.mL^{-1}(at $\lambda_{max,1}$=291 nm)	0.77
Regression equation at $\lambda_{max,1}$=291 nm:	
Slope	0.0203
Intercept	0.00048
Correlation coefficient (R^2)	0.9993
LOD(3.3SD), µg.mL^{-1}(at $\lambda_{max,2}$=360 nm)	0.28
LOQ (10SD), µg.mL^{-1}(at $\lambda_{max,2}$=360 nm)	0.85
Regression equation at $\lambda_{max,2}$=360 nm:	
Slope	0.00953
Intercept	0.0010
Correlation coefficient (R^2)	0.9990
RSD% at $\lambda_{max,1}$=291 nm	3.1
RSD% at $\lambda_{max,2}$=360 nm	3.6

Table 2: Spectrophotometric determination of RSV through oxidation rosuvastatin calcium by iodine and formation I_3^- complex in optimal conditions using calibration curve in acetonitrile.

X_i, µg.mL^{-1} (taken)	λmax, nm	$*\overline{X}$, µg.mL^{-1} (found)	SD, µg.mL^{-1}	$\frac{SD}{\sqrt{n}}$, µg.mL^{-1}	$\bar{x} \pm \frac{t.SD}{\sqrt{n}}$ µg.mL^{-1}	RSD %
2.408	291	2.47	0.077	0.034	2.47± 0.096	3.1
	360	2.37	0.085	0.038	2.37± 0.106	3.6
4.815	291	4.71	0.15	0.062	4.71± 0.17	3.1
	360	4.67	0.17	0.075	4.64± 0.21	3.6
7.223	291	6.97	0.21	0.094	6.97± 0.26	3.0
	360	7.18	0. 25	0.11	7.18± 0.31	3.5
9.631	291	9.83	0.29	0.13	9.83± 0.36	2.9
	360	9.55	0.33	0.15	9.55± 0.41	3.5
14.446	291	14.75	0.41	0.19	14.75± 0.53	2.8
	360	14.45	0.49	0.22	14.45± 0.61	3.4
19.262	291	20.44	0.55	0.25	20.44± 0.69	2.7
	360	19.45	0.64	0.29	19.45± 0.80	3.3
24.077	291	25.17	0.63	0.28	25.17± 0.78	2.5
	360	24.45	0.78	0.35	24.45± 0.97	3.2
28.892	291	29.56	0.71	0.32	29.56± 0.89	2.4
	360	28.55	0.89	0.40	28.55± 1.11	3.1
38.523	291	39.90	0.92	0.41	39.90± 1.14	2.3
	360	39.00	1.17	0.52	39.00± 1.44	3.0
48.154	291	48.16	1.06	0.47	48.16± 1.30	2.2
	360	48.09	1.49	0.67	48.09± 1.86	3.1

* n=5, t= 2.776

Table 3: Regression equations and correlation coefficients for determination of RSV in some Syrian pharmaceutical preparations using spectrophotometric method through oxidation rosuvastatin calcium by iodine and formation I_3^- complex in acetonitrile at $\lambda_{max,1}$=291 nm.

Pharmaceutical preparations	RSV In tab., mg	Operating modes			
		Regression equations*	Correlation coefficients	m', µg.mL^{-1}	Amount of RSV (m), mg/tab.
Rosuvastatin tablets, Balsam pharma Co.	5	y=0.0201x+0.1930	R^2=0.9986	9.60	$m_{RSV/tab.}$=0.5m'=4.80
Rosuva tablets, Unipharma	5	y=0.0205x+0.1952	R^2=0.9989	9.52	$m_{RSV/tab.}$=0.5m'=4.76
	10	y=0.0204x+0.2034	R^2=0.9991	9.97	$m_{RSV/tab.}$=1m'=9.97
	20	y=0.0200x+0.2040	R^2=0.9991	10.20	$m_{RSV/tab.}$=2m'=20.40
Rosuvastatin-ElSaad tablets, ELSaad pharma	5	y=0.0198x+0.1897	R^2=0.9989	9.58	$m_{RSV/tab.}$=0.5m'=4.79
	10	y=0.0201x+0.2004	R^2=0.9990	9.97	$m_{RSV/tab.}$=1m'=9.97
	20	y=0.0199x+0.2070	R^2=0.9991	10.40	$m_{RSV/tab.}$=2m'=20.80

*****y= n A; x= concentration of rosuvastatin (µg.mL^{-1})= m' = intercept/slope.

Table 4: Determination of RSV in some Syrian pharmaceutical preparations using spectrophotometric method through oxidation rosuvastatin calcium by iodine and formation I_3^- complex in acetonitrile at $\lambda_{max,1}$=291 nm.

Commercial name	Contents, mg/tab.	$*\overline{X}$, mg/tab.	RSD%	Recovery %
Rosuvastatin tablets, Balsam pharma co.	5	4.80	4.1	96.0
Rosuva tablets, Unipharma	5	4.76	4.1	95.1
	10	9.97	3.8	99.7
	20	20.40	3.7	102.0
Rosuvastatin-ElSaad tablets, ELSaad pharma	5	4.79	4.1	95.8
	10	9.97	3.7	99.7
	20	20.80	3.7	104.0

* n=5

CONCLUSION

A simple, sensitive and economical spectrophotometric method is developed for the determination of rosuvastatin calcium in pure form and its pharmaceutical formulations in acetonitrile. This method is based on the oxidation of rosuvastatin calcium by iodine and formation I_3^- complex. The formed complex was measured at 291 and 360 nm against the reagent blank prepared in the same manner. The optimum experimental parameters are selected. Beer's law is valid within a concentration range of 2.408-48.154 µg.mL^{-1}. The developed method is applied for the determination of rosuvastatin calcium in pure and its pharmaceutical formulations without any interference from excipients with average recovery of 95.8 to 104.0%, the results obtained agree well with the contents stated on the labels. The results obtained by this method were validated by RP-HPLC [24].

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