

## Spectrophotometric Determination of Atorvastatin Calcium and Rosuvastatin Calcium in Bulk and Dosage Form Using P-Dimethylaminobenzaldehyde

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### Abstract

A simple and sensitive spectrophotometric method is described for determination of atorvastatin calcium and rosuvastatin calcium in bulk and tablet forms. The method depends on the formation of colored chromogen between atorvastatin calcium and rosuvastatin calcium and p-dimethylaminobenzaldehyde (PDMAB) in acidic conditions and the reaction mixture exhibits maximum absorbance at  $\lambda_{max}$  540 and 570 nm for atorvastatin calcium and rosuvastatin calcium, respectively. Under the indicated conditions, this method was linear over the concentration range of 20-160  $\mu\text{g/ml}$  and 2-16  $\mu\text{g/ml}$  for atorvastatin calcium and rosuvastatin calcium, respectively. The method was statistically applied for the determination of drugs in both bulk and tablet forms. Results were compared with reference methods and no significant difference was obtained.

**Keywords:** Spectrophotometric; Chromogen; Atorvastatin; Rosuvastatin; Calcium; p-Dimethylaminobenzaldehyde; Acidic condition

### Introduction

Atorvastatin Calcium is chemically, [(3R,5R)-7-[3-(phenyl carbamoyl)-5-(4-fluorophenyl)-2-isopropyl 4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, calcium salt] Figure 1. It has a molecular formula of  $\text{C}_{66}\text{H}_{68}\text{CaF}_2\text{N}_4\text{O}_{10}$  and a molecular weight of 1155.34 g/mol [1]. It acts by inhibiting the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-co A) reductase [2]. Several analytical methods, including spectrophotometric methods [3-7], spectrofluorometric [8], chromatographic methods [9-16] and potentiometric method [17] have already been reported for its determination, either alone or in combination with other drugs. Rosuvastatin calcium is chemically, [(E) - (3R, 5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[(methyl (methane sulfonyl amino)] pyrimidin-5-yl)-3, 5-dihydroxyhepten-6-oic acid, calcium salt] Figure 1. It has a molecular formula of  $\text{C}_{44}\text{H}_{54}\text{CaF}_2\text{N}_6\text{O}_{12}\text{S}_2$  and a molecular weight of 1001.14 g/mol [18]. It is a competitive inhibitor of HMG-Co A reductase. It catalyses the reduction of 3-hydroxyl-3-methylglutaryl coenzyme A to mevalonate, which is a rate limiting step in hepatic cholesterol synthesis [19]. Several analytical methods, including spectrophotometric methods [20-24], chemometric methods [25] and chromatographic methods [26-30] have already been reported for its determination, either alone or in combination with other drugs. P-dimethylaminobenzaldehyde has been utilized as a chromogenic reagent for the spectrophotometric determination of a few compounds of pharmaceutical interest such as olanzapine [31], Eflornithine hydrochloride [32] and Benzocaine [33]. In this study, the proposed method has many advantages over other analytical methods due to its rapidity, environmental safety, highly sensitive, having good resolution, reproducible and cost effective.

### Material and Method

#### Apparatus

Labomed<sup>®</sup> Spectro UV-VIS Double Beam (UVD-2950) Spectrophotometer with matched 1 cm quartz cells connected to Windows compatible computer using UV Win 5 Software v5.0.5.

#### Material and reagents

All chemicals used are of analytical reagent grade.

Atorvastatin calcium was provided by Eipico Company, Egypt, 99.06% Purity. Ator<sup>®</sup> tablets labeled to contain 10 mg of atorvastatin calcium. Batch No. 1302776 (Eipico, Egypt).

Rosuvastatin calcium was provided by Hikma Company, Egypt, 99.5% Purity. Suvikan<sup>®</sup> tablets labelled to contain 10 mg of rosuvastatin calcium. Batch No. 017 (Hikma Pharmaceutical).

P-dimethylaminobenzaldehyde was purchased from (Fisher chemical).

The solution was prepared by dissolving 2 g of PDMAB in case of atorvastatin calcium and 0.1 g in case of rosuvastatin calcium in 100 ml absolute methanol (99.8%).

Sulphuric acid (97-99%) was purchased from El Nasr Pharmaceutical Chemicals Company, batch No.2354117).

### General Procedures

#### Preparation of standard drug solutions

Atorvastatin calcium stock standard solution equivalent to 2 mg/ml of atorvastatin calcium was prepared by dissolving 200 mg of pure drug in 20 ml methanol and diluting to 100 ml in calibrated flask with methanol. Stock solution of rosuvastatin calcium equivalent to 0.2 mg/ml was prepared by dissolving 20 mg of the pure drug in 20 ml acetone and diluting to 100 ml in calibrated flask with acetone.

### Procedures

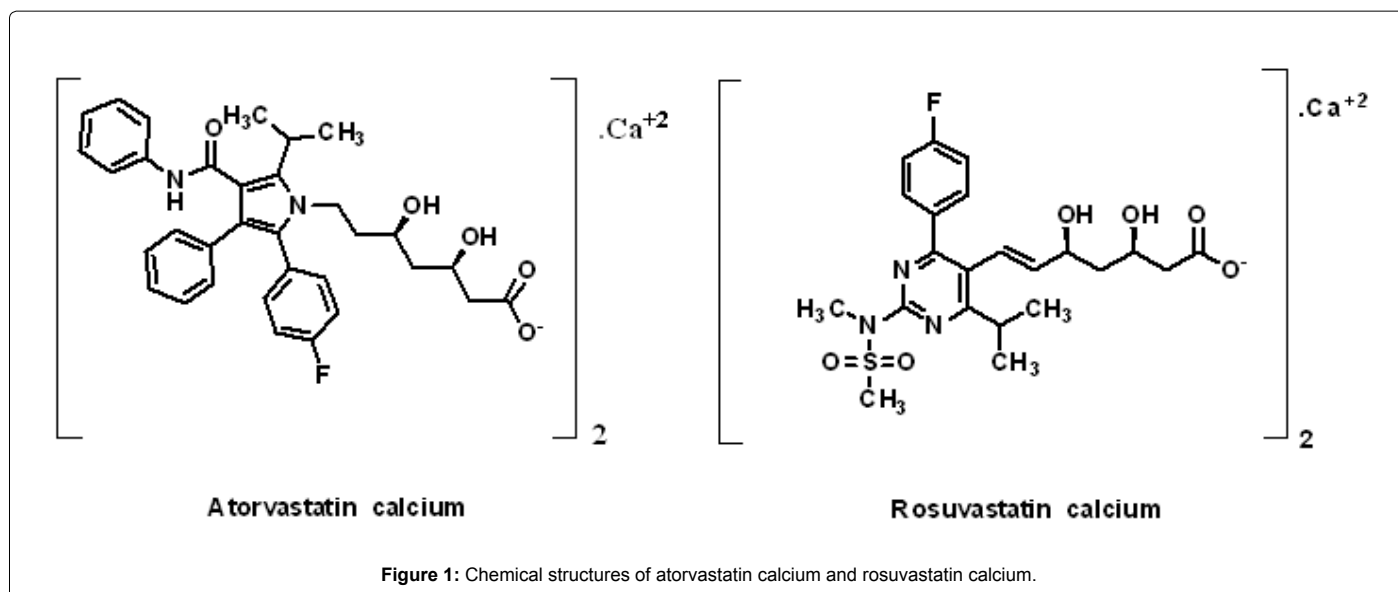
To a series of 10 ml calibrated flasks, an increasing volume covering the concentration range 20-160  $\mu\text{g/ml}$  of atorvastatin calcium solution

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and 2-16  $\mu\text{g/ml}$  of rosuvastatin calcium were transferred, followed by addition of 1.6 ml of 2% w/v PDMAB in case of atorvastatin calcium and 0.8 ml of 0.1% w/v PDMAB in case of rosuvastatin calcium and 2 ml of concentrated sulphuric acid were added for both drugs, while cooling under a tap with constant shaking then kept aside 10 min for colour development, finally the volume was brought up to the mark with absolute methanol for atorvastatin calcium and with acetone for rosuvastatin calcium. The absorbance was measured at 540 and 570 nm for atorvastatin calcium and rosuvastatin calcium respectively versus reagent blank Figure 2. A calibration graph was prepared by plotting the measured absorbance versus concentration. The concentration of the unknown was read from the calibration graph or computed from the regression equation derived using Beer's law data.

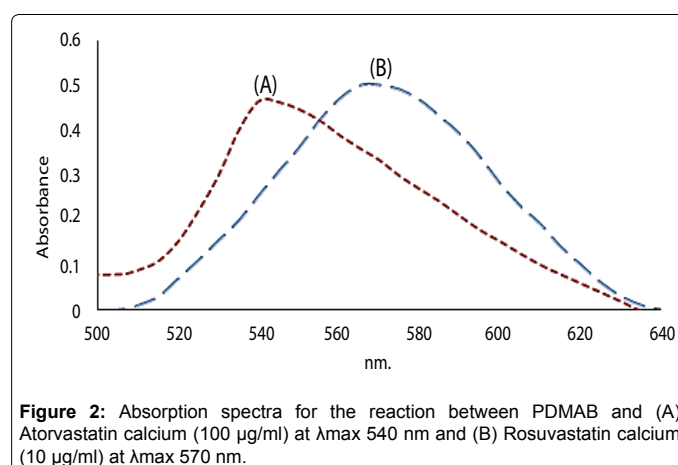
## Pharmaceutical Preparation

### Ator<sup>®</sup> tablets

Twenty tablets of Ator<sup>®</sup> tablets were weighted and powdered. An accurately amounts of the powder equivalent to 200 mg of atorvastatin calcium were dissolved in 100 ml of methanol and shaken for about 5-10 min, filtered through whatman filter paper to remove the insoluble matter. The residue was washed with 10 ml portions of methanol three times then collected, completed with methanol to 100 ml in a volumetric flask. Aliquots from these solutions equivalent to those in authentic samples were used for the application of the proposed methods applying standard addition techniques.

### Suvikan<sup>®</sup> tablets

Twenty tablets of Suvikan<sup>®</sup> tablets were weighted and finely powdered. An accurately weighed amount of the powder equivalent to 20 mg of rosuvastatin calcium were dissolved in 100 ml acetone and stirred for about 5-10 min, filtered through whatman filter paper to remove the insoluble matter. The residue was washed with 10 ml portions of acetone three times. The solution was filtered through whatman filter paper to remove the insoluble matter then collected and completed with acetone to 100 ml in a volumetric flask. Aliquots from these solutions equivalent to those in authentic samples were used for the application of the proposed methods applying standard addition techniques.



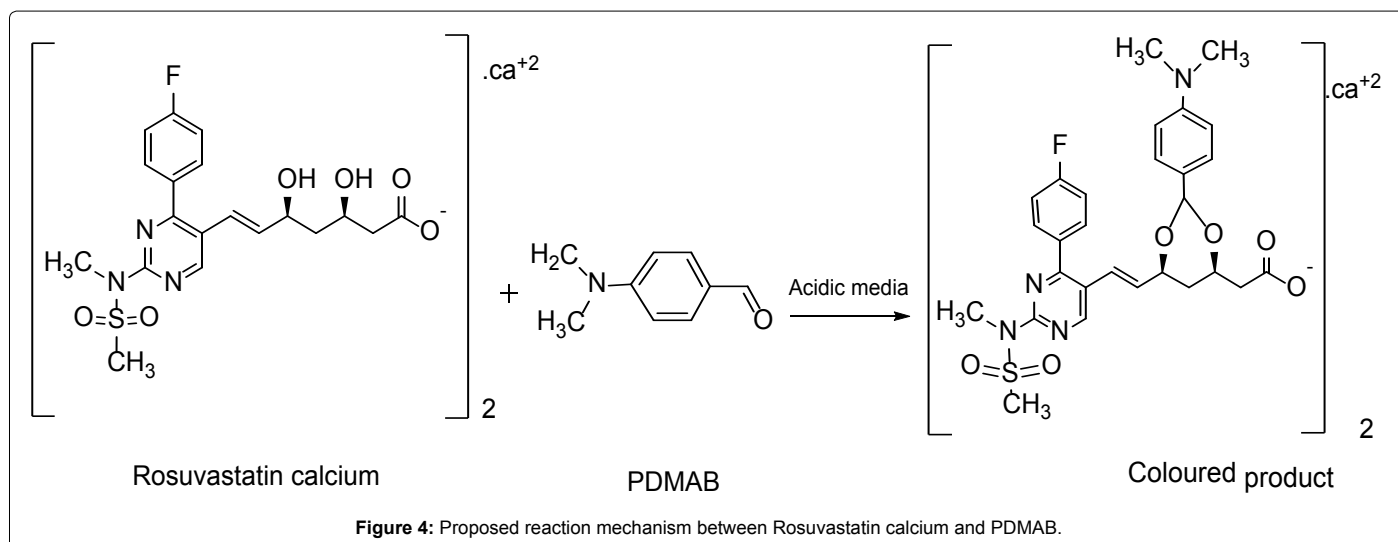
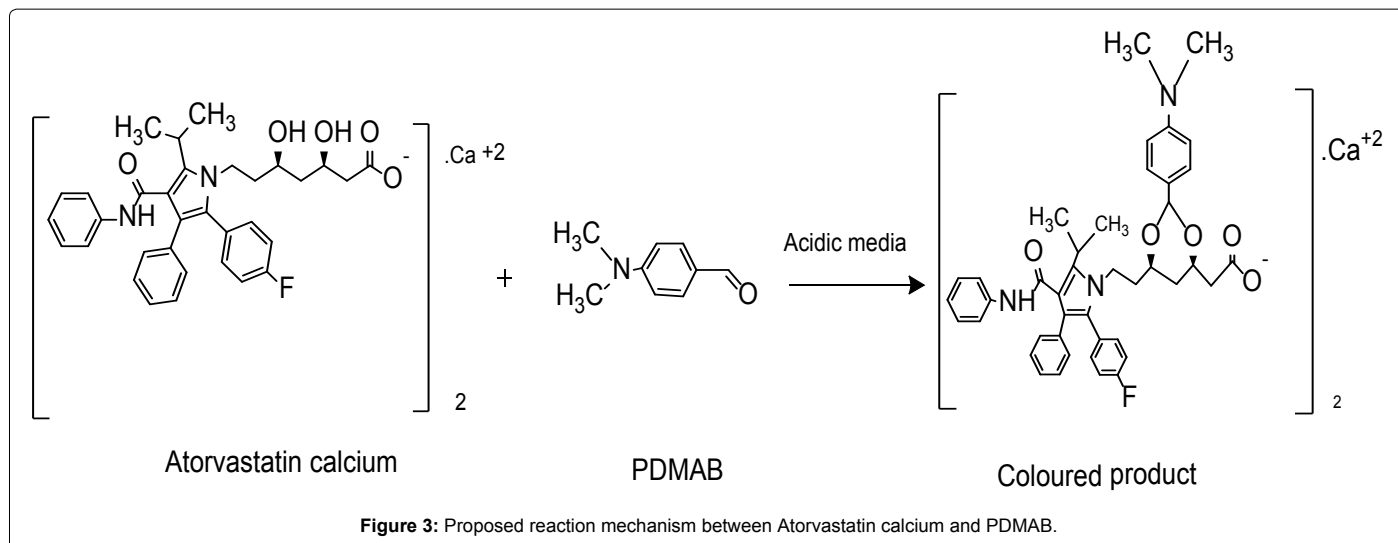
## Results and Discussion

Acetalisation is the organic reaction that involves the formation of an acetal (or ketal) through the nucleophilic addition of an alcohol to an aldehyde or ketone. First hemiacetal molecule is formed then it's hydroxyl group becomes protonated and is lost as water, the carbocation that is produced is then rapidly attack by another molecule of alcohol. Loss of the proton from the attacked alcohol gives the acetal [34,35]. The proposed method is based on the formation of acetal between the aldehyde group of PDMAB and hydroxyl groups of atorvastatin calcium or rosuvastatin calcium. The absorption spectrum of the coloured chromogen formed between atorvastatin calcium and rosuvastatin calcium and PDMAB was recorded at 540 and 570 nm respectively.

The most probable mechanisms for the formation of Acetal between drugs and PDMAB is presented in Figures 3 and 4 [36-38].

## Study of the Experimental Parameters

The different experimental parameters affecting the development of the reaction products were carefully studied and optimized. Such factors were changed individually while others were kept constant.



### Effect of PDMAB volume and concentration

The effect of PDMAB on the sensitivity of the reaction was studied. It was observed that when 0.5-2 ml of 2% and 0.1% (w/v) was examined, 1.6 and 0.8 ml PDMAB gave maximum colored chromogen in case of atorvastatin calcium and rosuvastatin calcium respectively (Figures 5 and 6).

### Effect of acid volume

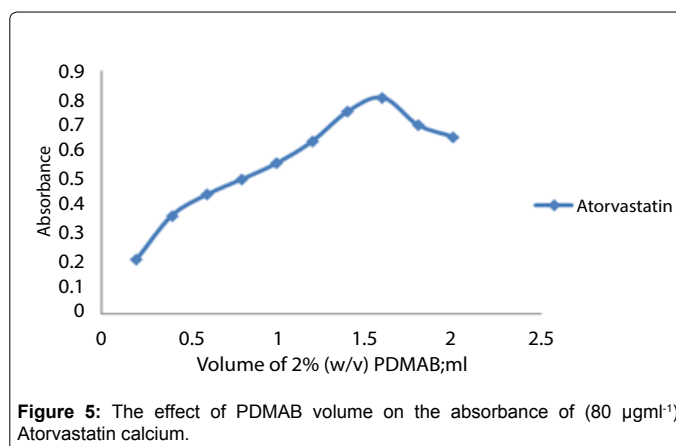
The reaction proceeds very slowly in dilute acid medium, thus concentrated sulphuric acid was used. The intensity of the colored product was found to be maximum on using 2 ml of sulphuric acid (Figure 7).

### Stoichiometry of the Reaction

The molar ratio of the reagent and the two drugs in the reaction was studied by using the continuous variation method (Job's method). The molar ratio was found to be 1:2 (drug: reagent) as seen in Figure 8.

### Method Validation

The validity of the proposed method was tested regarding linearity, range, limits of detection, limits of quantification, accuracy, precision, robustness and specificity according to ICH recommendations [36].



### Linearity and Range

The calibration graphs obtained by plotting the values of the absorbance versus the final Concentrations (µg/ml) were found to be rectilinear over the concentration ranges cited in the Table 1 and Figure 9.

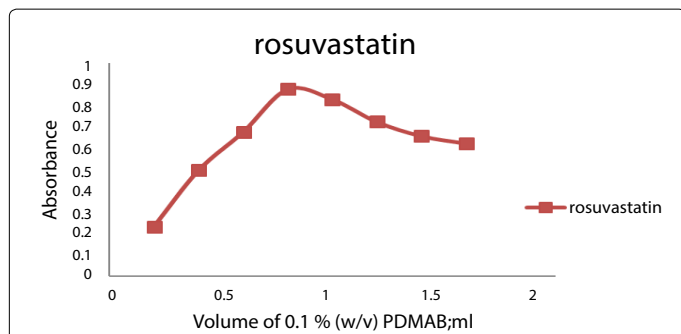


Figure 6: The effect of PDMAB volume on the absorbance of (8 µgml<sup>-1</sup>) Rosuvastatin calcium.

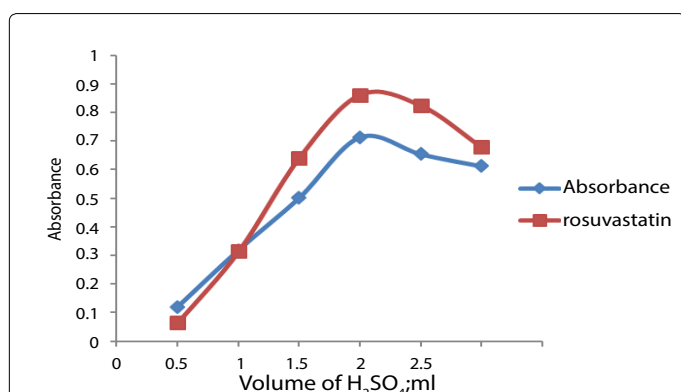


Figure 7: The effect of acid volume on the absorbance of (80 and 8 µg/ml) Atorvastatin calcium and Rosuvastatin calcium respectively.

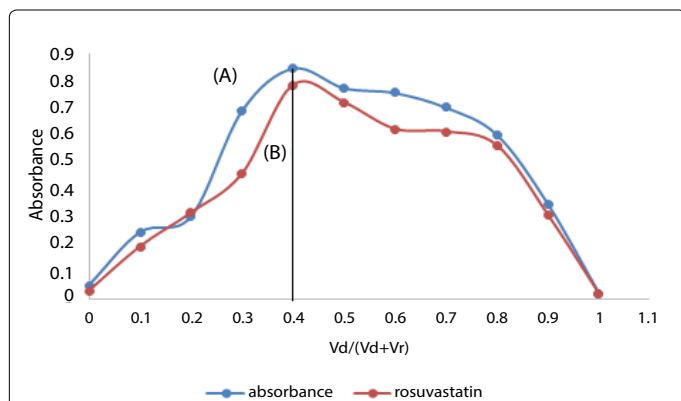


Figure 8: Continuous variation plots for the reaction between: (A)  $5 \times 10^{-2}$  M of PDMAB and  $5 \times 10^{-2}$  M of Atorvastatin calcium and (B)  $5 \times 10^{-3}$  M of PDMAB and  $5 \times 10^{-3}$  M of Rosuvastatin calcium.

The calibration graph is described by the equation:  $Y = a + bX$

(Where Y= absorbance, a=intercept, b=slope and X=concentration in µg/ml).

Correlation coefficient, intercept and slope for the calibration data are summarized in Table 1.

### Limits of Detection and Limits of Quantification

The limit of detection (LOD) was determined by evaluating the lowest concentrations of the analyte that can be detected according to the following equation:  $LOD = 3.3 S/K$ . The limit of quantification (LOQ)

was determined by establishing the lowest concentrations that can be quantified according to the following equation:  $LOQ = 10 S/K$  Where S is the standard deviation of the three replicate determination values under the same conditions as for the sample analysis in the absence of analyte and K is the sensitivity, namely, the slope of calibration graph. The results are summarized in Table 2.

### Accuracy and Precision

Accuracy was evaluated as percentage relative error between the measured concentration for atorvastatin calcium and rosuvastatin calcium. The accuracy of the proposed methods was checked by performing recovery experiments through standard addition technique. The results are shown in Table 3; show that the accuracy is good. The precision of the method was calculated in term of intermediate precision (intraday and inter-day).

Three different concentrations five times of atorvastatin calcium and rosuvastatin calcium were analyzed during the same day (intra-day precision) and five consecutive days (inter-day precision). The standard analytical errors, relative standard deviations (RSD) and recoveries obtained by the proposed method were found to be acceptable. The results are summarized in Table 4.

### Robustness

Robustness was tested by making small incremental change in concentrated sulphuric acid concentration ( $\pm 0.05$  ml) and change in the volume of the PDMAB ( $\pm 0.05$  ml) were studied on the percentage recovery of drugs, Table 5.

### Analysis of Pharmaceutical Preparations

The proposed methods were applied to the analysis of the drug in dosage forms and the results were statistically compared with reference methods [39,40] by calculating Student's t- and F-values. The evaluated t-and F-values were less than the tabulated values at the 95% confidence level and the results are listed in Table 6 showing that there is no statistical significance difference between the proposed and reference methods.

### Conclusion

The proposed method requires sulphuric acid and PDMAB as reagents which are readily available in any analytical laboratory, inexpensive, have excellent shelf life, no pH adjustment is required and the procedures do not involve any critical reaction conditions or tedious sample preparation. Moreover, the proposed method is accurate and

Parameters	Atorvastatin calcium	Rosuvastatin calcium
$\lambda_{max}$ , nm	540	570
Volume of C.H <sub>2</sub> SO <sub>4</sub> (ml)	2	2
Reagent Conc. % w/v	2	0.1
Reagent volume (ml)	1.6	0.8
Temperature (°C)	25 ± 5°C	25 ± 5°C
Diluting solvent	Methanol	Acetone
Beer's law limits (µg ml <sup>-1</sup> )	20-160	Feb-16
Regression equation	Slope (b)	0.0049
	Intercept (a)	0.0249
Correlation coefficient	0.9999	0.9995

\*A=a+bC where A is absorbance, C is the concentration of the drug in µg/ml

Table 1: Analytical parameters and regression equation for spectrophotometric determination of Atorvastatin calcium and Rosuvastatin calcium through the proposed method using PDMAB.

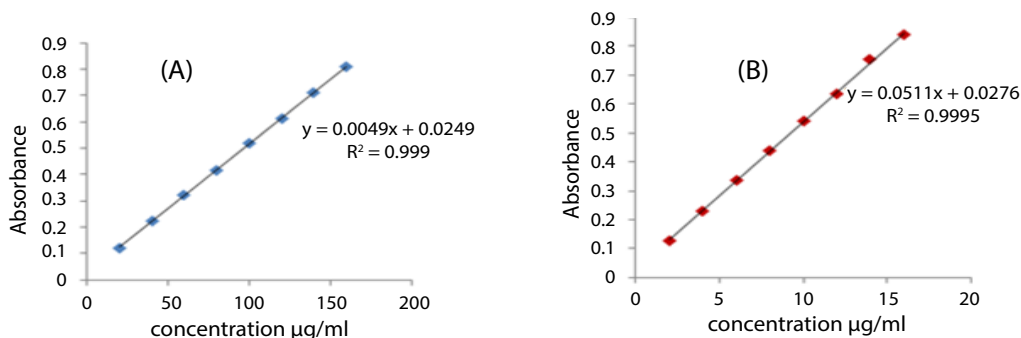


Figure 9: Calibration curve for the reaction between PDMAb and Atorvastatin calcium and Rosuvastatin calcium at  $\lambda_{max}$  540 nm and 570 nm, respectively.

Parameters	Atorvastatin calcium			Rosuvastatin calcium		
	Conc. taken $\mu\text{g/ml}$	Conc. found	Recovery %	Conc. taken $\mu\text{g/ml}$	Conc. found $\mu\text{g/ml}$	Recovery %
	20	19.8163	99.0816	2	1.96478	98.2388
	40	40.0204	100.051	4	3.98043	99.51076
	60	60.4286	100.714	6	6.015655	100.2609
	80	79.8163	99.7704	8	8.050881	100.636
	100	100.225	100.225	10	10.04697	100.4697
	120	119.408	99.5068	12	11.88649	99.0541
	140	139.612	99.723	14	14.21526	101.5376
	160	160.429	100.268	16	15.85909	99.11937
Mean <sup>*</sup>			99.92			99.85
N			8			8
SD			0.5066			1.062
RSD			0.507			1.064
SE			0.17914			0.375
Variance			0.2566			1.128
LOD ( $\mu\text{gml}^{-1}$ )			5.66966			0.5377
LOQ ( $\mu\text{gml}^{-1}$ )			18.8989			1.7923
Sandell's sensitivity( $\mu\text{gml}^{-1}$ per 0.001A)			0.02428			0.0027
Apparent Molar absorptivity <sup>**</sup> L Mol <sup>-1</sup> cm <sup>-1</sup>			6145.17			55776.9

\*Mean of three different experiments.

\*\* Calculated in the basis of molecular weight of the drug.

Table 2: Statistical data for the reaction of Atorvastatin calcium and Rosuvastatin calcium with PDMAb.

	Ator <sup>®</sup> tablets				Suvikan <sup>®</sup> tablet			
	Added from pure drug ( $\mu\text{g/ml}$ )	Taken from Ator tablet ( $\mu\text{g/ml}$ )	Conc. found $\mu\text{g/ml}$	Recovery* %	Added from pure drug ( $\mu\text{g/ml}$ )	Taken from suvikan tablet( $\mu\text{g/ml}$ )	Conc. found $\mu\text{g/ml}$	Recovery* %
	40	0	39.4286	98.5714	4	0	3.98837	99.7093
	40	20	60.449	100.748	4	2	6.03156	100.526
	40	40	79.6326	99.5408	4	4	7.94186	99.2732
	40	60	100.041	100.041	4	6	10.0183	100.183
	40	80	120.245	100.204	4	8	12.0947	100.789
					4	10	13.9385	99.561
Mean*				99.76				100.007
N				5				6
S.D.				0.7499				0.589
R.S.D				0.7517				0.5895
V				0.56245				0.347
S.E				0.3062				0.241

\*Mean of three different experiments.

Table 3: Application of standard addition technique for the determination of Ator<sup>®</sup> and suvikan<sup>®</sup> tablets form through reaction with PDMAb.

Item	Conc µg/ml	Intraday		Inter-day	
		mean ± SD	RSD	mean± SD	RSD
Atorvastatin calcium	40 µg/ml	100.39 ± 1.559	1.553	100.76 ± 1.229	1.219
	80 µg/ml	100.195 ± 0.966	0.964	99.82 ± 1.390	1.393
	120 µg/ml	100.02 ± 1.19	1.19	99.643 ± 1.22	1.23
Rosuvastatin calcium	4 µg/ml	99.64 ± 1.72	1.724	99.58 ± 1.40	1.41
	8 µg/ml	99.71 ± 1.255	1.258	99.58 ± 1.25	1.26
	12 µg/ml	99.02 ± 0.978	0.988	99.09 ± 0.778	0.786

**Table 4:** Results of the intraday and inter-day precision for the determination of Atorvastatin calcium and Rosuvastatin calcium using PDMAB.

Robustness		
Percent (%) of recovery ± SD		
Rosuvastatin calcium	Atorvastatin calcium	Item
99.81 ± 0.991	100.62 ± 0.534	PDMAB+0.05 ml
99.79 ± 1.05	99.73 ± 1.335	PDMAB-0.05 ml
99.80 ± 0.995	100.06 ± 0.456	H2SO4+0.05 ml
99.77 ± 1.17	99.31 ± 1.02	H2SO4+0.05 ml

**Table 5:** Results of the robustness for the determination of Atorvastatin calcium and Rosuvastatin calcium using PDMAB method.

Statistics	Ator® tablet		Suvikan® tablet	
	Reference method [37]	Proposed method	Reference method [38]	Proposed method
Mean recovery' ± SD	99.82 ± 1.05	99.76 ± 0.7499	99.9 ± 0.455	100.007 ± 0.589
N	5	5	6	6
Variance	1.1025	0.56245	0.207	0.347
t-test**		0.104 (2.306) a		0.352 (2.228)a
F-ratio**		1.962 (6.388) b		1.676 (5.050)b

\* Average of three experiments, a and b are Theoretical Student t-values and F-ratio at p=0.05.

**Table 6:** Statistical data for the determination of pharmaceutical tablets Ator® and Suvikan® through the proposed methods using PDMAB compared with the reference methods.

precise as indicated by good recoveries of the drugs and low RSD values. The recovery percentage obtained by the proposed method is between 98.12% and 101.8%, within the acceptance level of 95% to 105%. The proposed method could be applied for routine analysis and in quality control laboratories for quantitative determination of the cited drugs in the pure and dosage forms.

#### Acknowledgment

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