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Spectrophotometric Estimation of Rosuvastatin, Simvastatin and Olmesartan in Bulk and Dosage Forms Using Bromatometric Method

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Abstract: **Background:** A simple and sensitive spectrophotometric method is described for determination of rosuvastatin, simvastatin and olmesartan in bulk and dosage forms using bromate-bromide and methyl orange as reagents.

Material and methods: Drugs are treated with known excess of insitu generated bromine and residual un-reacted bromine is determined by treating with fixed amount of methyl orange then measuring absorbance at 510 nm. The amount of bromine consumed corresponds to the amount of each drug reacted. Various analytical parameters have been evaluated such as effect of acidity, bromate-bromide volume and time on the absorption and the results were validated according to ICH guidelines.

Results: Beer's law was obeyed in the range of 6–11 µg/mL for rosuvastatin, 1–3.50 µg/mL for simvastatin and 2–7 µg/mL for olmesartan.

Conclusions: The method was satisfactory applied for the determination of drugs in both bulk and pharmaceutical forms and results were compared statistically with reference methods.

Keywords: Rosuvastatin, Simvastatin, Olmesartan, Bromate-bromide, Methyl Orange.

INTRODUCTION

Atherosclerosis is a disease in which plaque accumulate inside arteries. Arteries are blood vessels that carry oxygen-rich blood to the heart and other body organs. Plaque may be consisting of fat, cholesterol, calcium, or other substances found in the blood. Over time, plaque narrows and hardens the arteries and this limits the flow of oxygen-rich blood to the remaining body organs. Atherosclerosis can lead to serious problems, including heart attack, stroke, or even death [1].

Rosuvastatin (ROS) and Simvastatin (SIM) (Figure 1) are used to lower "bad" cholesterol and fats (such as LDL, triglycerides) and raise "good" cholesterol (HDL) in the blood. It belongs to a group of drugs known as "statins" which act through reducing the amount of cholesterol made by the liver. Lowering "bad" cholesterol and triglycerides and raising "good" cholesterol decreases the risk of heart disease and helps to prevent strokes and heart attacks [2].

Hypertension is another name for high blood pressure which leads to severe complications of heart disease, stroke, or death. The pressure depends on the co-ordination between work being done by the heart and the resistance of the blood vessels. The World Health Organization (WHO) suggests that the growth of the processed food industry has impacted the amount of salt in diets worldwide, and that this plays an important role in raising hypertension level. Olmesartan (OLM) (Figure 1) is used to treat high blood pressure as it belongs to a class of drugs called angiotensin receptor blockers (ARBs) which work

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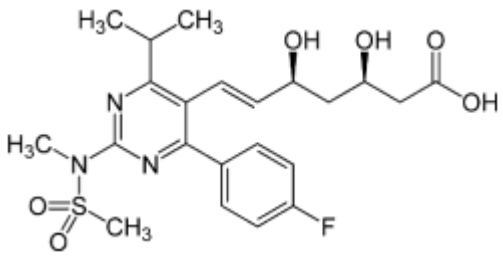
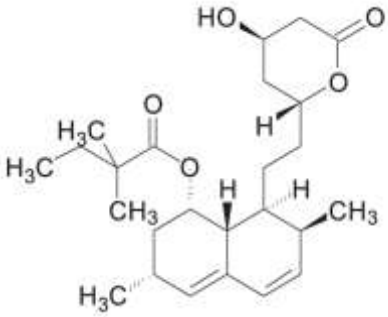
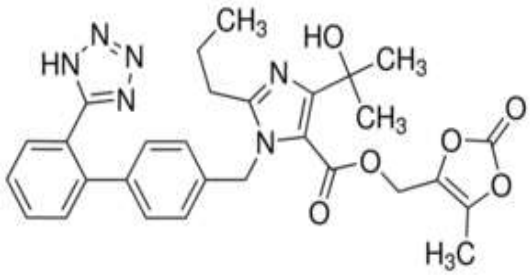
by relaxing blood vessels so that blood can flow more easily. However, there is a synergistic vascular protective effect between statins and ARBs if combined together [3].



ROS



SIM



OLM

Figure 1: Chemical structures of rosuvastatin (ROS), simvastatin (SIM) and olmesartan (OLM).

Several spectrophotometric and UPLC methods had been developed for determination of these drugs individually or in combination with other drugs [4-28]. However, several reported visible spectrophotometric methods suffered from some disadvantages such as poor sensitivity, complicated experimental setup and meticulous control of experimental variables. To the best of our knowledge, there is no reported spectrophotometric method for the determination of these three drugs using bromate-bromide reagent. As such, the proposed method was found to be unique, accurate, very sensitive, reproducible, and consistent.

EXPERIMENTAL

1. Apparatus

Labomed® 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.

2. Materials and Reagents

All solvents and reagents were of analytical grade and double distilled water was used throughout the work. **Rosuvastatin**, **Simvastatin** (El Debeiky for Pharmaceutical Industries, Obour, Egypt) and **Olmesartan** (Deltapharma, 10th of Ramadan, Egypt) standard solutions of 100 µg/mL were prepared by dissolving 10 mg of each pure drug in 100 mL bi-distilled water. **5 M HCl** (El-Nasr Chemicals, Egypt) was prepared by diluting 225 mL of concentrated HCl (36%) with bi-distilled water to 500 mL. **Methyl Orange** (Universal Fine Chemicals, India) standard solution of 60 µg/mL was dissolved in 20 mL methanol then completed to 100 mL with bi-distilled water (stable for 2 weeks at least). **Bromate-Bromide** stock solution of 1 mg/mL was prepared by dissolving 0.10 gm of potassium bromate (Winlab, England) and 1 gm of potassium bromide (Winlab, England) in 100 mL bi-distilled water (stable for 10 days at least). Working solution (12.5 µg/ml) was freshly prepared daily by diluting 1.25 mL of stock solution to 100 mL with bi-distilled water.

3. Pharmaceutical Preparations

The following available pharmaceutical preparations were analyzed; **Novistoric®** tablets labeled to contain 10 mg rosuvastatin per tablet (Future pharmaceutical industries (fpi), Egypt), **Zocor®** tablets

labeled to contain 40 mg simvastatin per tablet (MSD, Egypt) and **Erastapex®** tablets labeled to contain 20 mg olmesartan per tablet (Multi Apex pharma, Egypt).

4. Procedures

- **General Spectrophotometric Procedure and Construction of Calibration Curves**

To 0.8 mL bromate-bromide working solution in 10 mL volumetric flasks, add 0.6 – 1.1 mL *(in case of ROS)*, 0.1 – 0.35 mL *(in case of SIM)* and 0.2 – 0.7 mL (*in case of OLM)* drug solution then acidify using 0.2 mL 5 M HCl, close flasks and stand for 2 minutes (*in case of ROS and SIM)* and 35 minutes (*in case of OLM*), add 1 mL dye working solution and stand for 2 minutes then complete to mark with bi-distilled water and measure absorbance against reagent blank similarly prepared without drug at 510 nm.

- **Procedure for Pharmaceutical Preparations**

5 tablets of **Novistoric®, Zocor® and Erastapex® tablets** were weighed and powdered. An accurately amounts of the powder equivalent to 10 mg of each drug was dissolved in bi-distilled water, filtered into 100 mL measuring flask and completed to volume with bi-distilled water to give final concentration of 100 µg/mL. The procedure was then conducted as mentioned above under the general procedure through applying standard addition techniques.

RESULTS AND DISCUSSION

The proposed spectrophotometric method is indirect based on the determination of the residual un-reacting bromine (insitu generated by a mixture of potassium bromate and potassium bromide in presence of 5 M HCl) after allowing the reaction between each drug and a measured amount of bromine to be complete. The surplus bromine was determined by reacting it with a fixed amount of methyl orange dye. The method relies on the bleaching action of bromine on the dye due to bromination of this dye as shown in Figure 2. ROS, SIM or OLM, when added in increasing amounts to a fixed amount of the insitu generated bromine, they consume the latter proportionately with a concomitant decrease in the concentaration of bromine. When a fixed amount of dye is added to the decreasing amounts of bromine, a concomitant increase in the concentration of dye results. Consequently, a proportional increase in the absorbance at the respective λ_{max} is observed with increasing the concentration of each drug.

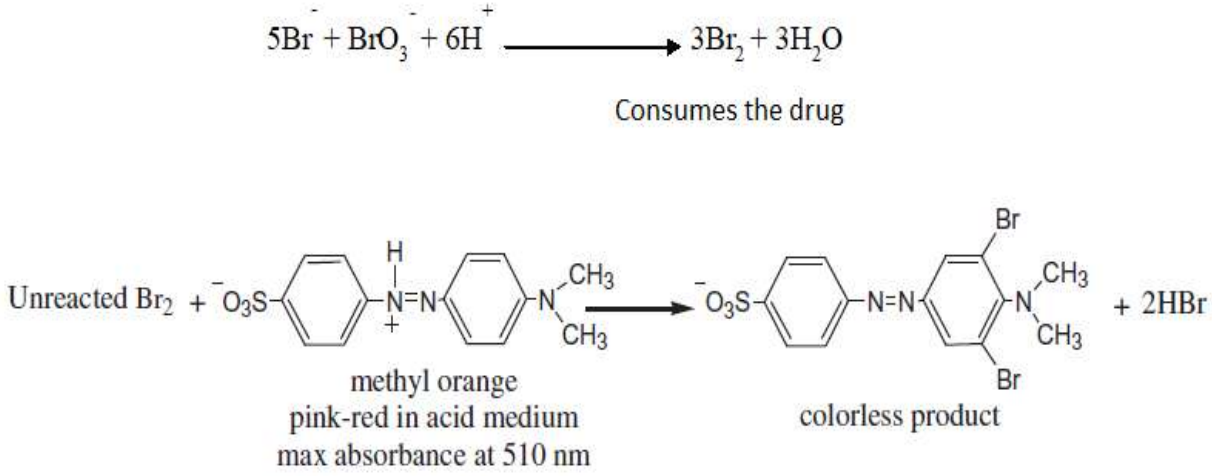


Figure 2: Proposed mechanism of methyl orange bromination [29].

1. Absorption Spectra

Absorption spectra for the determination of ROS, SIM and OLM were studied over a range of 400 - 600 nm. After oxidation of all drugs and portions of dyes with bromine, residual un-oxidized methyl orange is absorbed at 510 nm (Figure 3).

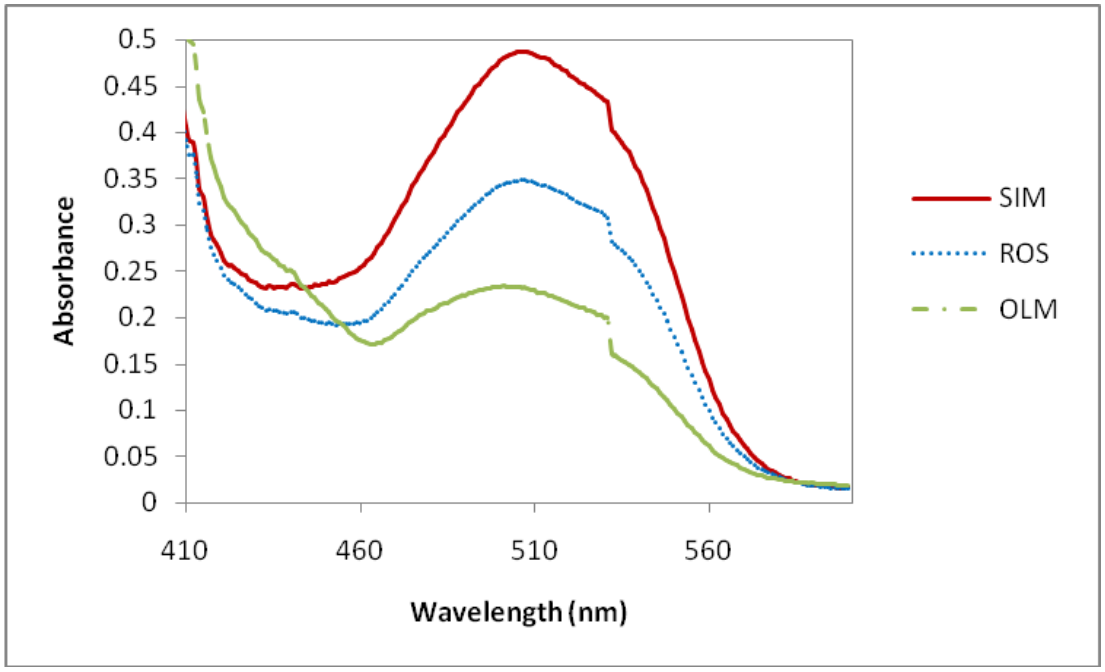


Figure 3: Overlain spectra of 3 µg/mL rosuvastatin (ROS.....), 5 µg/mL simvastatin (SIM___) and 7 µg/mL olmesartan (OLM_._._) at maximum wavelength of 510 nm for all drugs.

2. Effect of Acidity

Different acids were tested as a medium for bromine generation including sulphuric acid, hydrochloric acid and nitric acid. Hydrochloric acid produced the most precise and accurate results. Therefore, 5 M HCl was used throughout experiments and it was found that 0.2 mL of 5 M HCl (accurately measured) is the most appropriate acid volume while increasing HCl volume has no any notable effect on increasing the absorption (Figure 4).

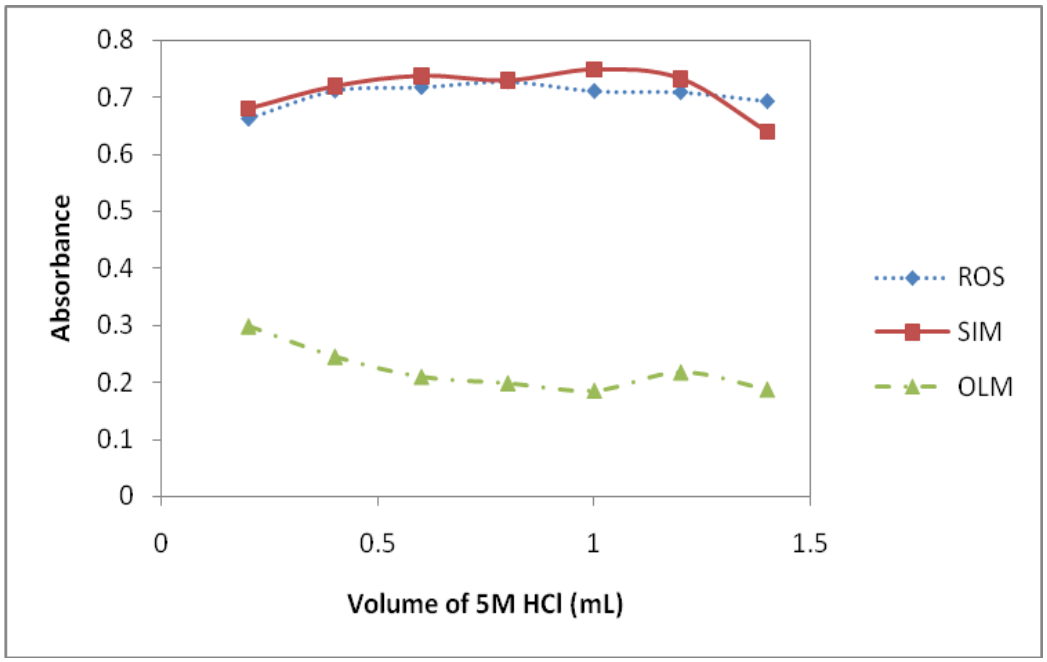


Figure 4: Effect of volume of 5M HCl on methyl orange absorbance in presence of rosuvastatin (ROS.....), simvastatin (SIM___) and olmesartan (OLM_._._) at 510 nm.

3. Effect of Bromate-bromide Volume

Bromate-bromide volume was studied by varying the reagent volume while other factors were held constant. It was found that 0.8 mL of bromine solution is sufficient for its bleaching action to the dye as depicted in Figure 5.

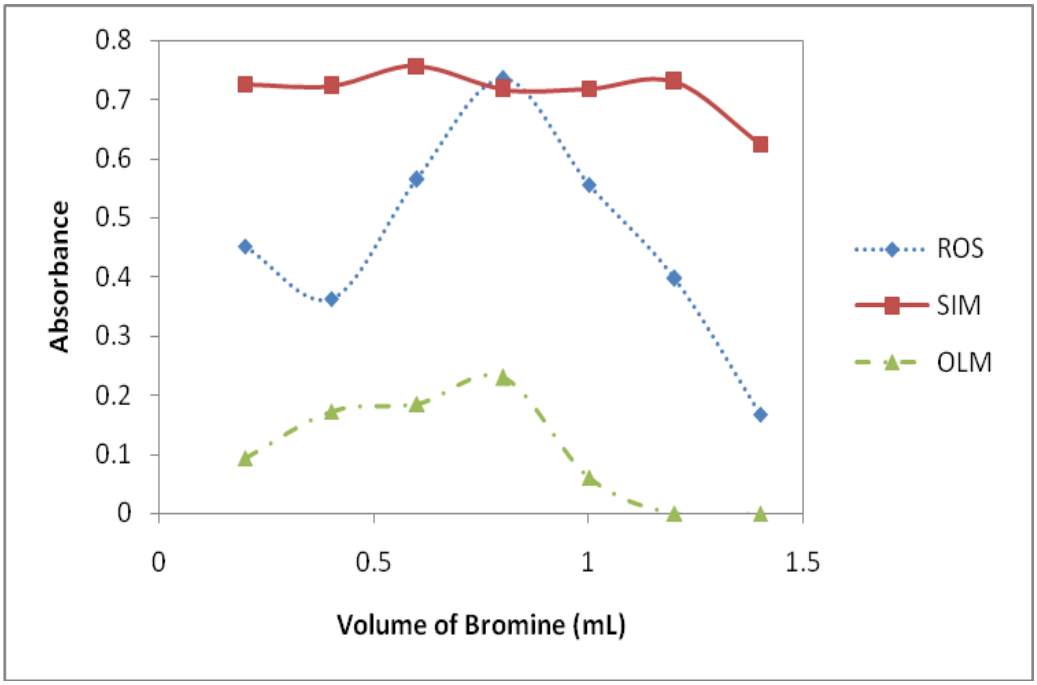


Figure 5: Effect of volume of Bromate-Bromide mixture (12.5 µg/mL) on methyl orange absorbance in presence of rosuvastatin (ROS.....), simvastatin (SIM___) and olmesartan (OLM_._._) at 510 nm.

4. Effect of Time

Time required to brominate and oxidize the drug before addition of dye and time required to irreversibly brominate dye after its addition was studied. The bromination reaction was found to be complete within 2 minutes for ROS and SIM and within 35 minutes for OLM while contact times up to 45 minutes had been examined and no further bromination was detected (Figure 6). A contact time within 2 minutes was necessary for the dye color bleaching by the residual bromine (Figure7) and the color of the dye remains stable for at least three days.

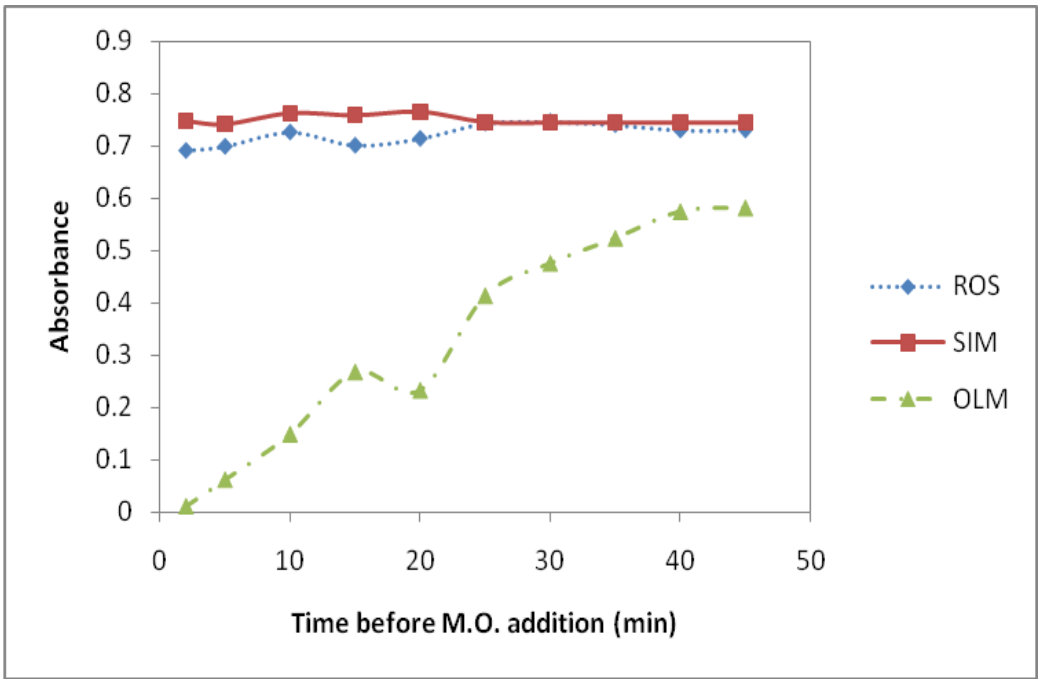


Figure 6: Effect of time before methyl orange addition on absorbance in presence of rosuvastatin (ROS.....), simvastatin (SIM___) and olmesartan (OLM_._._) at 510 nm.

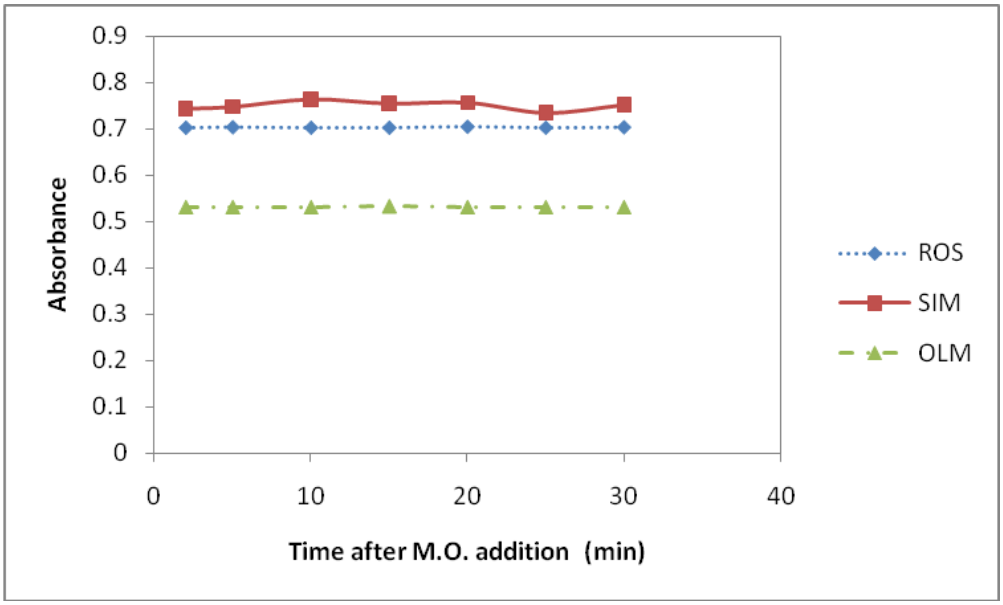


Figure 7: Effect of time after methyl orange addition on absorbance in presence of rosuvastatin (ROS.....), simvastatin (SIM___) and olmesartan (OLM_._._) at 510 nm.

5. Method Validation

The developed method was validated according to international conference of harmonization guidelines (ICH) [30].

- **Linearity**

Six different concentrations of ROS, SIM and OLM were prepared for linearity studies. The linearity ranges of absorbance as a function of drug concentration (Table 1) provided acceptable indication about sensitivity of reagents used. Beer's law was obeyed in the range of 6–11 µg/mL for ROS, 1–3.50 µg/mL for SIM and 2–7 µg/mL for OLM. Linear regression equations were found to be y = 0.0828x - 0.2705, y = 0.2089x - 0.0031 and y = 0.0983x + 0.0103, while the regression coefficient values (R^2) were found to be 0.9992, 0.9991 and 0.9993, for ROS, SIM and OLM respectively, indicating a high degree of linearity for all drugs (Figure 8).

Table 1: Results of analysis for rosuvastatin (ROS), simvastatin (SIM) and olmesartan (OLM) in pure form using the proposed method.

Parameters	**ROS**				**SIM**				**OLM**			
	Taken µg/mL	**Found µg/mL**	**Recovery %**	**Accuracy %**	**Taken µg/mL**	**Found µg/mL**	**Recovery %**	**Accuracy %**	**Taken µg/mL**	**Found µg/mL**	**Recovery %**	**Accuracy %**
	6	6.008	100.14	0.14	**1**	1.01	101.48	1.48	**2**	1.98	98.98	-1.01
	7	6.95	99.29	-0.07	**1.50**	1.49	99.34	-0.65	**3**	2.95	98.23	-1.76
	8	8.001	100.01	0.015	**2**	1.96	98.27	-1.70	**4**	4.08	101.9	1.93
	9	9.06	100.7	0.71	**2.50**	2.48	99.50	-0.45	**5**	5.04	100.89	0.89
	10	10.06	100.54	0.54	**3**	3.04	101.50	1.52	**6**	5.98	99.69	-0.30
	11	10.93	99.04	-0.58	**3.50**	3.49	99.60	-0.36	**7**	6.97	99.56	-0.43
Mean			**100.02**	**0.02**			**99.96**	**-0.03**			**99.88**	**-0.116**
±SD			0.575				1.28				1.33	
±RSD			0.575				1.28				1.33	
±SE			0.23				0.52				0.54	
Variance			0.33				1.65				1.78	
LOD (µg/mL)			1.81				0.28				0.61	
LOQ (µg/mL)			6.03				0.95				2.03	

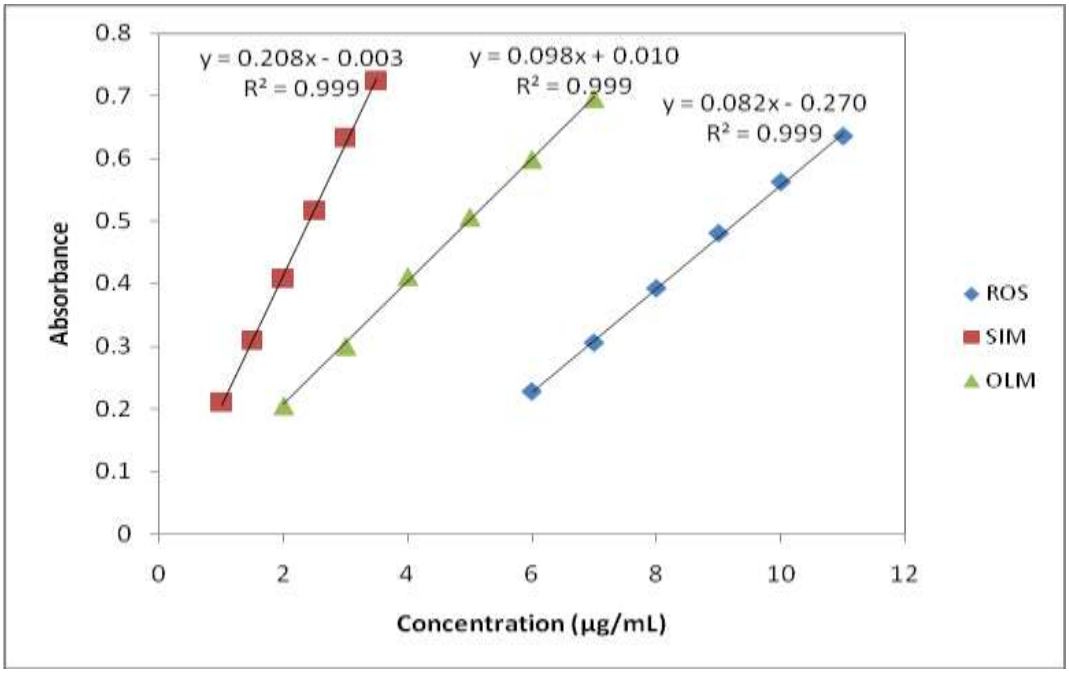


Figure 8. Calibration curves for rosuvastatin (ROS), simvastatin (SIM) and olmesartan (OLM) standard solutions using the proposed method.

- **Accuracy**

The **accuracy** of the method was determined by investigating the recovery of drugs in their pharmaceutical forms at concentration levels covering the specified range (three replicates of each concentration). The results showed excellent recoveries in the range of 101.79, 99.40 and 100.05, for ROS, SIM and OLM respectively, as shown in Table 2.

Table 2: Application of standard addition technique for the determination of Novistoric 10mg®, Zocor 40mg® and Erastapex 20mg® tablets using the proposed method.

	ROS (Novistoric 10mg®)					**SIM (Zocor 40mg®)**					**OLM (Erastapex 20mg®)**				
	Added pure drug (µg/mL)	**Taken tablet (µg/mL)**	**Conc. found (µg/mL)**	**Recovery**	**% Accuracy**	**Added pure drug (µg/mL)**	**Taken tablet (µg/mL)**	**Conc. found (µg/mL)**	**Recovery**	**% Accuracy**	**Added pure drug (µg/mL)**	**Taken tablet (µg/mL)**	**Conc. found (µg/mL)**	**Recovery**	**% Accuracy**
	3	**3**	6.10	101.75	1.75	1	**0**	0.99	99.09	-0.90	2	**0**	2.03	101.50	1.52
	3	**4**	7.08	101.19	1.19	1	**0.50**	1.49	99.30	-0.65	2	**1**	2.99	99.90	-0.06
	3	**5**	8.15	101.98	1.97	1	**1**	1.97	98.75	-1.24	2	**2**	4.04	101.17	1.17
	3	**6**	9.17	101.91	1.91	1	**1.50**	2.45	98.01	-1.98	2	**3**	5.07	101.50	1.50
	3	**7**	10.20	102.10	2.11	1	**2**	3.05	101.80	1.84	2	**4**	5.88	98.08	-1.92
	3	**8**	11.20	101.80	1.83	1	**2.50**	3.49	99.60	-0.36	2	**5**	6.87	98.10	-1.89
Mean				**101.79**	**1.79**				**99.40**	**-0.55**				**100.05**	**0.05**
SD				0.32					1.30					1.62	
CV (%)				0.31					1.30					1.62	
SE				0.13					0.53					0.66	
Variance				0.104					1.60					2.64	

- **Limits of Detection (LODs) and Limits of Quantification (LOQs)**

The calculations of LODs and LOQs were based on the following equations: LOD = 3.3 S/K and LOQ = 10 S/K, where S is the standard deviation of the seven replicate values for the blank and K is the sensitivity, namely, the slope of calibration graph. LODs were calculated to be 1.81, 0.28, and 0.61 µg/mL while LOQs were reported to be 6.03, 0.95 and 2.03 µg/mL, for ROS, SIM and OLM, respectively (Table 1) showing a high degree of the method sensitivity.

- **Precision**

Intra-day **precision** was evaluated by calculating standard deviation (SD) of 3 QC replicate determinations using the same solution containing pure drug within the same day. The SD values revealed the high precision of the method (values vary from 0 to 0.016). For inter-day **reproducibility** on a day-to-day basis, the QC solutions were analyzed each for 3 days. The day-to-day SD values were also in the acceptable range of 0.02 – 0.10 indicating the stability of the reaction solution for all drugs as reported in Table 3.

Table 3: Intra- & inter-day precision results using 3 quality control samples of rosuvastatin (ROS), simvastatin (SIM) and olmesartan (OLM) using the proposed method.

	Drugs	Concentrations (µg/mL)	Mean ± SD	CV (%)	Accuracy %
Intra-day runs (n=3)	**ROS**	6	100.36 ± 0.016	0.26	0.40
		10	100.53 ± 0.01	0.09	0.54
		11	99.45 ± 0.01	0.05	-0.54
	SIM	1	101.90 ± 0.005	0.54	1.96
		2.50	99.21 ± 0.005	0.22	-0.77
		3.50	99.53 ± 0	0	-0.45
	OLM	4	101.80 ± 0.005	0.14	1.82
		6	99.51 ± 0.01	0.16	-0.47
		7	99.60 ± 0.005	0.08	-0.36
Inter-day runs (n=3)	**ROS**	6	100.58 ± 0.02	0.36	0.6
		10	100.80 ± 0.02	0.26	0.82
		11	100.18 ± 0.10	0.93	0.18
	SIM	1	99.24 ± 0.02	2.02	-0.75
		2.50	98.36 ± 0.02	1.02	-1.60
		3.50	98.47 ± 0.04	1.17	-1.48
	OLM	4	102.40 ± 0.02	0.64	2.43
		6	99.83 ± 0.05	0.93	-0.13
		7	100.09 ± 0.05	0.78	0.10

- **Robustness**

The **robustness** of the method was evaluated by making small changes in the volume of acid, bromine and dye (± 0.05 ml) where the effect of the changes was studied on the percent recovery of all drugs. The changes had negligible influence on the results as revealed by small SD values (Table 4).

Table 4: Results of the robustness for the determination of rosuvastatin (ROS), simvastatin (SIM) and olmesartan (OLM) using the proposed method.

	ROS			SIM			OLM		
	Mean recovery ± SD	CV (%)	Accuracy %	Mean recovery ± SD	CV (%)	Accuracy %	Mean recovery ± SD	CV (%)	Accuracy %
Volume of HCl (- 0.05) mL	100.50 ± 1.35	1.35	0.52	100.84 ± 3.09	3.06	0.84	100.50 ± 1.95	1.94	0.50
Volume of HCl (+ 0.05) mL	99.70 ± 0.93	0.94	-0.28	101.83 ± 5.43	5.33	1.83	100.05 ± 1.37	1.36	0.05
Volume of bromine (- 0.05) mL	100.27 ± 0.84	0.83	0.27	100.23 ± 1.75	1.74	0.23	100.64 ± 2.22	2.20	0.64
Volume of bromine (+ 0.05) mL	99.80 ± 0.76	0.76	-0.18	99.75 ± 1.06	1.07	-0.24	98.19 ± 4.45	4.53	-1.80
Volume of dye (- 0.05) mL	99.80 ± 0.72	0.72	-0.15	100.26 ± 1.80	1.80	0.26	99.06 ± 2.48	2.50	-0.90
Volume of dye (+ 0.05) mL	100.34 ± 0.98	0.98	0.34	100.83 ± 3.07	3.05	0.84	100.28 ± 1.59	1.58	0.28

6. Applications

Novistoric®, Zocor® and Erastapex® tablets containing stated drugs have been successfully analyzed by the proposed method. Excipients did not show interference indicating high specificity of the method. Results obtained were compared to those obtained by applying reference methods [5, 7 & 10] where Student's t-test and F-test were performed for comparison. Results are shown in Table 5 where the calculated t and F values were less than tabulated ones which in turn indicate that there is no significant difference between our proposed method and reference ones relative to precision and accuracy.

Table 5: Statistical analysis of results obtained by the proposed method applied on Novistoric 10mg®, Zocor 40mg® and Erastapex 20mg® tablets compared with reference methods.

	ROS (Novistoric 10mg®)		**SIM (Zocor 40mg®)**		**OLM (Erastapex 20mg®)**	
	Proposed method	**Reference method [6]**	**Proposed method**	**Reference method [6]**	**Proposed method**	**Reference method [24]**
N	6	3	6	3	6	5
Mean Recovery	101.79	102.10	99.40	98.86	100.05	100.40
SE	0.13	0.32	0.53	0.34	0.66	0.37
Variance	0.104	0.31	1.60	0.36	2.64	0.71
Student-t	**1.09 (1.89)[a]**		**0.70 (1.89)[a]**		**0.46 (1.83)[a]**	
F-test	**3.05 (5.79)[b]**		**4.62 (5.79)[b]**		**3.72 (6.26)[b]**	

[a] and [b] are the Theoretical Student t-values and F-ratios at p=0.05.

CONCLUSION

The proposed method is so simple as it requires only bromate-bromide mixture and methyl orange dye which are cheap and readily available, no pH adjustment is required and the procedure does not involve any critical reaction conditions or tedious sample preparation. Moreover, the method is fast, accurate, adequately sensitive and free from interference by common additives or excipients which make it as choice for routine quality control analysis. The amounts obtained by the proposed method are within the acceptance level of 98% to 102%. The present method was found to be superior to the reference method with respect to both sensitivity and selectivity. The method has been successfully applied for the routine analysis of marketed tablets of our cited drugs.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that there is no conflict of interest in the manuscript.

Ethical Approval

This manuscript does not include any studies on human or animals.

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