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Spectrofluorimetric determination of Bisoprolol fumarate and Rosuvastatin calcium in a novel combined formulation and in human spiked plasma

Nada Sayed Abdelwahab [1], Nouruddin Wageh Ali [1], Marco Mounir Zaki [1,*], Adel Ahmed Ali [2] and Mohamed Mohamed Abdelkawy [3,4]

[1] *Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 62514, Egypt*
nadasayed2003@yahoo.com (N.S.A.), nour74ali@yahoo.com (N.W.A.), marcomounir11@yahoo.com (M.M.Z.)
[2] *Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 62514, Egypt*
adelahmed.ceutics@yahoo.com (A.A.A.)
[3] *Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt*
dr.mohabdelkawy@hotmail.com (M.M.A.)
[4] *Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Future University, Cairo 43528, Egypt*

* *Corresponding author at: Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 62514, Egypt. Tel: +2.012.27027144 Fax: +2.082.2317950 e-mail: marcomounir11@yahoo.com (M.M. Zaki).*

RESEARCH ARTICLE

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ABSTRACT

Sensitive, simple and rapid spectrofluorimetric method was developed for simultaneous determination of bisoprolol fumarate (BIS) and rosuvastatin calcium (ROS) in novel formulated tablets and in human spiked plasma depending on measuring their native fluorescence. The fluorescence intensity of BIS and ROS were measured in methanol at emission wavelength of 297 and 485 nm upon excitation at 227 and 242 nm, respectively. The emission spectrum of each drug reveals zero value at the emission wavelength of the other drug, thus allowing their simultaneous determination without any interference and without using any tedious derivatization steps. Excellent linearity was obtained over the range of 10-500 and 20-1000 ng/mL for BIS and ROS, respectively. The developed method was evaluated by applying to laboratory prepared mixtures and pharmaceutical formulation. The high sensitivity of the method was the motivation to its application for analysis of the cited drugs in spiked human plasma. Likewise, analytical and bioanalytical method validation was carried out following International Conference on Harmonisation guidelines and also statistical analysis with the reported methods was carried out and no significant difference was found. The developed method is the first developed spectrofluorimetric method for simultaneous determination of the newly formulated drugs.

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1. Introduction

Bisoprolol (Figure 1a), (*RS*)-1-[4-[[2-(1-methylethoxy) ethoxy] methyl]phenoxy]-3-[(1-methylethyl) amino]propan-2-ol, is a cardioselective beta blocker used mainly for treatment of hypertension [1,2]. Rosuvastatin (Figure 1b), (3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-(*N*-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid, working as a competitive inhibitor of hydroxyl methyl glutaryl coenzyme A reductase (HMG CoA), also it is a member of lipid lowering family called "statins" [3].

The combination of beta blockers and cholesterol-lowering agents is necessary for the treatment of patients with cardiovascular diseases, such as hypertension with/or susceptible to atherosclerosis, or hypercholesterolemia. The pharmaceutical formulations combining a beta blocker and a cholesterol-lowering agent in admixture with an inert and suitable adjuvant, was the invention related to Bondjers *et al.* [4] as United States Patent Application Publication No.: US 2003/0060477A1 Pub. Date: Mar. 27, 2003.

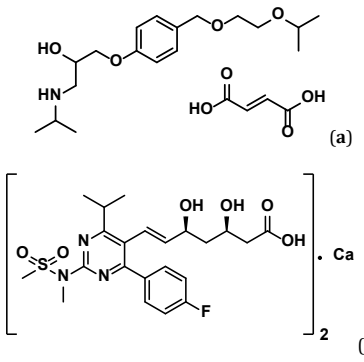

Figure 1. Chemical structure of bisoprolol fumarate (a) and rosuvastatin calcium (b).

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Table 1. Composition of the prepared tablet formulation.

Component	Amount (mg)
Rosuvastatin calcium	5.0
Bisoprolol fumarate	5.0
Avecil PH 101	15.0
Pharmaburst	15.0
Aerosil	15.0
Magnesium stearate	1.5
Lactose monohydrate	150.0

The literature survey revealed that no analytical methods were reported for the simultaneous estimation of BIS and ROS in combination. On the other hand, determination of each drug was reported either alone or in other combinations. BIS was selectively determined by several methods like non aqueous potentiometric titration [1], spectrophotometric [5-8], spectrofluorimetric [8], and voltammetric methods [9]. Also, it was analyzed by different chromatographic methods such as HPTLC [10-12], HPLC [13-16], UPLC [17,18], and LC-MS/MS methods [19,20]. Rosuvastatin calcium was determined either alone or in its different combined dosage forms by several methods including titrimetric [21], different spectrophotometric [22-28], spectrofluorimetric [29], HPTLC [30-33] and HPLC [34-37] methods.

From the previous literature review, it observed that the combination of BIS and ROS has not been analyzed by any analytical method. So, it was thought worthwhile in this study to develop and validate a simple, precise and accurate spectrofluorimetric method to resolve this binary mixture. In the present study, a laboratory prepared pharmaceutical preparation of BIS and ROS was used for developing and evaluating the suggested method. In the same way, application of the method to spiked human plasma was carried out which promotes application of the developed method in further clinical studies of the proposed drugs. The developed spectrofluorimetric method is the first developed method for analysis of this new formulation. It is characterized by its simplicity, selectivity and sensitivity.

2. Experimental

2.1. Apparatus

Fluorescence spectra were recorded using an Agilent Cary Eclipse scanning spectrofluorometer equipped with a Xenon flash lamp. Samples for fluorescence measurements were contained in 1×1 cm quartz cuvettes (3.5 mL volume). The following requirements are taken into consideration: data mode used was fluorescence, scan mode was emission, excitation and emission slit width was adjusted to be 10 nm while the scan rate was 600 nm/min, and data interval: 1 nm. On the other hand, the average time was 1.00 and the excitation filter was adapted to be Auto while the Emission filter was let to be open and PMT voltage was Medium.

2.2. Materials

2.2.1. Chemicals and reagents

All chemicals and solvents used throughout this work were of analytical grade and were used without further purification such as: methanol, acetonitrile were HPLC grade (SDS, France), while sulfuric acid and deionized water were from El-Nasr Pharmaceutical Chemicals Co., Abu-Zabaal, Cairo, Egypt. For tablets formulation used, Avecil PH 101, pharmaburst, aerosil, magnesium stearate, and lactose monohydrate were purchased from Sigma-Aldrich Company, Egypt. Finally, pooled blank plasma was obtained from hospital of Beni-Suef University, Beni-Suef, Egypt.

2.2.2. Pure standard

Bisoprolol fumarate was kindly supplied by Amoun Pharmaceutical Co. Egypt. Its purity was reported to be 99.50% according to the company's certificate of analysis. Rosuvastatin calcium was kindly supplied by Astrazeneca Co., Cairo, Egypt. Its purity was reported to be 99.50% according to the company's certificate of analysis.

2.2.3. Standard solutions

The Stock standard solutions of BIS and ROS were prepared in the concentration of 1000 µg/mL in methanol. Then, the working standard solution of BIS and ROS (5 µg/mL) were prepared from their respective stock standard solutions (1000 µg/mL) in methanol. All stock standard solutions were freshly prepared on the day of analysis and stored in the refrigerator to be used within 24 h.

2.3. Procedures

2.3.1. Tablets formulation

Different formulations were prepared using, the pure drugs, Avecil PH 101, pharmaburst, aerosil, magnesium stearate, and lactose monohydrate with suitable rations to get the target tablet weight 150 mg according to Table 1. The calculated amounts of the drug and diluents were mixed using mortar and pestle then the calculated amount of magnesium stearate was added. Tablets were prepared by means of single punch machine; concave 8 mm punch and die set. The target tablet weight was 150 mg.

2.3.2 Construction of calibration graphs

2.3.2.1. For pure standards of BIS and ROS

Aliquots of 0.1-5.0 µg and 0.2-10.0 µg each of BIS and ROS, respectively, were separately transferred from their respective standard working solutions (5 µg/mL) into two separate series of 10 mL volumetric flasks and the volume was completed using methanol to obtain final concentrations in the range of 0.01-0.50 µg/mL for BIS and 0.02-1.00 µg/mL for ROS. Emission intensity was measured at 297 and 485 nm using an excitation wavelength of 227 and 242 nm for BIS and ROS, respectively.

Calibration curves were then constructed relating the recorded emission intensity to the corresponding concentrations of BIS and ROS from which regression equations were computed.

2.3.2.2. For spiked human plasma samples

Different volumes of BIS and ROS were transferred from their respective working solutions (5 µg/mL) into two separate series of 10 mL volumetric flasks to prepare samples in the range of 0.02-0.50 µg/mL for BIS and 0.03-1.00 µg/mL for ROS. To each sample 1 mL of plasma was added, then the volume was adjusted with methanol. Samples were mixed by vortexing for 5 min and then centrifuged at 4000 rpm for 10

minutes to separate the precipitated plasma protein. The clear supernatant was carefully transferred to a clean tube and then the fluorescence intensity were recorded at $\lambda_{emission}$ = 297 and 485 nm after excitation at $\lambda_{excitation}$ = 227 and 242 nm, respectively, and then the calibration curves were constructed.

2.3.3. Quality control samples preparation

Quality control (QC) samples were prepared by the same way followed for preparation of calibration curves samples. The prepared quality control samples were of concentration 0.03, 0.10, 0.40 µg/mL for BIS and 0.05, 0.20, 0.70 µg/mL for ROS. These concentrations represented the low, medium and high concentrations, respectively. The QC samples were used to validate the extraction, recovery, matrix effect, and precision of the method. Both the calibration standards and QC samples were kept at -80 °C till analysis.

2.3.4. Laboratory prepared mixtures

Different laboratory prepared mixtures containing different ratios of BIS and ROS were prepared by accurately transferring different volumes of each from its respective standard working solutions to series of 10 mL glass volumetric flasks and then volume was completed by methanol. Fluorescence intensity was measured at 297 and 485 nm after excitation at 227 and 242 nm, respectively. The previously constructed regression equations were then used to calculate concentrations of the studied drugs.

2.3.5. Assay of the formulated tablets content

The content of 20 formulated tablets were powdered and mixed well. An amount of the powdered tablets equivalent to 100 mg of each drug was accurately weighed and transferred to 100 mL glass volumetric flask, 75 mL methanol was added and the prepared solution was ultra-sonicated for about 30 minutes. The solution was then cooled well; the volume was completed with methanol to get 1000 µg/mL stock solution and, then filtered. Suitable dilutions were made to obtain concentrations of both BIS and ROS in their linearity ranges. Then, the procedure illustrated under construction of calibration curves was followed.

2.3.6. Method validation

2.3.6.1. Linearity

Different volumes of BIS and ROS were transferred from their respective working solutions (5 µg/mL) into two separate series of 10 mL volumetric flasks to prepare samples in the range of 0.01-0.50 µg /mL and 0.02-1.00 µg/mL for pure standards of BIS and ROS, respectively, and 0.02-0.50 µg/mL for BIS and 0.03-1.00 µg/mL for ROS for spiked human plasma samples. Calibration curves were then constructed relating the recorded emission intensity to the corresponding concentrations of BIS and ROS from which regression equations were computed.

2.3.6.2. Accuracy

For pure standards of BIS and ROS, the previously mentioned procedure under linearity was repeated for different concentrations of BIS and ROS in triplicates. The concentrations were calculated from the previously calculated regression equations. Further assessment for accuracy was performed by application of standard addition technique, the concentrations were then calculated from the corresponding regression equations and then the mean recoveries were calculated. While for spiked human plasma samples, quality control samples were used for testing method accuracy by five determinations at the three concentration levels.

2.3.6.3. Precision

For pure standards of BIS and ROS, precision of the developed methods was checked by testing intra-day (repeatability) and inter-day (intermediate precision) variations by analyzing three concentrations of each drug. While for spiked human plasma samples intra- and inter-day precision were determined by analysis of five replicates of QC samples at three different concentration levels within the same day and on three consecutive days, respectively. The intra and inter-day precision values should not exceed 15% of their theoretical concentrations.

2.3.6.4. Specificity

The specificity of the method was ascertained by application of the developed method to laboratory prepared mixtures containing different ratios of BIS and ROS following the procedure under linearity.

2.3.6.5. Sensitivity

Sensitivity of the methods was established with respect to limit of detection (LOD) and limit of quantification (LOQ) for BIS and ROS. LOD and LOQ were established by slope method (calculation method) using the lowest part of the calibration curves and the slope of the regression equations as mentioned below.

LOD = 3.3 × (Standard deviation of the response/Slope of the calibration curve) (1)

LOQ = 10 × (Standard deviation of the response/Slope of the calibration curve) (2)

3. Results and discussion

The aim of our work is to improve the patient compliance by preparing that novel formulated tablets and providing sensitive method useful to analysis and validate the newly formulated combination that can be used for further quality control analysis of the studied drugs. Furthermore, application of the method to spiked human plasma permits its application for monitoring of these drugs.

3.1. Evaluation of the formulated tablets

The formulated tablets were evaluated according to the quality control criteria.

Uniformity of weight: The average weight of ten tablets was calculated [38]. The data in Table 2 revealed that, all the prepared tablets showed acceptable weight variation range and not more than two tablets were allowed to deviate from the average weight by more than twice the previous percentage [39].

Tablet thickness and diameter: The diameter and thickness of 10 tablets were measured [38] and Table 2 revealed that the prepared tablets had uniform thickness and diameter.

Content uniformity: The results in Table 3 were found to lie within the official acceptable range for the tablets content analysis. Tablets should not contain less than 85% and not more than 115% of the labeled potency [1,13] and the standard deviation should be less than 2%.

Friability: It is obvious from Table 2 that all the prepared tablets showed a percentage fine ranging around the acceptable limit and did not exceed the permissible limit of 1.4% [38].

Table 2. Data of average weight, thickness, diameter, friability, and hardness of different formulated tablets.

Tablet no	Uniformity of weight (mg)	Tablet thickness (mm)	Tablet diameter (mm)	Friability (%)	Hardness (Kg)
1	153.20	2.99	8.06	0.28	8.1
2	149.20	3.05	8.04	0.41	8.1
3	150.30	2.99	8.05	0.44	8.1
4	150.00	2.95	8.05	0.23	8.5
5	151.60	2.99	8.06	0.40	7.9
6	151.70	3.08	8.05	0.27	8.2
7	150.20	3.02	8.04	0.21	7.8
8	149.40	2.95	8.06	0.51	7.8
9	150.60	2.98	8.05	0.46	7.9
10	149.70	2.99	8.06	0.40	8.2
Mean	150.76	3.00	8.05	0.36	8.06
S.D.	1.310	0.004	0.008	0.107	0.230

Table 3. Results of analysis of laboratory prepared mixtures and assay of the formulated tablets content by applying the proposed method and application of standard addition technique.

Sample	Methanol		Human spiked plasma	
	BIS	ROS	BIS	ROS
Lab prepared mixtures [a] (Mean±SD)	99.74 ±0.563	100.11±0.727	96.65±0.958	97.48±1.154
Formulated tablets [b] (%Recovery±SD)	100.39±0.765	100.28±0.596	-	-
Standard addition [a]	99.89± 0.368	100.46±0.733	-	-

[a] Average of 3 determinations.
[b] Average of 6 determinations.

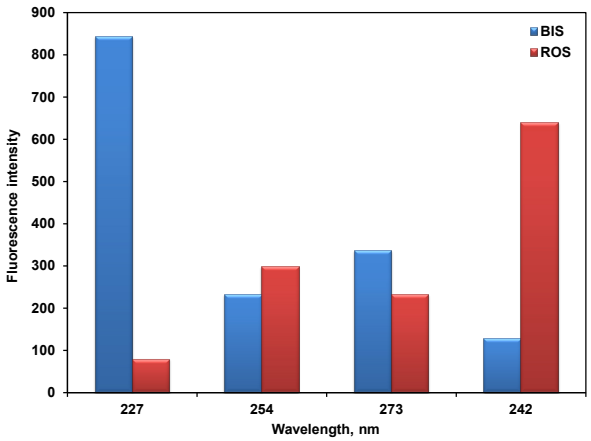

Figure 2. Effect of different excitation wavelength on the fluorescence intensity at 297 and 485 nm for bisoprolol and rosuvastatin, respectively.

Hardness: The complied data in Table 2 revealed that, all tablets showed hardness values ranged from 8.5 to 10.2 kilograms with standard deviation less than 2% [40].

3.2. Optimization of experimental conditions

Different factors affecting the fluorescence intensity have been investigated and optimized in order to improve the sensitivity and selectivity of the method.

Excitation wavelength: Different excitation wavelengths were tested in order to increase sensitivity and selectivity (227, 273, 300 and 242 nm); it was found that on using 227 and 242 nm as excitation wavelengths for the determination of BIS and ROS, respectively (Figure 2). The emission spectrum of each drug revealed zero value at the emission wavelength of the other drug, thus allowing their simultaneous determination without any interference

Excitation and emission slit width: In order to improve resolution between peaks and sensitivity of the method, different slit widths (5, 10 and 15 nm) were checked and it was found that 10 nm is the optimum slit width for both excitation and emission.

Influence of the used solvent: The effect of different solvents on sensitivity and selectivity of the method was investigated. Different solvents were tested such as 0.1 N sulfuric acid, methanol, acetonitrile and water. It was found that methanol was the optimum solvent for measuring BIS while for ROS it was noticed that 0.1 N sulfuric acid and methanol nearly gave the same florescence intensity (Figure 3). On the other hand, all the tried solvents gave the same selectivity for both drugs. Accordingly, methanol was the solvent of choice for resolving the studied binary mixture.

Under the chosen optimum conditions, BIS and ROS has been selectivity determined without any interference from each other as shown in Figures 4 and 5.

3.3. Method validation

3.3.1. For pure standards of BIS and ROS

Validation of the proposed methods was performed according to International Conference on Harmonisation (ICH) [41] guidelines. The Linearity of the calibration curve was constructed by plotting the fluorescence intensity of each drug against its corresponding concentrations. The curves were found linear over the range of 0.01-0.50 and 0.02-1.00 µg/mL for BIS and ROS, respectively. The obtained correlation coefficient values assure good relationships between the studied concentrations and the response Table 4. Good percentage recoveries were obtained when testing methods accuracy and results are given in Table 4.

Table 4. Assay and validation parameters obtained by applying the proposed method.

Parameter	Methanol		Human spiked plasma	
	BIS	ROS	BIS	ROD
Range (µg/mL)	0.01-0.50	0.02-1.00	0.02-0.50	0.03-1.00
Slope	1866.300	618.100	1194.500	508.460
Intercept	62.041	33.500	39.670	27.026
Correlation coefficient	0.9999	0.9999	0.9998	0.9990
Accuracy (Mean±SD)	99.65±0.909	99.98±0.375	-	-
Precision (SD)				
Repeatability	0.257	0.141	-	-
Intermediate precision	0.513	0.358	-	-
LOQ (µg/mL)	0.01	0.02	0.02	0.03
LOD (µg/mL)	0.003	0.006	0.006	0.010

Table 5. Recovery results for determination of bisoprolol fumarate and rosuvastatin calcium in plasma by the proposed method.

Drug	Concentration spiked (µg/mL)	Mean recovery%±RSD	E_r (%)
BIS	0.03	95.64±2.13	-4.36
	0.10	110.58±5.52	10.58
	0.40	104.22±8.74	4.22
ROS	0.05	106.45±4.58	6.45
	0.20	94.77±4.05	-5.23
	0.70	97.52±6.48	-2.48

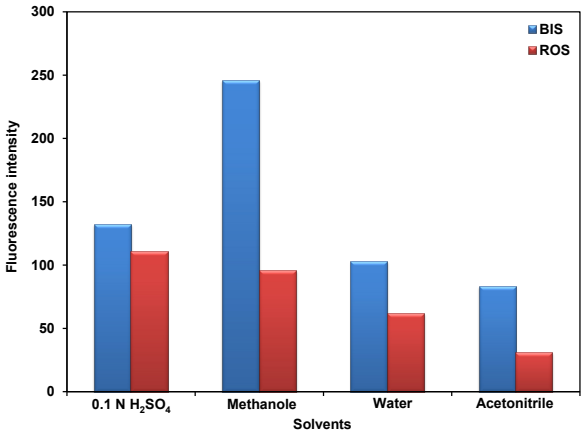

Figure 3. Effect of different solvents on the fluorescence intensity.

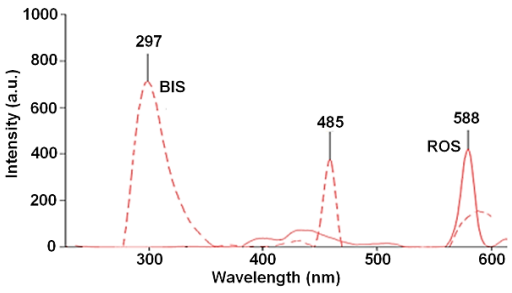

Figure 4. Emission spectra of bisoprolol fumarate and rosuvastatin calcium after excitation at 227 nm in methanol.

Accuracy was further assessed by applying the standard addition technique on the formulated tablets where good results were obtained revealing the good accuracy of the proposed methods and proving that excipients did not interfere, Table 3.

The calculated LOD and LOQ values for BIS and ROS showed high sensitivity for the proposed method, Table 4. The proposed methods provided acceptable intra- and inter-day variations, confirming their acceptable precision and that they are suitable for quality control studies of the suggested components Table 4. Also, specificity of the method was confirmed from the good recovery percentages 99.74±0.563 and 100.11±0.727 for BIS and ROS, respectively, obtained when it was applied for determination of BIS and ROS in laboratory prepared mixtures, Table 3.

3.3.2. For spiked human plasma samples

Validation of the proposed methods after application on the human plasma spiked samples was performed. The linearity of the calibration curves were constructed by plotting the emission intensity of both drugs in spiked human plasma samples over the range of 0.02-0.50 and 0.03-1.00 µg/mL for BIS and ROS, respectively. The linearity of the graphs was confirmed from the sufficient correlation coefficient (*r*) for both analytes, Table 4.

The accuracy of the proposed method in spiked human plasma samples was tested with five replicates of the three QC samples, low, medium, and high quality control samples (0.03, 0.10 and 0.40 µg/mL) of BIS and 0.05, 0.20 and 0.70 µg/mL for ROS).

Table 6. Intra-day and inter-day precision for determination of bisoprolol fumarate and rosuvastatin calcium in human plasma by the proposed method.

Drug	Concentration added (µg/mL)	Intra-day		Inter-day	
		Mean recovery% ± RSD	E_r (%)	Mean recovery% ± RSD	E_r (%)
BIS	0.03	106.75±6.85	6.75	89.55±8.04	-10.45
	0.10	107.63±4.58	7.63	112.05±7.04	12.05
	0.40	88.78±6.95	-11.22	109.45±7.25	9.45
ROS	0.05	95.62±2.09	-4.38	89.99±4.78	-10.01
	0.20	94.27±5.12	-5.73	105.25±6.81	5.25
	0.70	97.85±4.85	-2.15	92.85±5.89	-7.15

Table 7. Statistical comparison between the results obtained by the proposed method and the reported methods.

Parameter	BIS Found%		ROS Found%	
	Spectrofluorimetric	Reported [14] [b]	Spectrofluorimetric	Reported [34] [c]
Accuracy	99.65±0.910	100.04±0.720	99.98±0.374	100.12±0.449
N	6	6	6	6
Student t-test [a] (2.228)	0.821	_	0.563	-
F-value [a] (5.050)	1.596	_	1.439	-

[a] The values in the parenthesis are corresponding theoretical value at degree of freedom p = 0.05.
[b] Reported method for determination of BIS by HPLC on cyano column (4.6 mm × 250 mm, 5 µm) with the isocratic mobile phase of 0.1 M aqueous phosphate buffer, acetonitrile and tetrahydrofuran (85:10:5, , *v:v:v*) at a flow rate of 1.0 mL/min. The UV detection was carried out at 225 nm.
[c] Reported method for determination of ROS by HPLC on C_{18} column (4.6 mm × 250 mm, 0.5 µm) using acetonitrile and 1 % acetic acid in water (80:20, *v:v*) with a flow rate of 1 mL/min and UV detection at 252 nm.

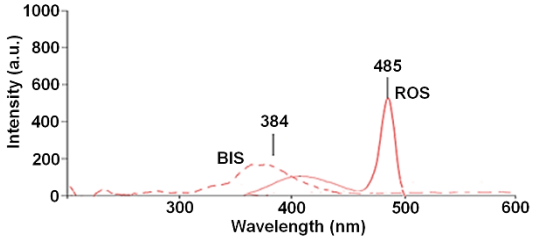

Figure 5. Emission spectra of bisoprolol fumarate and rosuvastatin calcium after excitation at 242 nm in methanol.

It was found to be within ±10.58% and ±6.45% for BIS and ROS, respectively, Table 5.

To assess the precision, human plasma samples spiked with the same three previous concentrations of both drugs were analyzed by the proposed method. Intraday precision was performed by carrying out the analysis five times on the same day, while it was carried out on three different days for interday precision. RSD% were calculated and the obtained values indicated the high degree of method precision, Table 6.

Finally, when the statistical comparison of the results obtained by the proposed and the reported methods [14,34] for BIS and ROS, respectively, the values of the calculated t and F values were found to be less than the tabulated ones, which revealed that there was no significant difference with respect to both accuracy and precision between the proposed and the reported methods, Table 7.

4. Conclusion

In this work new promising combination between beta blockers and statin has been formulated together in tablet dosage form for the prophylactic and treatment of patients with cardio vascular diseases such as hypertension. Those tablets were evaluated and investigated and also passed the quality control criteria. The developed spectrofluorimetric method was the first developed ones for determination of the newly formulated combination. The spectrofluorimetric method is simple, has high sensitivity and does not need complex algorithms. Moreover, it does not need derivatization reactions compared with the reported spectrofluorimetric methods [8,29].

Accordingly, the proposed method can be applied for routine analysis of the studied drugs either in their pure powders or the new formulated dosage form. Also, the method was applied to spiked human plasma that promotes its application for further pharmacokinetics study of the studied drugs without any preliminary separation steps.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

ORCID

Nada Sayed Abdelwahab
http://orcid.org/0000-0002-0700-7542
Nouruddin Wageh Ali
http://orcid.org/0000-0002-1077-2974
Marco Mounir Zaki
http://orcid.org/0000-0001-8379-6865
Adel Ahmed Ali
http://orcid.org/0000-0002-1328-5987
Mohamed Mohamed Abdelkawy
http://orcid.org/0000-0002-9043-9644

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