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Green UV- Spectrophotometric Assessment of Nimodipine in Presence of its Degradation Products in Pure and in Pharmaceutical Dosage Form

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Abstract: Different stress conditions were applied to the antihypertensive drug nimodipine. It was found that the drug degraded under alkaline, acidic, and oxidative conditions. IR and mass spectrometry were used to identify the degradation product. Four simple, economical and precise UV spectrophotometric methods were used to estimate nimodipine in the presence of its degradation products: zero order, first derivative (^{1}D), ratio difference (RD), and derivative ratio (^{1}DR). The linearity of the proposed methods was observed across concentration range of 3.0-18.0 µg mL^{-1}. ICH criteria were used to validate accuracy, precision, specifications, and all procedures. Good recoveries of intact nimodipine were achieved using the proposed methods, even in the presence of (5-70%) of its degradates, demonstrating their specificity. Moreover, the four methods used were considered environmentally friendly according to the Eco-Scale and Green Analytical Procedure Index (GAPI) guidelines. The suggested methods were effectively used to determine nimodipine in its dosage forms.

Keywords: Green; UV- Spectrophotometry; Nimodipine; Degradation; Eco-Scale; GAPI.

1. INTRODUCTION

Nimodipine is 3-(2-Methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. Organic solvents as ethanol, DMSO, and DMF can dissolve it but aqueous solution cannot. Nimodipine is classified as a calcium channel blocker of the 1, 4-dihydropyridine variety [1, 2].

Various analytical techniques, such as spectrophotometry [3-12], spectrofluorimetry [13-14] HPLC [15-24], GC [25- 26], voltammetry [27], and electrophoresis [28] have been documented for nimodipine analysis. The current work aims to establish sensitive, accurate and simple UV-spectrophotometric methods for nimodipine determination in presence of its degradation products, as well as to evaluate their greenness using Eco-scale analysis and the Green Analytical Procedure Index.

Theoretical background of the suggested methods

Derivative spectrophotometry - Derivative spectrophotometry has become a valuable tool for solving a variety of analytical problems. It is utilized in numerous disciplines, such as pharmaceutical, forensic, clinical, biochemical, and inorganic and organic analysis[29,30].

Ratio Difference [RD] method [31] **-** When the spectra of two substances X and Y overlap, a ratio spectrum is generated by dividing the spectrum of X by a divisor of a specific concentration of Y. Additionally, a linear relationship can be established between the concentration of X and the difference in amplitudes at any two wavelengths. In contrast, the ratio spectrum of Y will be a constant-amplitude linear line parallel to the x-axis, with no amplitude difference between any two wavelengths of Y.

Derivative ratio [^{1}DR] - The outcome of dividing a compound's absorption spectra by another compound's spectrum is a straight line whose amplitude remains constant and goes parallel to the baseline. In contrast, the ratio spectrum is

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created by dividing the absorption spectra of one compound (X) by the absorption spectrum of another compound (Y). In the absence of Y interference, the amplitude of the ratio spectrum's first or second derivative is proportional to the concentration of X [32].

2. METHODS

2.1. Instruments

- UV-Visible 1601 PC spectrophotometer by Shimadzu, Tokyo, Japan.
- pH meter paired with glass electrode (Adwa model AD1030 pH/ mv).

2.2. Chemicals and reagents

Analytical grade 0.1 M sodium hydroxide, 0.1 M hydrochloric acid, and 30% hydrogen peroxide (El-Nasr Co., Egypt). Analytical grade methanol and DMSO (Sigma-Aldrich, Germany).

2.3. Pure and market samples

- **Nimodipine;** B.N. TV0020813 was provided generously by Pharco -Pharmaceuticals, Alexandria. According to the information provided by the provider, the purity was 97.6%.
- **Nimotop® tablets,** B. N. 0251152, each tablet containing 30 mg nimodipine, manufactured by Bayer for pharmaceutical industry (Germany)**.**

2.3.1. Standard solution

Nimodipine standard stock solution (1 mg mL^{-1}) was made by dissolving 100 mg of nimodipine in the smallest possible volume of dimethyl sulfoxide, followed by methanol dilution to 100 mL. A working standard solution of (0.1 mg mL^{-1}) was then prepared from the stock solution.

2.3. 2. Degraded samples

-Nimodipine alkaline and acidic Degradation: 100 mg of pure drug was refluxed with 100 mL 0.1 M NaOH or 100 mL 5 M HCL for 8h or 6h at 80 ºC, respectively. Each solution was then chilled, neutralized with 0.1 M HCL or 5 M NaOH to about pH 7, and evaporated to dryness under vacuum.

- Nimodipine oxidative degradation: For 0.5 h, 100.0 mg of nimodipine was refluxed with 100 mL of 3.0% aqueous H_2O_2. After that, the solution was boiled to remove hydrogen peroxide and evaporated to dryness under vacuum.

Three separate extractions with 25 mL of methanol were performed on each residue in order to make degradate, stock solution formed from 1 mg mL^{-1} of intact drug. Then each solution was filtered into a 100-mL volumetric flask and diluted to the mark with methanol.

2.4. Procedures

2.4.1. Spectral characteristics

Over the range of 200-500 nm, zero-order absorption spectra of pure nimodipine, its alkaline, acidic and oxidative degradates were recorded against a blank of methanol and saved in the computer.

2.4.2. Linearity

Aliquots of a nimodipine standard working solution (0.1 mg mL^{-1}) equivalent to a range of 0.03-0.18 mg, was placed into a series of 10-mL volumetric flasks. After that, the volume in these flasks was adjusted by adding methanol to the desired volume. The absorption spectra of nimodipine in zero order were recorded and saved in the computer over the wavelength range of 200 to 450 nm.

I. Zero order - Nimodipine absorbance was measured at 354 nm. By establishing a relationship between the absorbance values of the prepared solutions and the concentrations that correspond to them of nimodipine in µg mL^{-1}, a calibration curve was generated. Subsequently, the regression equation for this curve was calculated.
II. (^{1}D) First derivative - Peak amplitude of zero crossing wavelength at 389 nm of ^{1}D spectra of intact drug against methanol using (Δλ 15 nm) and SF=10 was measured. The calibration curve was generated to establish the relationship between peak amplitude and the concentration of the pure drug, measured in µg mL^{-1}. Subsequently, a regression equation was calculated.
III. (RD) Ratio difference method – Ratio spectra of pure drug (200-400 nm) were obtained by using 9 or 6 or 10 µg mL^{-1} of alkaline, acidic or oxidative degradate as a divisor. Then absorbance difference ΔP was measured between (370.7- 388.5 nm) or (368.8- 386.4 nm) or (351.1- 361.6 nm) to determine the pure drug in presence of its alkaline or acidic or oxidative degradates; respectively. Plotting the observed peak amplitude differences against the respective concentrations in µg mL^{-1} led to the creation of the calibration curves.
IV. (^{1}DR) First Derivative of ratio spectra- ^{1}D of the ratio spectra were acquired by employing SF 10 and Δλ 8 nm. Amplitude values were recorded at 392.5 nm, 395.6 nm, and 363.3 nm, respectively, to determine the drug in presence of alkaline, acidic or oxidative degradate; respectively. The regression equations were computed after plotting these values against the drug concentrations.

2.4.3. Mixtures of intact nimodipine and its degradates that made in laboratory.

Aliquots comprising (95-30 µg) of nimodipine standard and working standard solution (1& 0.1 mg mL^{-1}) in methanol were added into a set of 10-mL volumetric flasks containing (5-70 µg) of its acidic, alkaline, or oxidative degradate solutions, then diluted to volume with methanol. Suggested methods given under **"2.4.2. Linearity"** were followed and concentration of nimodipine was determined using the regression equation that corresponded to it.

2.4.4. Application to dosage form

Nimotop® tablets were finely ground, well-mixed, and then weighed. 100 mg of precisely weighed nimodipine powder dissolved with least amount of DMSO then 70 ml methanol was added into a volumetric flask. After 30 minutes of sonication, the flask was filled to mark with methanol and filtered. The quantification of the filtrate, which was labeled to contain 1 mg mL^{-1} nimodipine, was conducted using UV spectrophotometric techniques as recommended. The relevant regression equations were utilized to ascertain the drug concentrations.

3. RESULTS & DISCUSSION

The objective of this research is to provide green indicating UV-spectroscopic methods that can accurately and selectively detect nimodipine in the presence of its degradation products, whether in bulk form or in dosage form. These were zero order, [^{1}D], [RD] and [^{1}DR] spectrophotometric approaches.

The literature review for the determination of nimodipine includes four stability indicating methods. Sameera Razi Khan [12] developed stability spectrophotometric determination of nimodipine kinetic reaction only without separation or elucidation of degradates. Y S Hu [15] utilized mobile phase composed of methanol: water 65:35 v/v for HPLC stability study of nimodipine injection. Manoela K. Riekes[17] developed stability HPLC method for nimodipine determination using acetonitrile–methanol–water (55:11:34, v/v/v) as a mobile phase without identification of degradation products. Sagar Suman P. [23] used methanol: water (pH 3.5 maintained by o-phosphoric acid), 80:20, v/v as mobile phase for LC stability determination of nimodipine.

By comparing the suggested UV methods with the other reported methods; it was found that the suggested methods were simpler, lower cost, non-destructive and ecofriendly than others reported methods.

3.1. Forced degradation

The degradation products were characterized using IR and MS spectroscopy, **Fig S1,2. Table S1** illustrated the explanation of degradation mechanisms and **scheme S1** explored the suggested degradation pathway. Nimodipine had been subjected to other stress condition as photodegradation and thermal effect. It was found that nimodipine was stable under these conditions.

3.2. UV- Spectrophotometric methods

Zero order - Intact nimodipine was found to exhibit a robust band at 354 nm with no interference from acidic or oxidative zero order- spectra, whereas alkaline degradate spectra exhibit overlap with intact drug spectra. Therefore, nimodipine can be determined in presence of acidic and oxidative degradates by zero order method. **Fig 1.**

First derivative (^{1}D)- ^{1}D- spectra at 389 nm was chosen where alkaline, acidic and oxidative degradates showed zero crossing utilizing a scaling factor of 10 and a Δλ 15 nm, **Fig 2.**

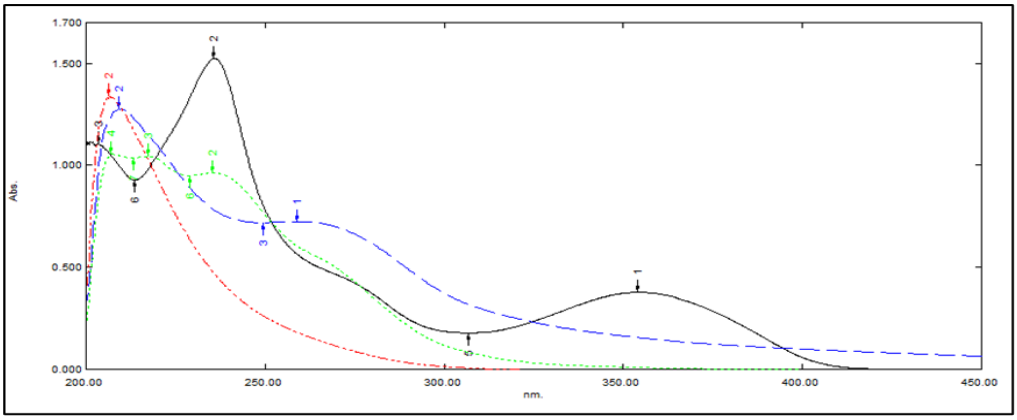

Figure 1. Zero order spectra of nimodipine 10 µg mL^{-1} (____) and 10 µg mL^{-1} of its alkaline degradate (_ _ _), 10 µg mL^{-1} of its acidic degradate (….) and 10 µg mL^{-1} of its oxidative degradate (-.-.-).

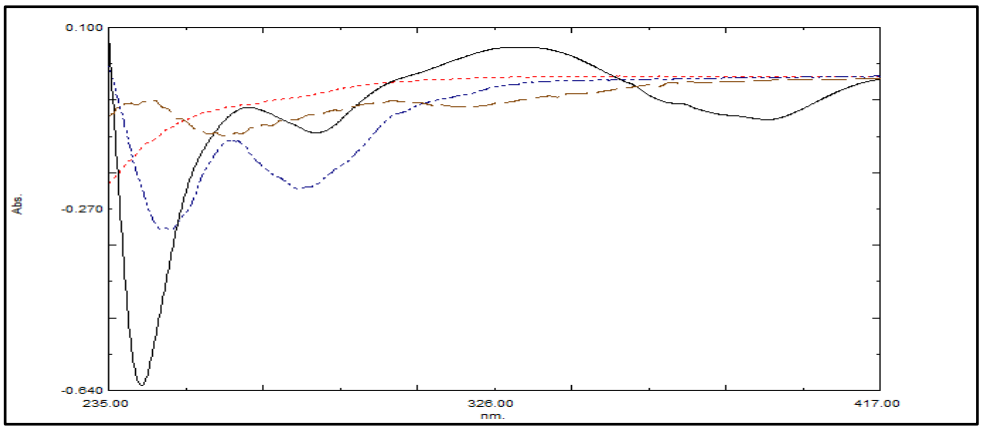

Figure 2. First derivative spectra of nimodipine and its alkaline, acidic and oxidative degradates.

Ratio difference (RD) - This method required careful divisor concentration selection. Various concentrations of alkaline, acidic, or oxidative degradates (3-12 µg mL-1) were investigated. The best outcomes were obtained with divisor concentration of (9 µg mL^{-1} or 6 µg mL^{-1} or 10 µg mL^{-1}) of alkaline or acidic or oxidative degradates; respectively; see **Fig 3.**

^{1}DR spectrophotometric method- The first derivative of the aforementioned ratio spectra was computed and smoothed at 10 nm using a scaling factor of 20. As shown in **Fig 4**, the amplitudes of the ^{1}DR spectra of (Nimodipine/alkaline, acidic, or oxidative degradates) were measured at 392.5nm, 395.62 nm, and 363.27nm, respectively.

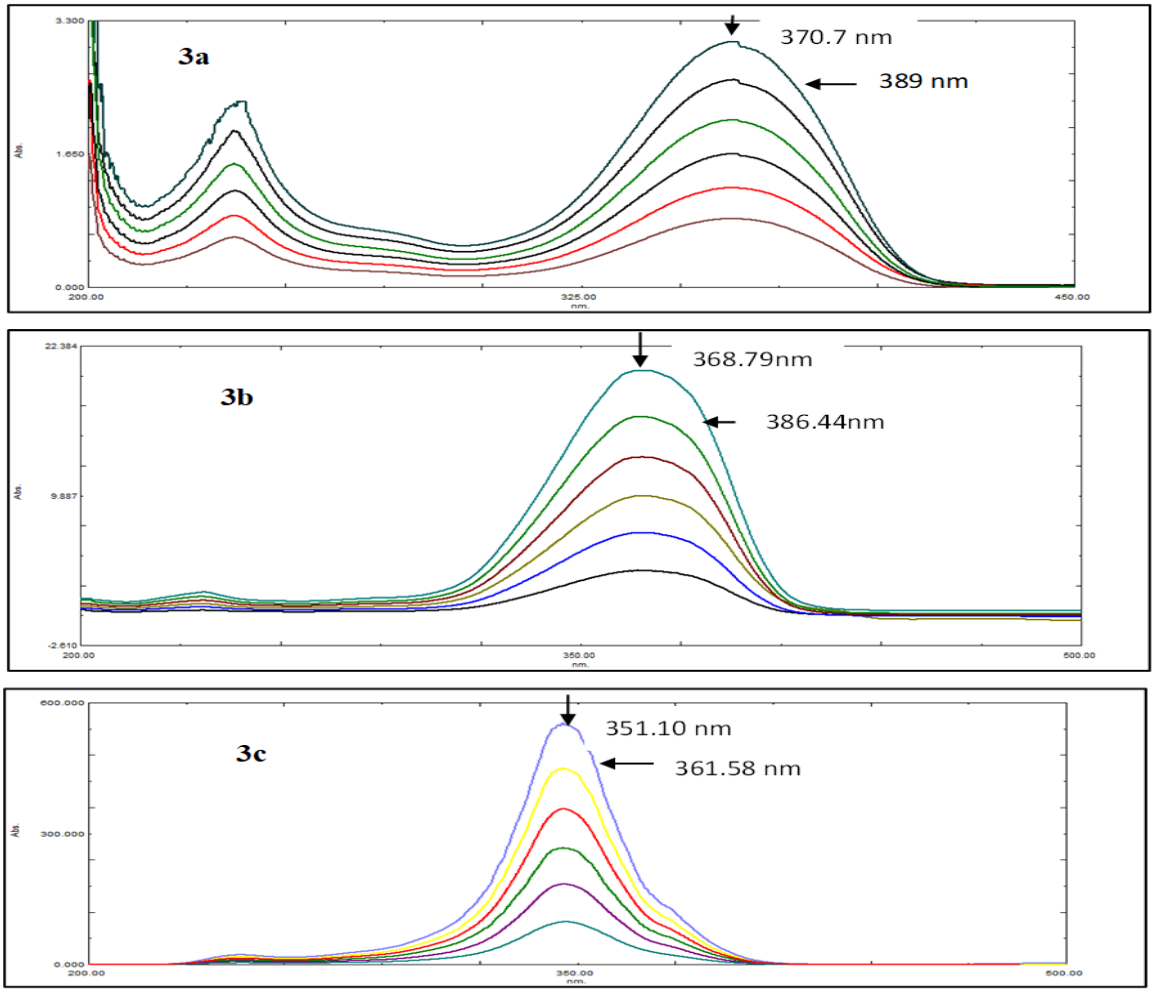

Figure 3. Ratio spectra of (3-18 µg mL^{-1}) of nimodipine using: a), (9 µg mL^{-1}) of its alkaline degradate as a divisor, b) (6 µg mL^{-1}) of its acidic degradate as a divisor, c) (10 µg mL^{-1}) of its oxidative degradate as a divisor.

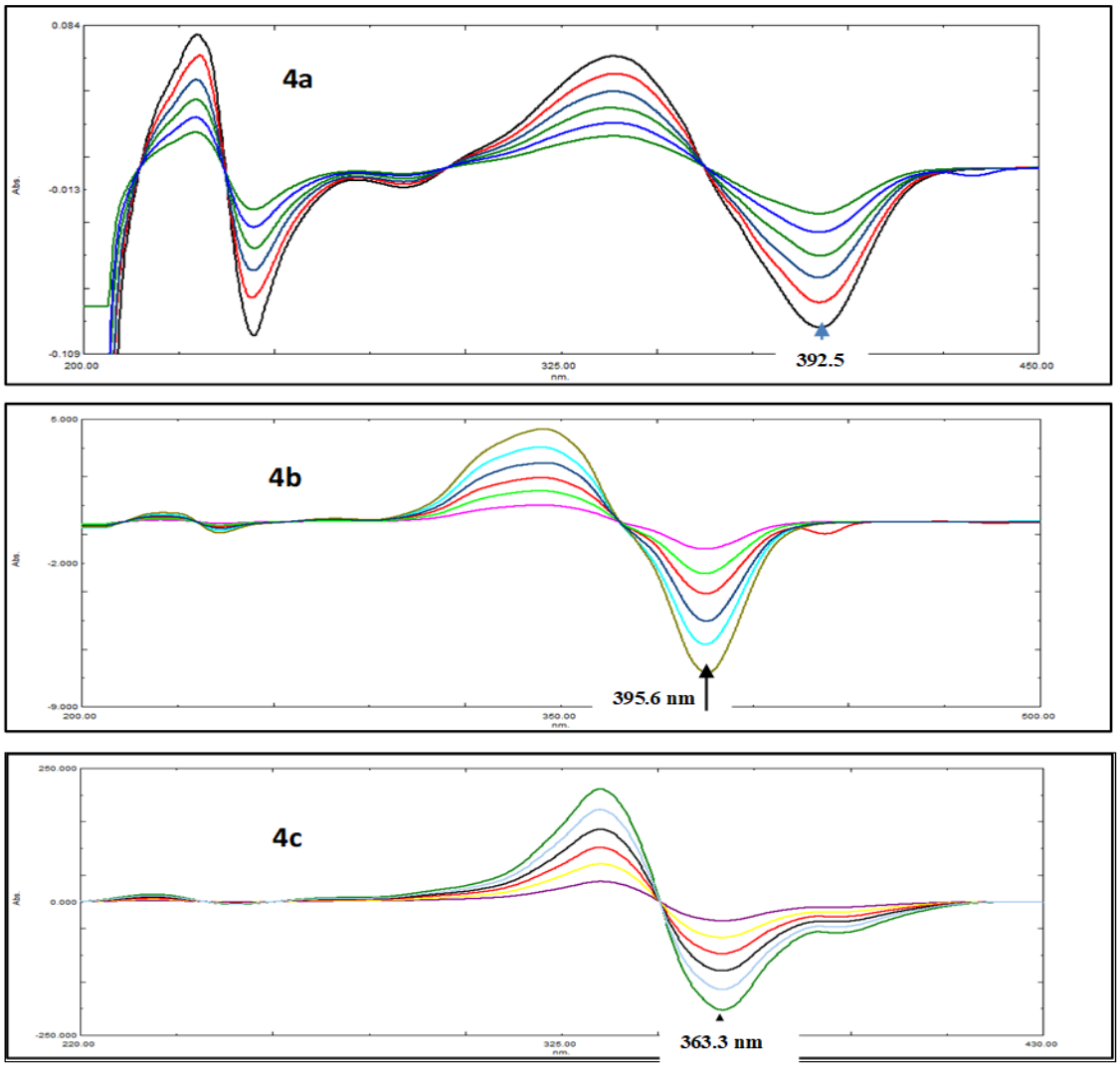

Figure 4. [1]DR spectra of (3-18µg mL-1) of nimodipine using: a) (9 µg mL^{-1}) of its alkaline degradate as a divisor, b) (6 µg mL^{-1}) of its acidic degradate as a divisor, c) (10 µg mL^{-1}) of its oxidative degradate as a divisor.

3.3. Method validation

The procedures were verified in accordance with ICH guidelines [33].

Linearity- Plotting the response to comparable drug concentrations over a range of 3-18 µg mL^{-1} allowed for the creation of calibration curves for the suggested methods. Regression parameters were estimated and provided in **Table 1.**

Detection and Quantitation Limits – ICH criteria were followed in determining LOD and LOQ. The lowest detectable analyte concentration (LOD = 3.3σ/S) is evaluated by LOD. The calibration curve's threshold for nonlinearity is determined by LOQ (LOQ = 10σ/S), where "S" denotes the calibration curve's slope and "σ" is the standard deviation of the residuals' intercept. **Table 1** lists the LOD and LOQ results of various suggested methods for the investigated drug.

Accuracy – Three distinct concentrations of pure nimodipine (3, 9, and 18 µg/mL) that cover the linearity range were measured three times each. Accuracy was assessed as a recovery percentage (R%), **Table 1**. Good R% ranged from (98.45 to 101.48) which confirms excellent accuracy.

Precision - The assessment of repeatability included calculating (% RSD) for three distinct concentrations of a pure drug. This assessment was conducted in triplicate on the same day (intra-day) as well as on three consecutive days (inter-day). (RSD) values, which were observed to be less than 2, suggest that these methods exhibited a high level of precision. **Table 2.**

Specificity – It was achieved by employing the four proposed UV spectrophotometric methods to laboratory-prepped combinations of the intact nimodipine and each of its degradates. The suggested procedures yielded good recoveries of intact nimodipine in the presence of (5- 70%) of its degradates proving the specifity of them; **Table 3**.

Application to tablet dosage form- The suggested UV- spectrophotometric methods were used to determine nimodipine in Nimotop® tablets after extracting the drug with very little amount of DMSO then diluted with methanol. The results showed that the mean % recoveries varied from 98.89±0.83 to 101.10±0.60; **Table S2.**
Additionally, the standard addition technique was employed to assess the recovery of the proposed methods. The results indicated that the four suggested UV-methods yielded satisfactory mean recoveries, which varied from 98.99 ±1.32 to 101.59 ±0.611. **Table S2.**
Statistical evaluation of the four proposed UV spectrophotometric methods to the reported method [(22)] revealed no significant difference in accuracy and precision within a 95% confidence interval; **Table 4.** The suggested processes were environmentally friendly, simple, quick, and exact. Furthermore, they demonstrated drug stability by assessing the drug in the presence of its acidic, alkaline, and oxidative degradates.

3.3.7. Evaluation of greenness of the proposed methods for nimodipine analysis

Eco-scale: The suggested methods effects on the environment were assessed utilizing an analytical eco-scale. Penalty points are calculated by the eco-scale for every step taken during the analytical process. The computed outcome is arranged according to a scale as follows: a score of more than 75 denotes an exceptional green analysis, a score of more than 50 denotes an acceptable green analysis, and a score of less than 50 denotes an unsatisfactory green analysis [34]; **Table 5.**

(GAPI) is a new tool that can assess the environmental friendliness of analytical procedure, from sample collection to final result. GAPI utilizes a distinct symbol consisting of five pentagrams to evaluate and measure the environmental impacts associated with various stages of an analytical procedure. This symbol employs a color scheme whereby green, yellow, and red represent low, medium, and high impact levels, respectively [35]. The quantification of chemical hazards is facilitated by the use of GHS hazard pictograms on reagent containers[36]. **Fig 5** illustrates the interpretation of the GABI pentagrams for the suggested UV – methods and their comparison with the reported HPLC method [22].

Both eco- scale and GAPI provide evident that the suggested methods exhibited a higher level of environmental sustainability compared to reported one [22]. Hence, they can be used for regular pharmaceutical analysis without any adverse effects on the environment.

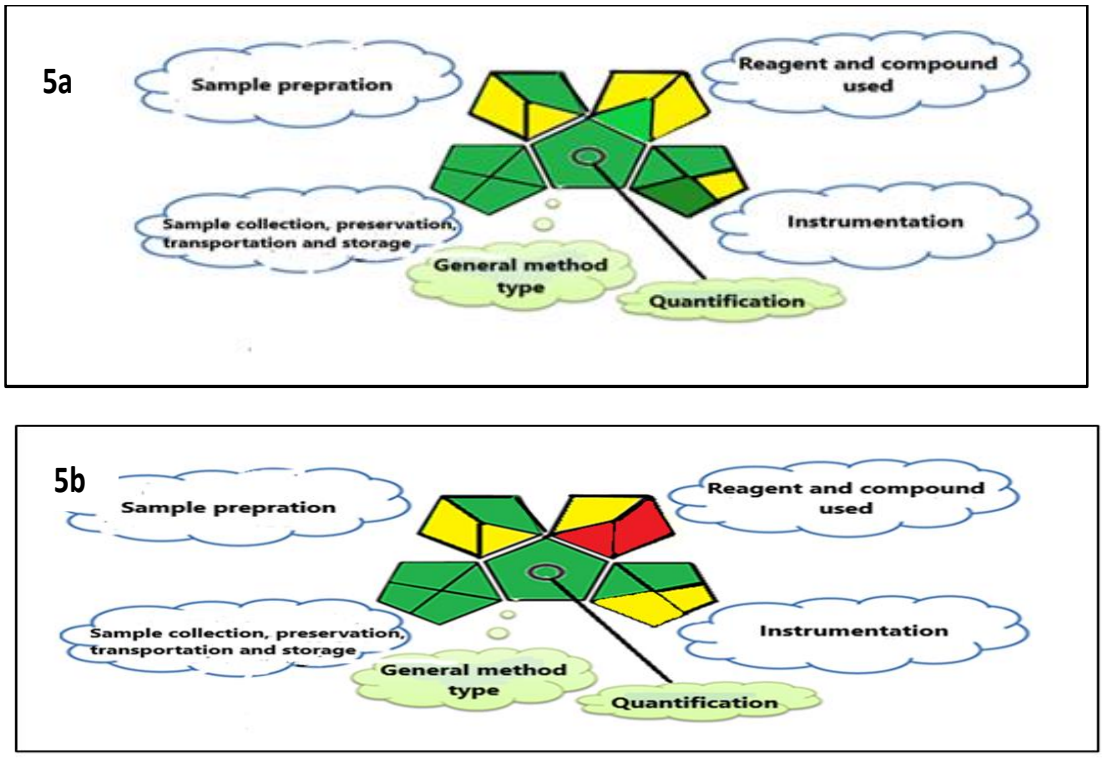

Figure 5. GAPI assessment tool: a) GAPI assessment tool 35 for the proposed UV spectrosphotometric methods. b) GAPI assessment tool for the reported HPLC22 chromatographic method

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Table 1. Assay parameters for the determination of nimodipine by the proposed UV- spectrophotometric methods.

parameter	Zero order method	^{1}D	Ratio Difference method			^{1}DR		
	In presence of acidic and oxidative degradates	In presence of acidic, alkaline and oxidative degradates	In presence of alkaline degradate	In presence of acidic, adegradate	In presence of oxidative degradate	In presence of alkaline degradate	In presence of acidic, adegradate	In presence of oxidative degradate
λ_{max} (nm)	354	389.5	370.7- 388.5	368.79-386.44	351.10-361.58	392.9	395.6	363.27
Linearity range	3-18	3-18	3-18	3-18	3-18	3-18	3-18	3-18
Regression equation								
Slope± SD	0.045±0.0003	0.006±0.0001	0.056±0.0007	0.184±0.0026	10.432±0.152	0.005±7.77x10^{-5}	0.395±0.005	10.295±0.133
Intercept± SD	-6.66 x10^{-5} ±0.004	-0.0168±0.0009	0.121±0.0089	0.232±0.031	4.063±1.774	0.010±0.001	0.099±0.065	1.836±0.931
SD of residual	0.004	0.001	0.0096	0.033	1.906	0.001	0.0705	1.667
Correlation coefficient (r)	0.9998	0.9994	0.9993	0.9992	0.9992	0.9994	0.9992	0.9993
LOD (µg mL^{-1})	0.269	0.515	0.524	0.551	0.561	0.651	0.547	0.497
LOQ (µg mL^{-1})	0.817	1.559	1.587	1.671	1.701	1.972	1.658	1.507
Accuracy	100.61± 0.226	101.04± 1.79	98.58± 1.086	101.24± 1.811	101.06± 1.585	98.73± 0.582	101.48± 1.588	98.45± 1.466

Nimodipine green UV- spectrophotometric assessment

Table 2. Precision for the determination of nimodipine by the proposed UV- spectrophotometric methods.

Procedures		Taken µg mL^{-1}	Intraday		Interday	
			Found*±SD µg mL^{-1}	Precision RSD%	Found*±SD µg mL^{-1}	Precision RSD%
Zero order At 354 nm		3 9 18	3.02±0.066 9.06±0.135 18.05±0.078	1.105 1.490 0.649	3.07±0.08 8.99±0.089 17.91±0.08	1.329 0.996 0.669
^{1}D At 389.5 nm		3 9 18	2.88±0.025 8.80±0.101 17.97±0.198	0.430 1.150 1.662	2.94±0.075 9.01±0.129 18.09 ±0.212	1.265 1.438 1.755
RD	**RD Difference between 370.7-384.5 nm**	3 9 18	3.03±1.485 9.12±1.916 18.18±1.507	1.471 1.892 1.492	3.06±1.485 9.06±1.699 17.99±1.50	1.454 1.687 1.502
	RD Difference between 368.79-386.44 nm	3 9 18	3.02± 1.811 8.86 ±1.446 18.18± 1.588	1.789 1.469 1.565	3.06 ±1.585 9.13± 1.392 18.11± 1.791	1.568 1.373 1.78
	RD Difference between 351.10-361.58 nm	3 9 18	3.06± 1.272 9.15±0.52 17.97±0.965	1.26 0.51 0.968	3.07±0.887 9.14±0.762 18.03±1.307	0.876 0.75 1.304
^{1}DR	**^{1}DR** At 392.9 nm	3 9 18	2.94±0.088 9.024±0.168 18.09±0.141	1.487 1.871 1.181	3.11±0.066 8.92±0.179 18.05±0.231	0.067 0.178 0.242
	^{1}DR At 395.6 nm	3 9 18	3.01±1.69 8.94±1.87 17.97±1.41	1.68 1.882 1.42	2.99± 1.69 8.95±1.685 17.89±1.69	1.69 1.694 1.70
	^{1}DR At 363.27 nm	3 9 18	3.12± 1.074 8.93±1.092 18.06±1.526	1.053 1.051 1.519	3.07±0.843 8.97±1.29 18.11± 1.644	0.833 1.294 1.649

* Average of three determinations.

Table 3. Determination of nimodipine in laboratory prepared mixtures with its degradates by the proposed UV- spectrophotometric methods.

Intact µg mL^{-1}	Degradate added µg mL^{-1}	% of degradate	Zero order		^{1}D			RD			^{1}DR		
			% of intact drug in presence of acidic degradate	% of intact drug in presence of oxidative degradate	% of intact drug in presence of alkaline degradate	% of intact drug in presence of acidic degradate	% of intact drug in presence of oxidative degradate	% of intact drug in presence of alkaline degradate	% of intact drug in presence of acidic degradate	% of intact drug in presence of oxidative degradate	% of intact drug in presence of alkaline degradate	% of intact drug in presence of acidic degradate	% of intact drug in presence of oxidative degradate
9.5	0.5	5	101.35	100.05	100.76	100.97	99.81	101.51	100.44	98.02	101.85	100.54	101.76
9	1	10	99.70	97.86	101.29	98.75	101.06	101.93	101.27	97.91	99.32	98.97	99.91
8	2	20	101.63	100.87	101.81	98.46	99.06	100.08	101.45	98.67	101.39	99.82	101.89
6	4	40	98.18	101.68	98.92	101.73	101.95	101.69	100.97	99.59	98.43	101.75	101.11
5	5	50	100.88	101.74	101.77	99.33	100.89	100.38	100.60	100.74	100.04	97.92	101.69
4	6	60	98.43	101.29	100.93	99.42	102.51	102.07*	101.39	100.03	99.13	100.33	100.06
3	7	70	99.06	99.31	99.85	102.14*	101.73	99.52	101.65	98.40	98.20	102.28*	99.46
Mean % ± SD			99.89± 1.41	100.40 ± 1.43	100.76± 1.05	99.77± 1.29	100.75± 1.12	100.85± 0.99	101.11± 0.45	99.05± 1.08	99.76± 1.41	99.88± 1.33	100.84± 1.01

Table 4. Results obtained by the proposed UV- spectrophotometric methods compared with reported method [22] for determination of Nimodipine in tablet dosage form.

Parameters	**Nimotop® tablets**								
	Zero order	**^{1}D**	**RD**			**^{1}DR**			**Reported method [22]**
λ_{max} (nm)	354	389.5	370.7-388.5	368.79-386.44	351.10-361.58	392.9	395.6	363.27	235
Linearity range(μgmL^{-1})	3-18	3-18	3-18	3-18	3-18	3-18	3-18	3-18	60- 180
N	5	5	5	5	5	5	5	5	5
Mean%	101.10	99.78	99.51	100.85	101.05	99.61	98.89	100.74	100.34
SD	0.601	1.167	1.696	1.127	0.968	1.422	0.831	0.670	1.19
Variance	0.361	2.79	2.88	1.615	0.937	2.02	0.692	0.449	1.42
t (2.306)	1.278	0.747	0.898	0.695	1.032	0.875	2.223	0.651	---
F (6.388)	3.923	1.039	2.031	1.114	1.511	1.429	2.046	3.152	---

The values in parenthesis are the theoretical t- and F- at P = 0.05. Reported method [22] for determination of nimodipine by HPLC method using methanol: tetrahydrofuran: water (30:20:50 v/v/v) as mobile phase with UV detection at 235 nm.

Table 5. Greenness assessment of the proposed spectrophotometric methods and reported chromatographic method [22] for the determination of nimodipine by Analytical Eco scale.

Reagents		Plenty point			
	Proposed Spectrophotometric methods				Reported method [22]
	Zero order method	1D Method	RD method	^{1}DR	
Methanol	6	6	6	6	6
Tetrahydrofuran					12
Water					0
		Instrument			
Energy (>0.1 kWh per sample)	0	0	0	0	0
Occupational hazards	0	0	0	0	0
Waste	5	5	5	5	5
Total pps	Σ11	Σ11	Σ11	Σ11	Σ23
Eco-Scale	89 Excellent green analysis	89 Excellent green analysis	89 Excellent green analysis	89 Excellent green analysis	77 Acceptable green analysis

4. CONCLUSIONS

Zero order spectra of nimodipine showed that the drug can be determined easily in presence of acidic and oxidative degradate but there was sever overlapping with alkaine degradate spectra. Therefore ^{1}DR, RD, ^{1}DR methods were selected for determination of drug in presence of its three degradates. Moreover, the simplicity of the proposed UV-spectrophotometric encourage their use in lab of routine analysis.

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Author Contribution: Authors Sawsan A. Abdel-Razeq and Manal. K. M. Darwish designed the study and wrote the protocol. Ebtesam. S. Mahmoud performed the experimental work and statistical analyses. Sawsan A. Abdel- Razeq and Manal. K. M. Darwish supervised the study. All authors wrote the first draft of the manuscript and managed literature searches. All authors read and approved the final manuscript.

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