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Development of a Green Spectrophotometric Method for the Determination of Amlodipine Besylate Using Ion-Pair Formation with Alizarin Red S and Its Application in Pharmaceutical Formulations

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Abstract

The aim of the presented work was to introduce simple, fast and sensitive spectroscopic technique for the determination of amlodipine besylate in bulk and dosage forms using UV-visible spectrophotometer based on formation of an ion-pair association with Alizarin Red S. The new absorption band at 570 nm was found for the formed complex. Results revealed that the recommended conditions were achieved at a concentration of dye 10 µg/mL, temperature 20–25 °C and stability of complexes up to 60 min. The results showed that maximum absorbance was obtained at pH = 5.52 without adding any acid or base and Job's method of mixture indicated that there was 1:1 ratio of amlodipine and dye. Linear calibration graph was obtained over the concentration range of 2.5–20 µg/mL with apparent molar absorptivity of 22511.89 $L \cdot mol^{-1} \cdot cm^{-1}$ and Sandell index of 0.02518 $\mu g/cm^2$. Accuracy, precision and reproducibility were also satisfactory and determined low concentrations. LOD was found to be 0.1261 µg/mL and LOQ was calculated as 0.3821 µg/mL. The applicability of the described method was checked with the commercial tablet formulation Amlopine. Method showed green chemistry index as 0.78 which is attributed to the usage of distilled water and minimized organic solvents and waste products. Proposed method can be successfully applied for determination of amlodipine in raw materials and pharmaceutical dosage forms.

Keywords

Amlodipine Besylate,
Alizarin Red S,
Ion Exchange,
Spectroscopic Analysis,
Green Chemistry.

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Introduction

amlodipine besylate is benzenesulfonate salt of amlodipine. The IUPAC name of amlodipine besylate is 3-ethyl-5-methyl-2-[(2-aminoethoxy) methyl] -4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate. The molecular formula and relative molecular mass of compound is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and 567.05 g/ mol [1] respectively. (Fig.1) [2].

Amlodipine besylate is a white to almost white powder which is practically water-insoluble, poorly soluble in 2-propanol, slightly soluble in absolute ethanol and very soluble in methanol [4,3]. It is used to treat high blood pressure. Amlodipine is also used for treating chronic stable angina and vasospastic angina (Prinzmetal's angina). Depending on the case, amlodipine can be taken by itself or with other medications [5]. Amlodipine has been analyzed using different analytical methods such as ultraviolet–visible (UV–Vis) spectroscopy [6–10], high-performance liquid chromatography (HPLC) [11–15], electrochemical [16, 17] and ultra-high-performance liquid chromatography (UPLC) [18].

Although drug quantification is achievable with these methods, most need multi-step preparations and expensive analytical instruments as well as consume large volume of solvents and chemicals which is contradictory to green chemistry and also increase cost of analysis. Hence, in this work, an ion-pair complex based novel spectroscopic method has been developed between amlodipine and alizarin red dye for the quantification of drug, as bulk drug substance as well as in its marketed dosage form keeping in mind the principles of green chemistry i.e. simplicity, time-economical, sensitive and low consumption of chemicals.

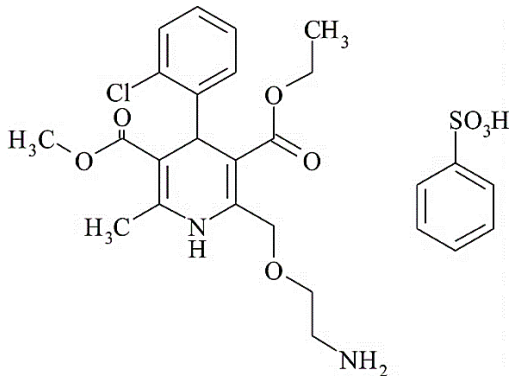

Figure (1) Chemical structure of amlodipine besylate [2]

Experimental Part

Instruments and Chemicals Used

The ultrasonic water bath (LabTech, Korea), double-beam UV–Visible spectrophotometer (UV-Visible-1800, Shimadzu, Japan), Sartorius high precision analytical weighing balance (Germany), and Jenway 3310 pH meter (UK) were used to conduct measurements. Analytical grade and highly pure materials were used during the study. These chemicals and reagents used are amlodipine besylate (Drug), alizarin red S, hydrochloric acid (HCI), and sodium hydroxide (NaOH) all of BDH brand.

Preparation of Solutions

Amlodipine Standard Solution (1000 µg/mL)

Correct amount of drug (0.025 g) was weighed out and placed in a 25 mL volumetric flask and dissolved in distilled water. The flask was filled to the calibration mark with distilled water and resulting stock solution was found to be 1000 µg/mL. From this stock solution 10 mL aliquot was diluted to 100 mL with distilled water in a volumetric flask to get working solution of concentration 100 µg/mL. The further measurements and calculations were carried out with the working solution.

Alizarin Red S Solution (1000 ug/ml)

Accurately weigh 0.025 g Alizarin Red S dissolve and dilute to volume with distilled water in a 25-mL volumetric flask to make a 1000 µg/mL stock solution. Serial dilutions with distilled water were performed to obtain desired concentrations for analysis. Transfer 10 mL of stock to a 100 mL volumetric flask and dilute to volume with distilled water. (100 µg/mL working solution)

A solution of hydrochloric acid with an approximate concentration of 0.1 molar

Hydrochloric acid (HCl) Solution was prepared by serial dilution. 0.83 mL of concentrated hydrochloric acid (12.06 M) was pipetted into a 100-mL volumetric flask, diluted to volume with water, which resulted in a 0.100 M HCl solution. The HCl solution was diluted further to create a 0.001 M hydrochloric acid solution used for analysis.

Approximate sodium hydroxide solution with a concentration of 0.1 molar

A stock NaOH solution was prepared by dissolving 0.400 g of the solid base into distilled water, which was then quantitatively transferred into a 100-mL volumetric flask and diluted to volume with distilled water. The stock alkali was serially diluted volumetrically to prepare the 0.001 M sodium hydroxide.

Amlopine Solution

One solution (Pharmaceutical formulation) of Amlopine (Prepared by pharmacy company in Saudi Arabia) was prepared by dissolving the homogenous powder obtained from well grinded 10 tablets of Amlopine. Weight of each tablet was calculated which was found to be 0.010 g (10 mg) of amlodipine. Then transferred the obtained powder in to a 100 mL volumetric flask, and added 80 mL distilled water. Then shake the solution vigorously then sonicated the content using ultrasonic water bath for 30 min. Afterwards, diluted it to volume with distilled water and filtered using suitable filter paper to yield a clear filtrate which was used as pharmaceutical formulation solution containing 100 µg/ mL of amlodipine.

Preparation of an Ion Pair Complex

The ion-pair complex was prepared by mixing 1 mL of the working solution of amlodipine (100 µg/mL) with 1 mL Alizarin Red S solution (100 µg/mL) into a 10-mL volumetric flask and was diluted with distilled water to mark. The final concentration of amlodipine and dye were made 10 µg/mL. The solution was scanned using a spectrophotometer at wavelength ranges from 190 to 800 nm to determine λmax. The spectra showed the formation of a new band at 570 nm due to interaction of ionizable complex of amlodipine and Alizarin Red S dye. The wavelength of 570 nm was selected as the analytical wavelength and was used to determine absorbance for further studies.

Results and Discussion

Experimental conditions

Optimal Dye Concentration

The dye level giving maximum complex formation with amlodipine was established by monitoring how the absorbance of the product varied with the amount of Alizarin Red S added. Accordingly, graded volumes of 0.25–3 mL of the 100 µg/mL Alizarin Red S standard were introduced into a series of 10-mL calibrated flasks, each already charged with 1 mL of the 100 µg/mL amlodipine solution. Dilution to volume with distilled water fixed the amlodipine level at 10 µg/mL, while the final dye concentrations ranged from 2.5 to 30 µg/mL. After preparing the solutions, the absorbance of the formed complex was measured at the specified analytical wavelength against a blank solution. The results showed an increase in the complex's absorbance as the concentration of Alizarin Red S dye increased, until the absorbance reached a maximum value at a dye concentration of 10 µg/mL, which was adopted as the optimal concentration for complex formation, the concentration of 10 µg/mL of Alizarin Red S dye was selected because it yielded the highest absorbance value for the complex formed with amlodipine compared to the other concentrations studied. This indicates that this concentration provides the appropriate conditions for the complex to form with the highest efficiency, thereby yielding the greatest analytical response and higher sensitivity for the spectrophotometric method.

When using concentrations higher than 10 µg/mL, the lack of an increase in absorbance or even a decrease may be attributed to the presence of excess dye that does not contribute to complex formation, which may result in increased background absorbance or interference from the absorbance of the free dye with the complex signal. Therefore, a concentration of 10 µg/mL was adopted as the optimal dye concentration in subsequent experiments, as it yielded the highest complex absorbance and the best analytical response under the experimental conditions studied, as shown in Table (1).

Table 1: Effect of Dye Concentration on Complex Composition

Optimal Dye Concentration	Absorbance
2.5	0.206
5	0.411
10	**0.623**
15	0.588
20	0.464
25	0.321
30	0.182

Effect of Temperature

The influence of different temperatures was investigated on complex formation between amlodipine and alizarin red S. The objective of temperature variation was to find the temperature providing the highest absorbance response for the formed ionic complex. Thus, aliquots of 1 mL each of amlodipine and alizarin red S standards were mixed in 10-mL volumetric flask and diluted with distilled water up to the mark. Absorbance of the formed complex was measured in the temperature range from 10–45 °C. Temperature range of 20-25 °C produced the highest absorbance and spectral response, indicating that complex formation is favored and stable under these conditions. Therefore, 20–25 °C temperature was chosen as optimum for the following measurements and experiments since it provided appropriate conditions for stable formation of the complex with the highest resulting spectral response and analytical sensitivity. Temperature above 25 °C may alter the equilibrium during complex formation process, i. e. increases its dissociation or instability, resulting in decreased sorption. On the other hand, low temperatures may lead to slow formation of the complex, which does not reach equilibrium during the measurement process. Table (2) showed that the most appropriate temperature providing stable complex and high analytical signal was 20-25 °C.

Table 2: Effect of Temperature on Complex Composition

T (℃)	Absorbance
10	0.534
15	0.587
20	**0.621**
25	**0.624**
30	0.597
35	0.571
40	0.553
45	0.532

Effect of Time

To verify the stability and consistency of the ionic complex formed between the drug amlodipine and the dye alizarin red S, the time needed to reach a steady absorption signal was examined. Aliquots of 1 mL of each standard solution (100 µg/mL) were mixed in a 10-mL volumetric flask and the mixture was diluted with distilled water up to the mark. The absorbance was followed from zero time up to 60 min to observe any shift in spectral response. As shown in Table (3) there was no significant change in absorbance with time, that is absorbance of the complex is stable over the study period.

This stability might be due to kinetic stability of the formed complex between amlodipine and Alizarin Red S. Kinetic stability suggests that the complex formation reaction takes place quickly and the composition of the complex does not change throughout the measuring process significantly (no extensive dissociation or change in concentration of absorbing

species occur). Therefore, there was no need to wait for a certain period of time before measuring and the absorbance value can be read immediately after the complex is formed. This is a very convenient feature of the analytical method considering its quickness and applicability.

Table 3: The Effect of Time on Complex Formation

Time	Absorbance
Immediately	0.621
5	0.623
10	0.622
15	0.623
20	0.628
30	0.624
40	0.625
50	0.623
60	0.626

Effect of pH

The pH at which maximum complexation occurs was determined by finding the pH at which the complex had the highest absorbance. So, the pH of the solution was changed using 0.001 M hydrochloric acid and 0.001 M sodium hydroxide. The change in pH was recorded and the absorbance of the product formed was measured at different pH values. The pH at which maximum absorbance occurs is pH = 5.52 (pH of the solution without any alterations to the media). We decided pH = 5.52 was used for subsequent measurements (See Table (4)). This is most likely because pH 5.52 allows both the Amlodipine and Alizarin Red S to form an ionic complex and not another type of complex. pH 5.52 allows both the reactants to be in their ionic species such that they can provide maximum stability to each other through electrostatic interactions. If pH is changed, then the sorption capacity will decrease. This is because the ionization of the species and the equilibrium between the species and complex will change. Hence, there was no need to add HCl or NaOH to alter pH during subsequent measurements. The pH of the solution was simply allowed to equilibrate at its natural pH of 5.52.

Table4: The Effect of Effect of pH

Addition	Volume (ml)	Absorbance	pH
HCl (0.001)M	0.1	0.562	5.44
	0.2	0.513	5.36
	0.3	0.477	5.23
	0.4	0.428	5.17
	0.5	0.388	5.08
With any addition		**0.624**	5.52
NaOH (0.001)M	0.1	0.511	5.61
	0.2	0.535	5.68
	0.3	0.489	6.77
	0.4	0.472	6.83
	0.5	0.451	6.91

Stoichiometric ratio of complex

Job's Method of Continuous Variation was employed to estimate the stoichiometry of the ion- pair association complex formed between amlodipine (D) and Alizarin Red S dye (R) [19]. Standards of drug and dye both were prepared at the same concentration (100 µg/mL). Graduated volumes (0.1–0.9 mL) of amlodipine standard solution were pipetted into a series of 10 mL volumetric flasks and graduated portions of the dye solution (0.9–0.1 mL) were added and diluted to volume with distilled water volume of drug and dye was constant in each flask. The absorbance of the mixture on dilution to volume with distilled water was measured against a reagent blank as indicated in Table (5).Maximum absorbance value was observed at the mole fraction 0.5 of drug and dye. It can be concluded that the stoichiometry between amlodipine (D) and Alizarin Red S dye (R) in the ion- pair association complex is 1:1 (D:R) Fig. (2).

The reason behind getting 1: 1 binding ratio between drug and dye is because one molecule of amlodipine associates with one molecule of dye in presence of suitable binding sites and due to the availability of ideal distribution of ionic charges between drug and dye. Which facilitates the formation of stable ion- pair complex with equivalent ratio of 1:1 (Drug: Dye).

Table 5: Job's Method of Continuous Variation for the Ion-Pair Association Complex of Amlodipine Drug

VD/ (VD+VR)	Absorbance	VR	VD
0.1	0.089	0.9	0.1
0.2	0.153	0.8	0.2
0.3	0.212	0.7	0.3
0.4	0.266	0.6	0.4
0.5	**0.311**	0.5	0.5
0.6	0.273	0.4	0.6

0.7	0.201	0.3	0.7
0.8	0.141	0.2	0.8
0.9	0.062	0.1	0.9

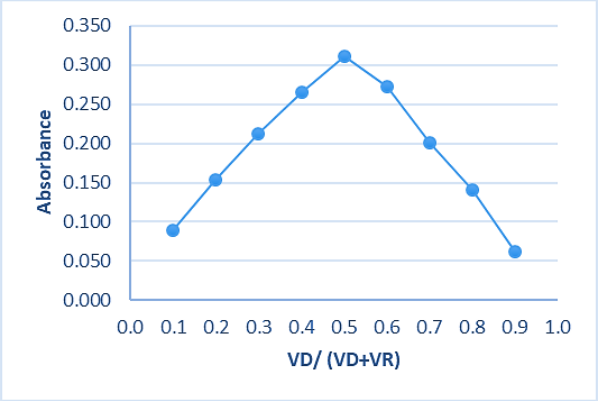

Figure (2): Binding Ratio of the Amlodipine Complex

Final Absorption Spectrum

Absorption spectrum of formed ion-pair association complex was measured against blank solution to spectrally confirm the formation of complex and study its absorption properties. As depicted in Figure (3) the absorption maxima of amlodipine and the dye were found to be at 238 nm and 422 nm, respectively. The appeared band at 570 nm was new and well defined. Appearance of new band at 570 nm, which was obviously shifted from the wavelength of maximum absorption of both amlodipine and the dye, provides spectral proof for an interaction to take place between the two species of the system and confirms the formation of new chemical species having different electronic transitions than those of the individual species. Shift in the spectrum can be rationalized by the formation of ion-pair association between amlodipine and Alizarin Red S dye which changes the electronic environment of the species causing the absorbance band to shift towards higher wavelength. Therefore, 570 nm was selected as the analytical wavelength of ion-pair association complex, because of appearance of new band at this wavelength and its applicability towards selective measurement of the complex as compared to the wavelength of maximum absorption of the individual species.

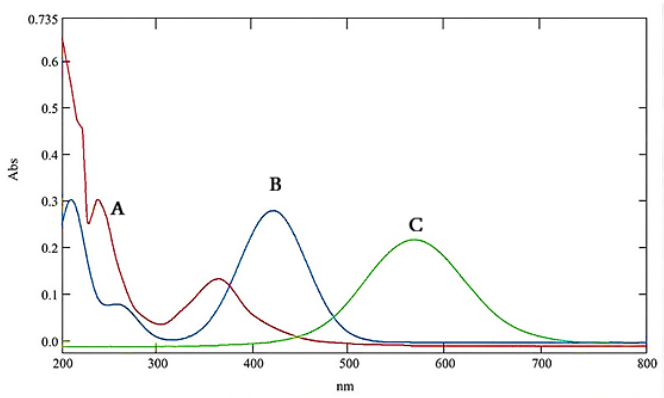

Figure (3): Absorption Spectra of A- Amlodipine Besylate, B- Alizarin Red S Dye, and C- the Amlodipine–Alizarin Red S Ion-Pair Association Complex.

Procedure and Construction of the Calibration Curve of the Complex

For calibration, 10 mL volumetric flasks were used. Each flask was charged with a graded portion of the amlodipine standard (100 µg/mL) (0.1 to 2.5 mL) and 1 mL of the Alizarin Red S standard (100 µg/mL). Final drug concentrations of 1-25 µg/mL were obtained by dilution to volume with distilled water. The measurements were carried out under optimum experimental conditions and the absorbance was recorded at the analytical wavelength of 570 nm. The results showed good linear relationship between the absorbance of the complex and the concentration of amlodipine in the range of 2.5–20 µg/mL as shown in Figure (4). This linearity shows that the spectrophotometric procedure is reliable for the determination of amlodipine in this range. The molar absorptivity (ε) value was found to be 22511.89 L. mol^{-1} $cm.^{-1}$ which indicated the good spectral sensitivity of the method, whereas the Sandell's sensitivity was found to be 0.02518 µg/cm^2. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.1261µg/mL and 0.3821 µg/mL respectively as per the statistical equations. These parameters taken together show that the proposed method has enough sensitivity and good applicability for the spectrophotometric determination of amlodipine, particularly in the linear range studied.

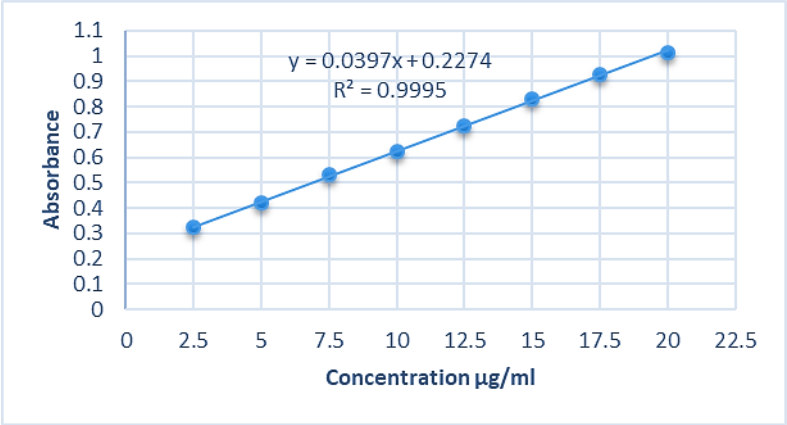

Figure (4): Calibration Curve of the Amlodipine Complex

Validation of the Method

The proposed analytical method for the determination of amlodipine was validated by the study of several analytical parameters such as limit of detection (LOD), limit of quantification (LOQ) and the precision and accuracy of the method to confirm the efficiency and the suitability of the method for the quantitative determination of amlodipine under the adopted experimental conditions.

Limit of Detection and Limit of Quantification

The limit of detection (LOD) and the limit of quantification (LOQ) of the ion-pair association complex of amlodipine with Alizarin Red S dye were estimated at the wavelength of 570 nm, by carrying out five replicate absorbance measurements at the lowest concentration on the calibration curve (2.5 µg/mL). Limits were calculated from the SD of these readings using the relationships LOD=3.3σ/S and LOQ=10σ/S where σ is the scatter of the analytical response and S is the slope of the calibration line. Table 6 shows the calculated values of both LOD and LOQ.

Table 6. Limit of detection and quantification of proposed method

Conce.	Slope	SD*	LOD	LOQ
2.5 µg / ml	0.0397	0.001517	0.1261	0.3821

*Average of five determinations

Accuracy and Precision

Accuracy and Precision were determined at three levels of amlodipine 2.5, 10 and 20 µg/mL by performing five replicate determinations. Accuracy was calculated as percentage recovery (Rec%), Precision and repeatability were determined as percentage relative standard deviation (%RSD) [20]. Table (7) revealed appropriate recovery percentages and %RSD values confirming good accuracy and precision of the proposed method and reproducibility of the analytical results over the studied concentration range.

Table 7: Accuracy and Precision of the Ion-Pair Association Complex of Amlodipine Drug

Concentration Taken µg/ml	Absorbance*	Concentration Found µg/ml	Rec%	RSD%
2.5	0.3246	2.4484	97.3300	0.4672
10	0.6238	9.9849	99.6474	0.2378
20	1.0138	19.8086	99.0428	0.2553

*Average of five determinations

Application of the Direct Method [21]

The method was further validated by application to Amlopine tablet formulation to investigate its practicability for routine analysis of pharmaceutical samples. Three different solutions were prepared in 10 mL volumetric flasks. To each flask added a previously prepared preparation solution (100 µg/mL) in 0.5, 1.0 and 1.5 mL quantities, respectively. 1 mL portion of Alizarin Red S standard solution was added to each flask and diluted to volume with distilled water to obtain final concentrations of amlodipine of 5, 10 and 15 µg/mL and the measurement was carried out under optimized conditions. The regression equation for calibration line was used to calculate the exact concentration of the analyte in the samples and thus determine the amount of API present in each tablet of the Amlopine formulation. The recovery % shown in Table (8) represents the agreement between the found content of API and the labeled claim of the tablet formulation which verifies the proposed method can be applied for determination of amlodipine in pharmaceutical preparations.

Table (8): Application of the Direct Method to the Ion-Pair Association Complex of Amlodipine Drug

Concentration Taken µg/ml	Absorbance*	Concentration Found µg/ml	Rec%	RSD%
5	0.4204	4.8615	97.2292	0.4321
10	0.6196	9.8791	98.7909	0.4361
15	0.8318	15.2242	101.4945	0.2870

*Average of five determinations

Evaluation of the Compliance of the Proposed Method with Green Chemistry Principles Using AGREEprep

The greenness assessment of the sample preparation method using the AGREEprep metric showed a high overall score of 0.78, indicating good compliance of the method with the principles of green analytical chemistry. The method showed excellent performance in Criterion 1, Criterion 2, Criterion 5, and Criterion 10, reflecting the efficiency of the method in terms of the location of sample preparation, handling of hazardous materials, reduction of the sample amount used, and operator safety. It also showed good performance in Criterion 3, Criterion 6, and Criterion 9, indicating appropriate use of sustainable materials, good sample throughput, and good compatibility with the subsequent analysis step. Criterion 4, on the other hand, indicates the possibility of improving the reduction of waste generated by the preparation process. Criteria 7 and 8 represent the aspects most in need of improvement, particularly with regard to integration and automation, and energy consumption [22]. Overall, the final score confirms that the proposed sample preparation method possesses good analytical greenness and is highly consistent with the principles of green chemistry, as illustrated in Figure (5).

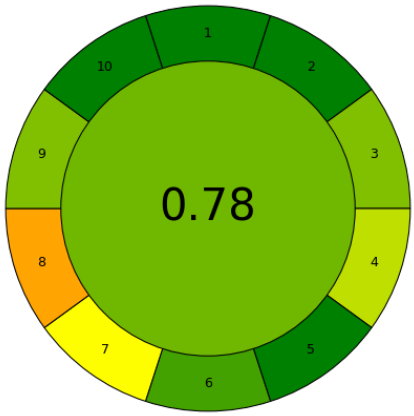

Figure (5): Greenness Assessment of the Sample Preparation Method Using the AGREEprep Metric

Conclusions

In this work ion-pair association procedure is established for amlodipine in bulk and Amlopine tablet formulation by using UV-Visible spectrophotometric method. The proposed method showed linear and suitable response in the studied concentration range and good analytical sensitivity. The percentage recovery (Rec%) and relative standard deviation (%RSD) values exhibited the good accuracy and precision of the method, whereas the limit of detection (LOD) and limit of quantification (LOQ) values proved the ability of the method for the efficient determination of low concentrations of amlodipine. The method was also successfully applied to the pharmaceutical preparation Amlopine.

The results agreed with the labelled content of the active ingredient, and hence confirmed the validity of the method to be used in routine pharmaceutical analysis. Also, the method was well orientated to the principles of green chemistry, because the green chemistry index value was 0.78, which means a good level of environmental sustainability of the method by reduction of hazardous chemical use, and reduction of waste generated during the analysis process. Thus, the proposed method is simple, accurate, precise and sensitive and applicable for pharmaceutical preparations and also fulfilling the requirements of green analytical chemistry. Thus, it can be concluded that the proposed method is a promising method for the determination of amlodipine in pharmaceutical samples.

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