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NOVEL ECO-FRIENDLY SPECTROPHOTOMETRIC DETERMINATION OF LERCANIDIPINE HYDROCHLORIDE IN TABLETS USING METHYL RED

Liubomyr Kryskiw, Mariana Horyn, Tetyana Kucher, Nadiya Zarivna, Olha Poliak, Liliya Logoyda

The aim of the work was to develop a simple, eco-friendly, quick, affordable and alternative spectrophotometric procedure that uses the azodye methyl red (MR) for the determination of lercanidipine in its dosage form considering the “green” chemistry principles.

Materials and methods. Analytical equipment: Shimadzu UV-1800 double beam UV-visible spectrophotometer (Japan) with included UV-Probe 2.70 software, RAD WAG AS 200/C precise analytical balance (Poland), Elmasonic EASY 40H ultrasonic bath.

Lercanidipine hydrochloride (purity 99 %) was purchased from Jiyan Chemicals (India). Lercanidipine tablets 10 mg and 20 mg were used in our experiments.

Results and discussion. To determine the amount of lercanidipine in tablets, a spectrophotometric method has been developed. To select the best dye for the method development, we tested a variety of dyes, including MR, bromocresol purple, bromophenol blue, cresol red, bromocresol green and bromothymol blue. We selected MR as the reagent based on the experimental studies' outcomes, and the solvent was an acetonitrile and ethanol mixture with a ratio of 95 to 5. The optimal parameters were determined for the quantitation of lercanidipine in tablets utilizing MR with 5×10^{-5} mol/L of dye concentration, 0.5 ml of MR solution, at a temperature of 25 °C without heating; detection wavelength was 498 nm and reaction time of 5 min. By using the molar ratios (saturation) method and Job's (continuous variations) approach, the stoichiometric coefficients of reacting components involving lercanidipine and dye were established to be 1:1. The proposed spectrophotometric procedure was linear within the concentration ranging from 6.48–32.41 µg/mL. Using the least squares method, a regression equation was generated: $y=0.0208x-0.0318$. The correlation coefficient was higher than 0.999, indicating that the analytical procedures' linearity is acceptable; the limit of detection and limit of quantitation were 1.19 µg/mL and 3.62 µg/mL, respectively. The robustness, accuracy and precision of the study results fell within acceptable limits. The proposed method was successfully applied to determine the content of lercanidipine in its tablet dosage forms. The analysis of the method's “greenness” using AGREE and GAPI tools yielded excellent results.

Conclusions. The method that has been developed can serve as an alternative approach for the routine control of lercanidipine content in its tablets

Keywords: lercanidipine, calcium channel blockers, spectrophotometry, methyl red, validation, quantitative determination, greenness assessment, AGREE, GAPI, tablets

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1. Introduction

Arterial hypertension is one of the main factors in the development of cardiovascular diseases, for the treatment of which drugs of various pharmacological groups and chemical structures are used. Our research is devoted to lercanidipine (zanidipine) – a synthetic highly lipophilic dihydropyridine antagonist of calcium channels of the III generation, which long-term lowers blood pressure in patients of various age categories and with various concomitant diseases, which is explained by good tolerability. It is quite important that, unlike the first and second generations, lercanidipine has a wider spectrum of pharmacological action and shows significantly fewer side effects [1].

The chemical structure of lercanidipine is 2[[3,3-diphenylpropyl) (methyl)amino]-1,1-dimethylethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5 -dicarboxylate (Fig. 1) [2].

The monograph on this substance is included in the European Pharmacopoeia, according to which the identification of impurities and the quantitative determination of lercanidipine are carried out by the method of liquid chromatography [3].

To control the quality of lercanidipine in substance and mono-preparations, as well as in combination with other drugs, various physicochemical methods are used: spectrophotometry [4, 5], TLC [6], HPTLC [7], high-performance liquid chromatography (HPLC) [8, 9], HPLC with tandem mass detection (MS/MS) [10, 11], ultra HPLC with MS/MS [12] and others [13, 14]. However, the vast majority of them are difficult to implement, long-term, expensive, not environmentally friendly, etc. The spectrophotometric method, unlike others, has a minimal negative impact on the environment and is therefore widely used in the analysis of medicinal substances. After review-

ing the literature, we concluded that the described spectrophotometric methods have some disadvantages: additional extraction, expensive and toxic solvents are used, buffer solutions to create a certain pH, negative impact on the environment, small range of application of the method, etc.

Scientists of the Pharmaceutical Chemistry Department of I. Horbachevsky Ternopil National Medical University developed spectrophotometric methods for the quantitative determination of ACE inhibitors and angiotensin receptor antagonists in tablet dosage forms using various dyes [15], including MR [16]. They tried to apply this line of research to calcium channel antagonists. Due to the presence of a tertiary aliphatic amino group, lercanidipine presumably forms a complex with MR, on the basis of which we developed a new spectrophotometric procedure.

Therefore, the aim of our study was to develop a simple, fast, affordable, reliable and “green” spectrophotometric method for the determination of lercanidipine in

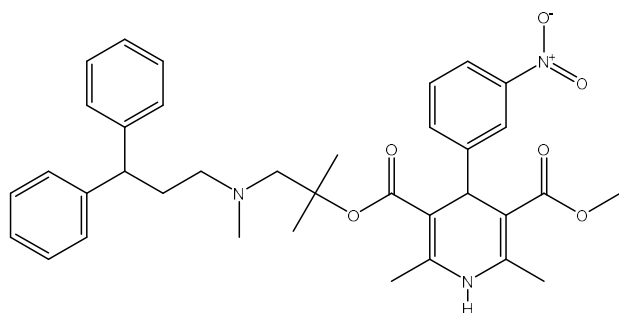


Fig. 1. The chemical structure of lercanidipine [2]

tablets based on the reaction with MR.

2. Planning of the research

The following is the methodology used in the investigation of a quick, easy and affordable alternative spectrophotometric procedure for determining the content of lercanidipine in tablets:

1. Examining scientific sources and Ph. Eur.
2. Choosing the reaction parameters for the dye-lercanidipine reaction (adjustment of reagent concentration and quantity, best solvent and detection wavelength and investigation of reaction stoichiometry).
3. Development and following validation of the spectrophotometric procedure for lercanidipine quantification in tablet form, which relies on the reaction with MR.
4. Application of the newly developed spectrophotometric procedure for the analysis of commercially available dosage forms lercanidipine. Lercanidipine tablets 10 mg and 20 mg were used in our experiments.
5. Evaluation of the developed spectrophotometric method's greenness profile with AGREE and GAPI tools.

3. Materials and methods

Objects of study, solvents and equipment.

Analytical equipment: Shimadzu UV-1800 double beam UV-visible spectrophotometer (Japan) with included UV-Probe 2.70 software, RAD WAG AS 200/C precise analytical balance (Poland), Elmasonic EASY 40H ultrasonic bath.

Lercanidipine hydrochloride (purity 99.0 %, HPLC) was purchased from Jiyan Chemicals (India). Lercanidipine tablets 10 mg (Lercanidipine Biogaran – Laboratories Biogaran, Lercamen – Berlin Chemie AG) and 20 mg ((Lercanidipine – Omnipharm, Recordati Pharma, Lercamen – Berlin Chemie AG) were used in our experiments. 2-(4-dimethylaminophenylazo) benzoic acid (MR) (purity 98.7 %, HPLC) was purchased from Merck Sigma-Aldrich, ACS reagent grade, CAS 493-52-7.

The procedure for the determination of lercanidipine is utilizing a reaction with MR.

Precise weight and crushing of twenty tablets were done. A 25.00 mL volumetric flask was filled with a sample of powder containing 7.00 mg of lercanidipine. The sample was then mixed with 15.0 mL of acetonitrile, adjusted using the same solvent to the mark and placed in an ultrasound bath for two minutes before being filtered. An aliquot of 0.60 ml of obtained filtrate was added to a 10.00 ml volumetric flask containing 0.50 ml of 1.00×10^{-3} M solution of MR in ethanol, followed by the addition of acetonitrile to the mark, and mixing resulted in volume. A 498 nm wavelength was used to measure the absorbance of the resultant solution against the compensating solution's background. Aliquots ranging from 0.20 to 1.00 mL were taken in order to investigate linearity.

4. Results

4.1. Selection of reaction conditions

Lercanidipine is practically insoluble in water and heptane and soluble in organic solvents such as ethanol, methanol, DMSO and dimethyl formamide [3, 17].

Lercanidipine is not a challenging substance for the development of spectrophotometric procedures, given the present functional groups (Fig. 1). Because our scientific group has experience developing spectrophotometric procedures for the determination of different APIs using reactions with various dyes, we tested the latter as possible reagents for developing future methods. Upon reviewing the scientific literature pertaining to the advancement of spectrophotometric techniques for lercanidipine quantitation in its tablets, no analytical approach utilizing MR dye as a reagent was discovered. To select the best dye for the next step in method development, we have tested a variety of dyes, including bromocresol purple, bromophenol blue, cresol red, bromocresol green, bromothymol blue, thymol blue and MR. There were issues with the bromophenol blue reagent processing that needed careful investigation; however, this dye might also be a useful reagent in the future. We decided on MR based on the findings of our preliminary investigations (Fig. 2).

In the presence of lercanidipine, a non-extraction binary complex between the latter and MR was formed based on ion-pair associates. This might be due to the presence of a tertiary aliphatic amino group in the lercanidipine structure. The formation of a coloured complex with MR (λ_{\max} at 498 nm) indicates that lercanidipine forms an ion-pair complex with MR selectively in an acetonitrile ethanol mixture. These lercanidipine ion pairs associated with the dye were barely soluble in

water, but in the appropriate testing conditions, they became freely soluble and did not require the addition of non-ionic surfactants or extraction with organic solvents. Fig. 3 displays the absorbance of the lercanidipine - MR complex.

To get the maximum absorbance, MR should be present at a concentration of 5.00×10^{-5} M. It was found that 0.5 mL of ethanol solution of MR was required.

We have focused on choosing the best solvent for the next phase of the study. Fig. 4 presents the solvent selection results.

For MR, acetonitrile and ethyl acetate were considered as the best solvents. For further development we chose acetonitrile which received a G score of 5.8 [19] according to the Hansen space green solvent selection tool, as illustrated in Fig. 5 (with waste, health, environment, safety impact as 2.8, 5.9, 8.9, 7.7 respectively).

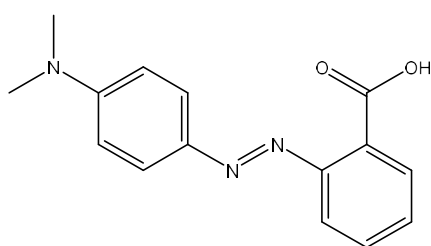


Fig. 2. The chemical structure of MR [18]

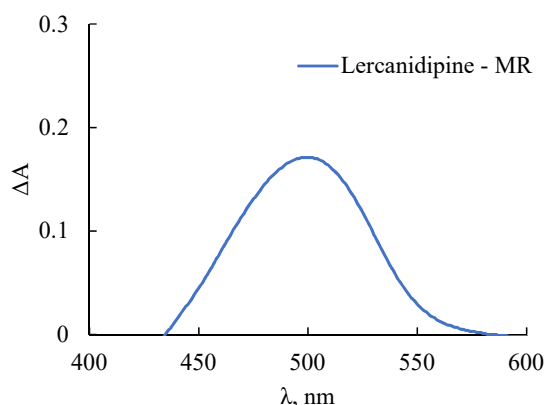


Fig. 3. Absorption spectra of lercanidipine (20 µM/l) – MR (52 µM/l) complex in acetonitrile – ethanol mixture), C % EtOH=5 %

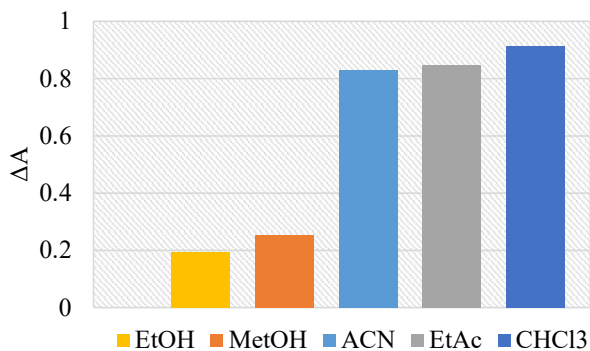


Fig. 4. Effects of solvents on lercanidipine (30 µM/l) – MR (52 µM/l) complex formation, C % EtOH=5 %

The influence of dye concentration on the increase in the absorption of its complex with lercanidipine at the

selected analytical wavelength was studied. It was shown that the optimal MR concentration is 50 µM (Fig. 6).

The presence of ethanol in the reaction mixture leads to an increase in absorption, it was found that its concentration at the level of 5 % is optimal (Fig. 7).

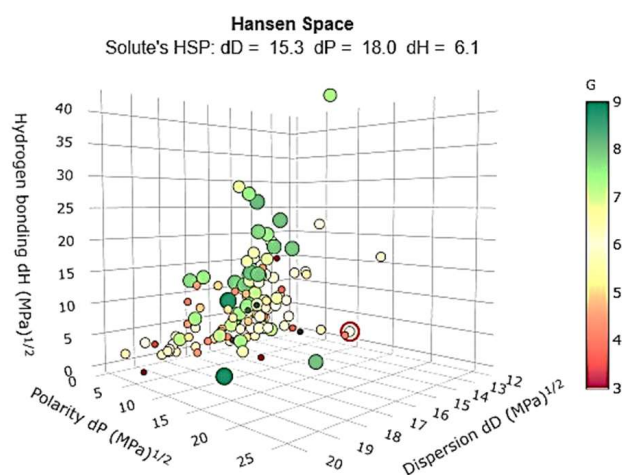


Fig. 5. Acetonitrile solvent sustainability level

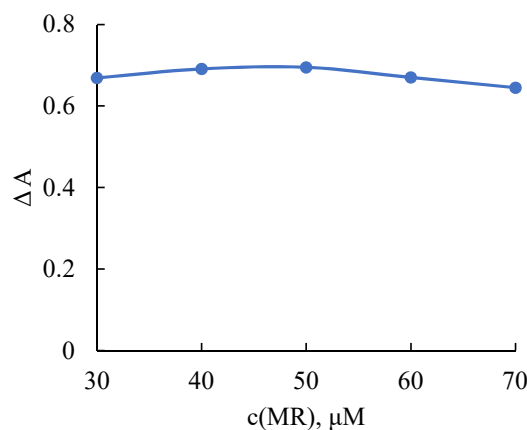


Fig. 6. Optimal MR concentration selection. c(lercanidipine)=30 µM/l, C % EtOH=5 %

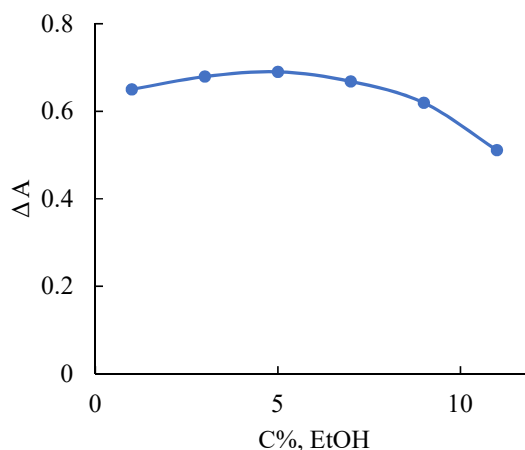


Fig. 7. Determination of optimal ethanol – acetonitrile ratio in the mixture. c(lercanidipine)=30 µM/l, c(MR)=52 µM/l, C % EtOH=5 %

It was investigated whether the ion-pair complexes of lercanidipine and MR were stable. Even though the ion pairs formed right away, steady absorbance values were

not measured until after the mixture had been at a constant temperature of 25 ± 2 °C for at least 5 minutes and had remained stable for 10 hours.

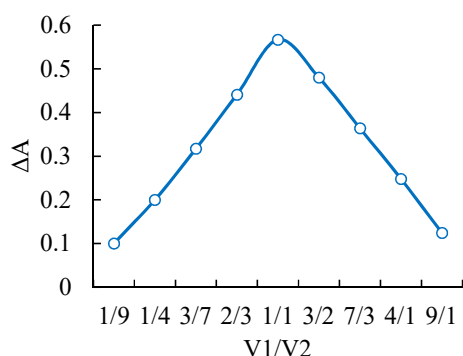
We can already consider developing the spectrophotometric method further at this point because we have chosen the reagent, its concentration and amount, the best solvent, the ratio of solvent components and the analytical wavelength. It is also important to determine the stoichiometric coefficients of the reacting components. By using the molar ratios (saturation) method and Job's (continuous variations) approach, the stoichiometric coefficients of the reacting components were ascertained. From Fig. 8, it can be concluded that the ratio of reacting components involving lercanidipine and dye equals 1:1.

The optimal parameters for lercanidipine spectrophotometric analysis via complex formation using MR are presented in Table 1.

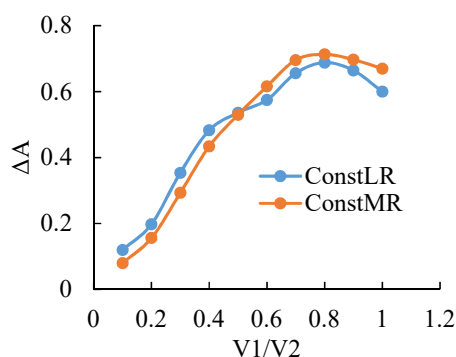
Table 1

The optimal parameters for lercanidipine spectrophotometric analysis via complex formation using MR

Conditions	Parameter
MR concentration, $\mu\text{M/l}$	50
MR volume, mL	0.5
Optimal solvent composition, V/V	Acetonitrile – ethanol, 95 – 5
Detection wavelength, nm	498
Reaction time, min	5
Ratio of reacting components	1:1
Operating temperature, °C	25 ± 2



a



b

Fig. 8. Study of stoichiometric coefficients by the reaction of lercanidipine with MR at $\lambda_{\text{max}} = 498$ nm, $c(\text{lercanidipine}) = c(\text{MR}) = 0.5$ mmol/L, $C\% \text{ EtOH} = 5\%$:
a – Job's method of continuous variations,
b – saturation method

4. 2. Determination of validation parameters

According to the requirements of State Pharmacopoeia of Ukraine (SPhU) [20], the spectrophotometric procedure for the determination of lercanidipine in tablets has been validated for the following characteristics: robustness, accuracy and precision, linearity and range of application.

4. 2. 1. Robustness assessment

During the method's development, the robustness was examined (stability of absorbance, variation in reagent volume, reaction time). It was found in earlier development experiments that adjustments made within $\pm 10\%$ during the robustness research do not substantially alter the absorbance value (Table 2).

Every computed result (inside the range of 98.0–102.0 %) satisfies the acceptance requirements.

Table 2

Robustness of lercanidipine determination using the proposed method

Method parameters	Recovery* \pm SD
Stability of solutions, h	
1	99.55 \pm 0.58
5	99.19 \pm 1.09
10	98.90 \pm 1.53
Volume of reagent, ml	
0.4	100.13 \pm 1.01
0.5	99.73 \pm 1.29
0.6	99.57 \pm 1.30
Time of reaction, min	
5	99.19 \pm 0.93
10	99.73 \pm 1.27
15	99.72 \pm 1.34

Note: * – average of the three results

4. 2. 2. Assessment of linearity and range of application

In compliance with the SPhU's criteria, the linearity of the proposed spectrophotometric procedure for the quantification of lercanidipine by reaction with MR was examined using regression analysis within the concentration ranging from 6.48–32.41 $\mu\text{g/ml}$. Table 3 provides some spectral characteristics and validation data for the evaluated spectrophotometric method.

Table 3

Validation parameters and spectral characteristics for the evaluated spectrophotometric procedure

Parameter	Value
λ_{max} , nm	498
Linearity, $\mu\text{g/mL}$	6.48–32.41
Correlation coefficient (R^2)	0.9992
Intercept \pm SD*	$-0.0318 \pm 7.53 \times 10^{-3}$
Slope \pm SD	$0.0208 \pm 3.50 \times 10^{-4}$
LOD**, $\mu\text{g/mL}$	1.20
LOQ***, $\mu\text{g/mL}$	3.62

Note: SD* – standard deviation; LOD** – limit of detection; LOQ*** – limit of quantitation.

The correlation coefficient was higher than 0.999, indicating that the analytical procedures' linearity is acceptable. The obtained results revealed that the limits of quantification (LOQ) and detection (LOD) were 3.62 µg/mL and 1.20 µg/mL, respectively.

4. 2. 3. Accuracy and precision assessment

To assess the accuracy of the proposed procedure, three lercanidipine concentration levels (6.48, 19.45 and 32.41 µg/mL) were investigated. As can be seen in Table 4, the obtained results demonstrated a strong agreement between the measured and actual ones, demonstrating the correctness of the established method.

Table 4

Accuracy assessment of the developed spectrophotometric determination of lercanidipine using MR

Sample nr.	Amount taken, µg/mL	Amount found, µg/mL	% Recovery*
1	6.48	6.46	99.67
2	19.45	19.58	100.67
3	32.41	32.18	99.28
Mean			99.87
SD	-		1.181
**RSD			1.183

Note: *Mean – of three parallel determinations; **RSD – relative standard deviation.

The recovery results vary from 99.0 to 101.0 percent on average. Every concentration level has a recovery value that falls between 98.0 and 102.0 percent. Less than 1.2 % is the RSD for individual recovery values.

Intra- and inter-day precision were used to measure how well the experimental results matched one another. Inter-day precision is achieved by monitoring the same concentrations over the course of three consecutive days, whereas intra-day precision is achieved by reproducing the determination of three lercanidipine concentration levels at three separate periods during the day. Table 5 presents the obtained results.

Table 6 displays our results considering the quantitative analysis of lercanidipine in tablets.

The minimal number of independent preparations required for the reference standard and sample was determined based on the data acquired in compliance with the guidelines [21]. Two sample preparations and at least one reference standard preparation are needed when utilizing MR. The analytical procedure's accuracy and repeatability are acceptable.

Table 5

Intra- and inter-day precision assessment

Concentration level	% Mean Recovery*±SD	
	Intra-day	Inter-day
1	99.67±1.46	99.50±1.57
2	99.42±0.69	100.61±1.27
3	99.81±1.30	99.13±1.62

Note: * – mean of three measurements

Table 6

The results of the quantitative determination of lercanidipine in tablet dosage form using reaction with MR

Dosage form	10 mg	20 mg
	9.696	19.919
	10.020	20.325
	9.873	19.551
	9.896	20.047
	10.027	20.258
	10.169	20.088
Average	9.947	20.031
SD	0.163	0.277
RSD	1.634	1.384

4. 3. Evaluation of the environmental friendliness of the developed procedure

In the twenty-first century, analytical methodologies' environmental friendliness is crucial and required. Prior to beginning our study, we wanted to create an ecological – that is, “green” – spectrophotometric procedure. When developing the method, we kept in mind twelve “green” chemistry principles. The developed method's “greenness” is greatly increased by using acetonitrile and ethanol mixture instead of hazardous organic solvents for the lercanidipine-dye complex extraction. Our methods' simplicity and quickness in preparing samples (without heating) is one of its significant pluses.

For evaluation of the «greenness» assessment, we used the Analytical GREENess (AGREE) calculator [22] and GAPI tool [23], which was compiled by Polish scientists. Figure 9 provides pictograms of analytical techniques utilizing the AGREE calculator and GAPI tool, respectively. The AGREE calculator shows a score of 0.69, with a resulting light green color, and the GAPI pictogram has many green and yellow areas, indicating an excellent “green” spectrophotometric determination.

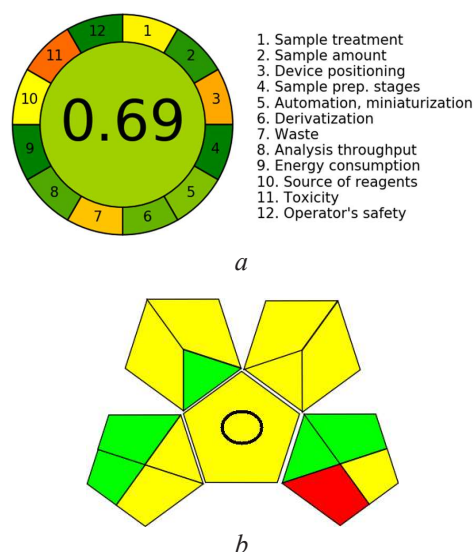


Fig. 9. Assessment of analytical «greenness» for developed procedures: a – AGREE; b – GAPI

5. Discussion of research results

Extensive scientific sources survey reveals that, in order to determine the content of lercanidipine in tablets

for regular pharmaceutical analysis, the base of spectrophotometric techniques has to be replenished. Many studies have shown that dyes are a promising reagent for spectrophotometric analysis of dosage forms. There isn't a spectrophotometric procedure in the scientific papers for lercanidipine assay involving reaction with MR. To choose the most suitable dye for the procedure development, we evaluated a variety of dyes, including MR, bromocresol purple, bromophenol blue, cresol red, bromocresol green and bromothymol blue. We selected MR as the reagent (Fig. 2) based on the experimental study findings, while a combination of acetonitrile and ethanol turned out to be the best solvent (Fig. 3, 4). The optimal parameters for quantification of lercanidipine content in tablets utilizing MR were determined (Table 1): the amount of dye is 50 μM (Fig. 6), the volume of MR solution in ethanol equals 0.5 ml (Fig. 7), no heating, detection wavelength – 498 nm, 5-minute reaction time and 25 °C solution temperature. As shown in Fig. 8, the stoichiometric coefficients were to be 1 to 1. In the concentration ranging 6.48–32.41 $\mu\text{g/mL}$, proposed spectrophotometric procedure utilizing MR was linear (Table 3). Using the least squares method, a regression equation was generated, $y=0.0208x-0.0318$ with $R^2=0.9992$, LOD and LOQ calculated to be 1.20 and 3.62 $\mu\text{g/mL}$ as well. The robustness study was assessed by observing the solutions' stability within 10 hours, the influence of MR volume ranging from 0.4–0.6 mL and reaction time from 5 to 15 min (Table 2). The analysis's results were unaffected by these alterations. The accuracy and precision of the study's results fell within acceptable limits. Based on the obtained data, the AGREE and GAPI pictograms (Fig. 9) demonstrate that an excellent «green» spectrophotometric procedure has been developed.

Practical Relevance. The content of lercanidipine in its tablets can be determined using the proposed spectrophotometric procedure.

Study limitations. It is not possible to use developed method with MR for lercanidipine determination in the presence of other APIs which may affect the analytical reaction.

Prospects for further research. In further studies, we plan to investigate the possibility of using bromophenol blue as a promising reagent for the determination of lercanidipine.

6. Conclusions

Based on the reaction with MR, we have developed a simple, eco-friendly, fast, affordable and alternative spectrophotometric procedure for lercanidipine assay in tablets. We have chosen straightforward parameters for sample preparation and determination procedure that enable accurate, fast and environmentally friendly determination of lercanidipine in tablets. Within the concentration ranging from 6.48–32.41 $\mu\text{g/mL}$, the analytical procedure was linear. In conclusion, the proposed spectrophotometric method for the lercanidipine assay in tablets has been developed as a replacement for the standard ones.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

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Data availability

Data will be made available at a reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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