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Original Article

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Fast Stability-Indicating HPLC Method for the Simultaneous Evaluation of Amlodipine Besylate, Indapamide, Perindopril Erbumine, and Their Degradation Products in Pharmaceutical Formulations

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Abstract

Background and Aims: This study aims to develop a stability-indicating and fast analytical method using reversed-phase high-pressure liquid chromatography (RP-HPLC) to determine amlodipine besylate (AMB), indapamide (IND), and perindopril erbumine (PRE) in pharmaceutical dosage forms.

Methods: In the developed chromatographic method, the active substances of pharmaceutical dosage forms were separated on an InertSustain C8 (150 mm × 4.6 mm, 3 µm) column using a mobile phase at pH 2 containing heptane acid sodium salt and acetonitrile as ion pair buffer and monitored at a detection wavelength of 215 nm. The column temperature of the method was 30 °C. The injection volume was 20 µL. The flow rate was 1.0 mL/min. The developed method was validated and then forced degradation studies were carried out according to the ICH guideline "Q2(R2) Stability testing of new drug substances and products".

Results: Under the chromatographic conditions described above, the retention times of PRE, IND, and AMB were recorded as 7.7 ± 0.5 min, 10.2 ± 0.5 min and 15.5 ± 0.5 min, respectively.

The linearity ranges were found out to be 0.2774–0.8322, 0.025–0.075, mg/ml and 0.0814–0.2442 mg/ml for AMB, IND, and PRE, respectively. Correlation coefficients were found to be more than 0.9990 for all. Acid, alkaline, oxidative, and photostability studies were performed for all three active ingredients.

Conclusion: This study demonstrated that a fast stability-indicating method has been developed for the simultaneous evaluation of amlodipine besylate, indapamide, and perindopril erbumine by RP-HPLC. The developed method has been successfully used for determining AMB, IND, and PRE in pharmaceutical dosage forms and their degradation products.

Keywords Amlodipine besylate · Indapamide · Perindopril erbumine · RP-HPLC · Stability indicating method · Validation

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INTRODUCTION

Hypertension is a common disease affecting the adult population and important health problem that increases cardiovascular risk. (Metwally et al., 2020). Although monotherapies are initially sufficient for patients with high blood pressure, combination therapies are needed to control cardiovascular risk as patients get older. Nowadays, fixed-dose combinations with complementary effects are widely used to control blood pressure in patients with arterial hypertension. Since it is beneficial in terms of time and cost to analyse with a single method of combined preparations containing more than one drug active ingredient in a single pharmaceutical form, there is a need to develop new methods for the simultaneous determination of such combinations. In this study, a fast stability-indicating RP-HPLC method was developed for estimating one of these combinations, amlodipine besylate (AMB), indapamide (IND), and perindopril erbumine (PRE), and their degradation products.

The chemical formula of AMB is 3-ethyl 5-methyl (4RS)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate (Figure 1A) AMB is a dihydropyridine calcium channel blocker or calcium ion antagonist. It inhibits the entry of calcium ions through the cell membrane into the cells of cardiovascular smooth muscles. The antihypertensive effect of amlodipine is due to its direct relaxing effect on the vascular smooth muscles. It is effective for the treatment of chronic stable angina pectoris and prinzmetal variant angina (Meredith & Elliott, 1992).

The chemical name of IND is 4-chloro-N-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-3-sulfamayl-benzamide (Figure 1B). It is a diuretic compound used for its antihypertensive effect. IND is an indole ring sulfonamide derivative that is pharmacologically related to thiazide diuretics. IND acts by inhibiting sodium reabsorption in the dilution segment of the cortex. It enhances urine output by promoting the excretion of sodium and chloride in urine and, to a certain extent, the excretion of potassium and magnesium, thereby showing an antihypertensive effect. It is used in patients with hypertension and heart failure (Caruso et al., 1983).

The chemical name of PRE is 2-methylpropan-2-amine (2S,3aS,7aS)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate (Figure 1C). PRE is an angiotensin-converting enzyme (ACE) inhibitor that can treat heart attack, stroke, and kidney problems (Patel et al., 2020). ACE inhibition causes a decrease in angiotensin II in the plasma, leading to increased plasma renin activity and decreased aldosterone secretion. As ACE inactivates bradykinin, ACE inhibition also increases the activity of the circulatory and local kallikrein-kinin systems. While this mechanism contributes to the blood pressure-lowering effect of ACE inhibitors, it is also partially responsible for some of their side effects (e.g. cough). PRE acts through its active metabolite, perindoprilat (Lees et al., 1992).

Fixed-dose combination therapy of AMB, IND, and PRE is an alternative therapy for treating the underlying conditions of patients with hypertension (Scheen et al., 2014; Kobalava et al., 2017; Chaudhary & Dave, 2020).

The novel fixed-dose combination of AMB, IND, and PRE fully embodies the principles of modern antihypertensive therapy. International studies have confirmed the blood pressure-lowering efficacy of this combination of ingredients (Kobalava et al., 2017).

When previously published methods for analysing AMB, IND, and PRE in combined dosage forms were examined, it was observed that some of them involved analyses in the binary combinations only (Al-Tannak, 2018; Zaazaa et al., 2013). Some of these methods are not stability-indicating methods (El-Bagary, 2017; Metwally et al., 2020; Patel et al., 2020). In the stability-indicating HPLC method previously reported for the combination of AMB, IND and PRE, by Chaudhary et al. (Chaudhary & Dave, 2020), the run time of the analysis was 65 min.

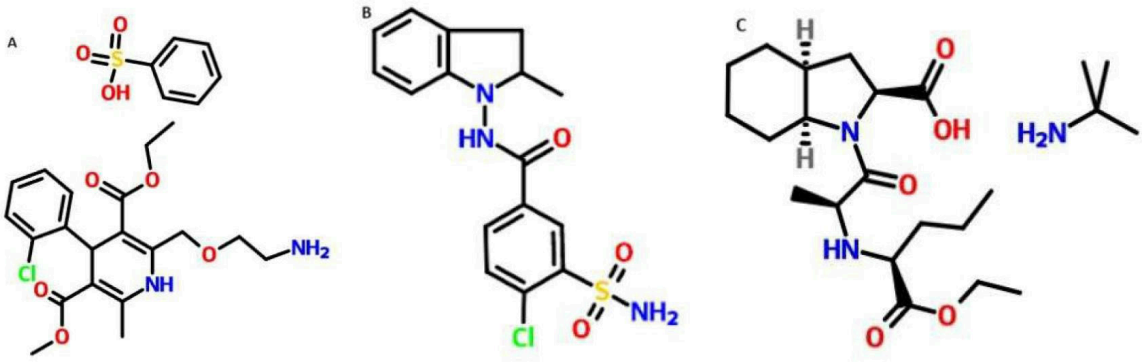

Figure 1. (A) Amlodipine besylate, (B) Indapamide, (C) Perindopril erbumine (Home sunshine pharma, 2024)

The aim of this work was to develop a validated, stability-indicating RP-HPLC method with a short analysis run time for the simultaneous determination of AMB, IND, and PRE in fixed-dose combinations.

MATERIALS AND METHODS

Materials

The AMB, IND, and PRE reference standards were obtained from Aurobindo Pharma Limited (Andhre Pradesh, India), Alchemia (Milano, Italy), and Hetero Drugs (Hyderabad, India), respectively. Preparations of reference standard: 0.5548 mg/mL AMB, 0.050 mg/mL IND, and 0.1628 mg/mL PRE. Solutions were prepared with mobile phases.

Reagents such as heptane sulphonic acid sodium salt, triethylamine, and perchloric acid were purchased from Merck (Darmstadt, Germany) as analytical grade and acetonitrile from JT Baker (New Jersey, United States) as HPLC grade. Fixed-dose combination drug products, such as 10 mg AMB/1.25 mg IND/4.07 mg PRE-film coated tablets, were used from Ali Raif Pharmaceuticals. Each tablet contains 10 mg AMB, 1.25 mg IND, and 4.07 mg PRE.

Instruments

A Shimadzu LC-20A Prominence HPLC System (Kyoto, Japan) with LabSolution software was used. The pump, autosampler, column oven, and diode array detector models were LC-20AT, LC-20ACHT, CTO-10ASVP, and SPD-M20A, respectively. The analytical balance was Mettler Toledo XP 205 (Greifensee, Switzerland), and the magnetic stirrer was Heidolph MR 3001(Schwabach, Germany).

Chromatographic Conditions

In the developed RP-HPLC method, an InertSustain HP C8 column (150 × 4.6 mm, 3 µm) was used for chromatographic separation. The mobile phase consisted of 0.005 M sodium heptane sulphonate (pH 2.0) - acetonitrile (65:35, v/v). The column temperature was set to 30 °C at a flow rate of 1.0 ml/min with isocratic elution. UV light was detected at 215 nm. The buffer solution was filtered with a 0.45 µm membrane filter and then degassed in an ultrasonic bath for 10 min before its use. The sample analysis was performed using an injection volume of 20 µl. The analysis run time was 20 min. Sample solutions were prepared with the mobile phase to final concentrations of 0.5548 mg/mL AMB, 0.050 mg/mL IND, and 0.1628 mg/mL PRE.

Validation of the Proposed Method

The validation of the developed RP-HPLC method was carried out according to ICH Q2 (R2) standards for accuracy, precision, robustness, specificity, linearity, range, and other parameters (Chavan & Desai, 2022; Ravisankar et al., 2015; Lavanya et al., 2013). In this method for specificity study; acidic, basic, oxidative, and photostability samples, reference standard (10 mg AMB/1.25 mg IND/4.07 mg PRE film coated tablet and placebo were injected into the RP-HPLC system. The peak purity value was checked to determine whether the method was a specific method with stability-indicating. To understand the linearity and range of the method, the graphs of the AMB, IND, and PRE solutions prepared at different concentrations were plotted against the obtained area values. Slope and y-intercept, correlation coefficients were checked. In the accuracy study, AMB, IND, and PRE concentrations were spiked over placebo at known concentrations, and recovery was evaluated within a 95% confidence interval. In the evaluation of precision results, parameters such as RSD%, number of theoretical plates, tailing factor, and statistical agreement of intra- and inter-laboratory analysis results were investigated. In this study, the researchers measured the robustness of the method by varying method parameters such as flow rate, wavelength and columns.

RESULTS

Specificity

The specificity of analytical method indicates its capacity to discriminate between the analyte(s) and other elements in the sample matrix (Le et al., 2019, Navya et al., 2015). To demonstrate specificity, mobile phase, placebo (Figure 2), AMB, IND, and PRE standards (Figure 3), spiked/unspiked samples (Figure 4) and degradation samples (Figure 5) were analysed using HPLC. All solutions were prepared as specified in the chromatographic conditions. It was observed that there was no interference between the AMB, IND, and PRE peaks and any other peaks in the chromatogram. The peak purity values for AMB, IND and PRE peaks were found to be between 0.99 and 1.00. All peak purity results were found to be 1.00. In the system suitability studies, the RSD % values between the standard peak areas were obtained from 6 consecutive injections of the standard solutions, and the retention times were found to be between 0.01% and 0.06%. Column efficiency (theoretical number of plates), symmetry/tailing factor, and capacity factor were recorded. These results are shown in Table 1.

Linearity and Range

In this study, the researchers evaluated the linearity of the method by preparing solutions in the concentration range of 50%-150%.

Concentrations and areas should have a correlation coefficient of at least 0.98. The variances obtained from linearity

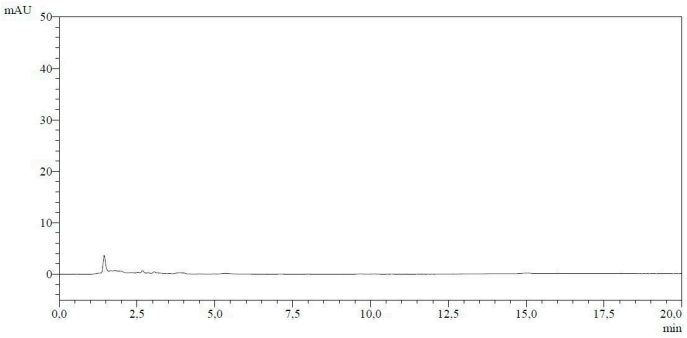

Figure 2. Chromatogram of placebo solution (10 mg AMB/1.25 mg IND/4.07 mg PRE-film-coated tablet)

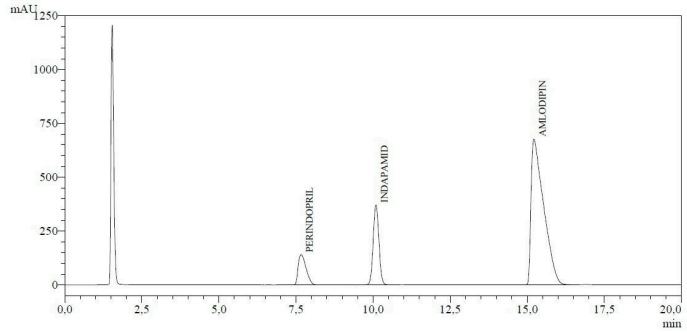

Figure 3. Chromatogram of standard solution containing 10 mg AMB/1.25 mg IND/4.07 mg PRE

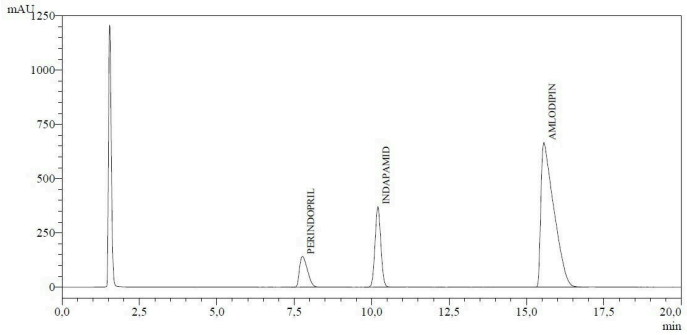

Figure 4. Chromatogram of sample solution containing 10 mg AMB/1.25 mg IND/4.07 mg PRE.

and the linear curve plot for each component should be within ±10% of the response at 100% concentration. The correlation coefficient $R^2 \geq 0.998$ and the Y-intercept% criterion were found to be between 0.78 and 1.17 (Table 1).

Accuracy

The degree to which the experimental results and actual amount of material in the matrix coincide is known as accuracy (Betz et al., 2011). To evaluate the accuracy of the assay, three different amounts of the active substance (50%, 100% and 150%) were added to a fixed amount of placebo. Individual and average recovery percentages, standard deviations, relative standard deviations, and 95% confidence intervals were calculated. Each recovery value was found to be in the range of 99.3%–101.5% (Table 1).

Precision

Precision is the measure of how close individual measurements of prepared solutions are to each other (Betz et al., 2011). Method precision was evaluated using repeatability and reproducibility. In the repeatability study, the RSD % values between the standard peak areas were obtained from 6 consecutive injections of the standard solutions, and retention times were found to be between 0.01% and 0.06% (Table 1).

In the inter-laboratory precision study, the results of the reproducibility (intra-laboratory precision) study were compared with those of the study conducted in a different laboratory (Araujo P., 2009). In addition, when the results of the intra-laboratory and inter-laboratory studies were compared, the assay results were found to be between 100.38% to 100.75% (Table 1). The mean of the results was found within the confidence interval.

Solution Stability

In solution stability studies, 3 injections were made at 0, 6, 12, 24, and 48 h from standard and sample solutions kept at room temperature (25 ºC) and refrigerated (2-8 ºC) conditions. The mean, standard deviation, and relative standard deviation of the analysis results and change% were calculated. The change% was found to be not more than 2.0% of the initial results. The standard solutions were stable for 48 h at room temperature (25ºC) and refrigerated (2-8ºC) conditions for AMB, IND, and PRE. The 10 mg AMB/1.25 mg IND/4.07 mg PRE-coated tablet sample solution was stable for 48 h at room temperature (25ºC) and refrigerated (2-8ºC) conditions (Table 1).

Robustness

The ability of an analytical process to yield objective data when minor adjustments are made to the experimental setup is known as robustness (Ferreira et al., 2016). The method parameters to be modified in robustness studies were summarized in Table 1. Retention time, symmetry factor, capacity factor, and theoretical number of plates did not show any significant differences compared with those obtained from the system suitability study.

Degradation Studies

Degradation studies were conducted to prove that a stability-indicating method was developed. Drug products are degraded under forced degradation like acidic, basic, and oxidative conditions (Blessy et al., 2014). To demonstrate forced degradation, the sample and placebo solutions were exposed to various stress conditions, such as acidic (1 N HCl and 70 °C), basic (1 N NaOH and 70 °C), oxidative (3% H_2O_2), and

Table 1. Performance characteristics of the AMB, IND, and PRE assays

Parameter AMB IND PRE			
System suitability results	Specific	Specific	Specific
RSD% Peak area	0.02%	0.06%	0.01%
Retention time	0.02%	0.01%	0.02%
Symmetry tailing factor	2.57	1.07	1.57
Capacity factor	8.60	5.36	3.87
Theoretical plate	5431	12679	3954
Linearity			
Range (mg/ml)	0.2764 - 0.8292	0.0256 - 0.0768	0.0816 - 0.2448
Slope	37570463	115052031	18205440
Intercept	1.17	0.78	1.09
Correlation coefficient	0.9994	0.9998	0.9994
Accuracy			
Recovery %	99.3	101.5	99.7
Confidence interval	0.86	0.89	0.58
RSD %	41275	42370	0.76
Repeability			
Peak area RSD%	0.02	0.06	0.01%
Retention time RSD%	0.02	0.01	0.02%
Intralaboratory			
Average %	100.58	100.09	100.72
Interlaboratory			
Average %	100.74	101.41	99.46
Confidence interval	0.69	1.07	1.09
RSD%	1.07	1.62	1.70
Solution stability (2-8 °C)			
Standart change%	0.07	0.24	1.28
Sample change%	1.48	0.21	0.90
Solution stability (25 °C)			
Standart change%	0.04	0.09	1.37
Sample change%	1.15	0.23	1.28
Robustness			
Flow rate (±0.1 mL/min)	Robust	Robust	Robust
Wavelength (±5 nm)	Robust	Robust	Robust

photolytic conditions. For photostability studies, the samples were exposed to light for an overall illumination of not less than 1.2 million lux hours and 300-800 nm (ICH Q1B).Under forced degradation conditions, PRE was significantly degraded under acidic conditions, severely degraded under alkaline and oxidative stress conditions, and moderately degraded under photolytic stress conditions. IND was severely degraded under alkaline and oxidative stress conditions and moderately degraded under photolytic stress conditions. AMB was significantly degraded under acidic conditions, severely degraded under alkaline and oxidative stress conditions, and moderately degraded under photolytic stress conditions. The results of these studies are presented in Table 2. Acidic, basic, oxidative, and photostability degradation studies were conducted to support the study by Chaudhary & Dave, 2020. Acidic and basic degradation studies were carried out under more difficult conditions, and more degradation was observed. The peak purity of all three active substances was found to be between 0.99 and 1.00 under all degradation conditions.

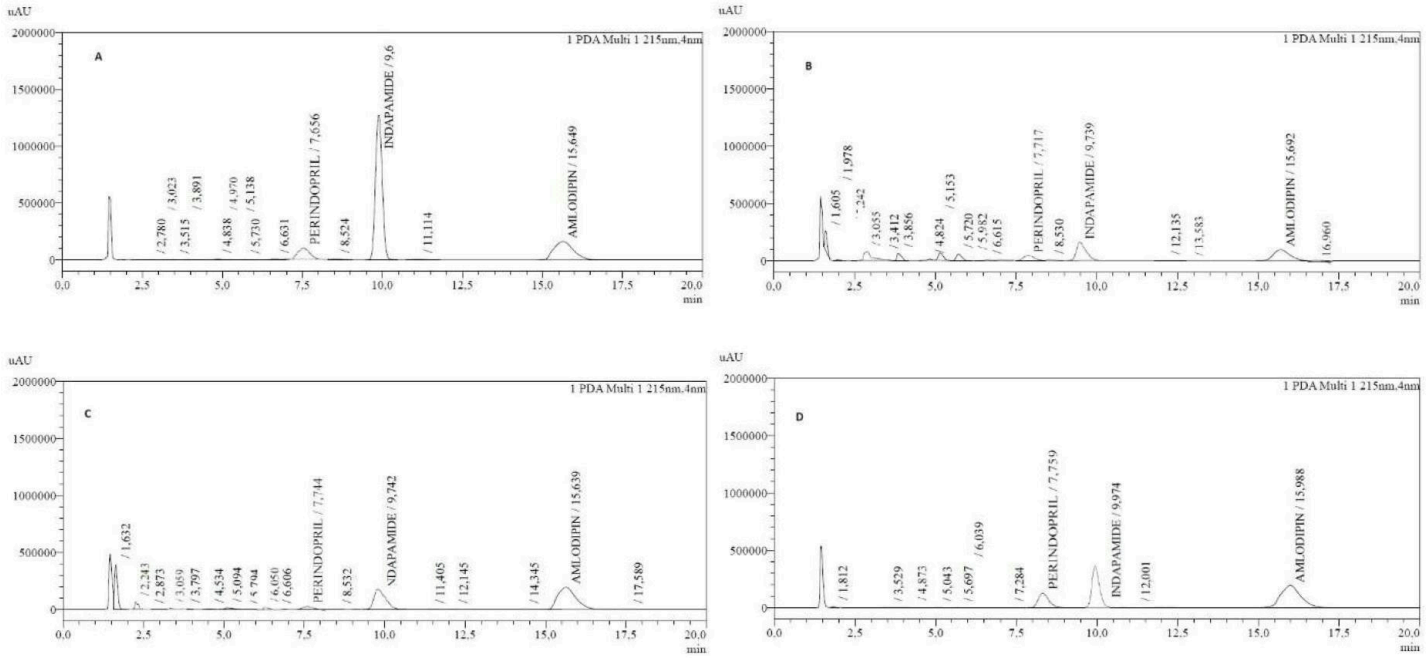

Figure 5. Chromatograms of A) acidic degradation, B) basic degradation, C) oxidative degradation, and D) Photostability

Table 2. Stress stability results of AMB, IND, and PRE

Degradation	AMB	IND	PRE
Acidic %	10.3	0.8	6.2
Basic %	53.2	15.6	68.0
Oxidative %	28.1	18.7	69.0
Photostability %	5.2	2.4	1.7

CONCLUSION

The developed RP-HPLC method was evaluated and validated for pharmaceutical dosage form analysis of AMB, IND, and PRE. The validation results and statistical data show that the proposed method is linear, precise, reproducible, selective, stable, and accurate. It was found applicable for routine pharmaceutical drug analysis. The simultaneous analysis of the three active ingredients in a shorter timeframe using by this method reduced the time, effort, price, energy and solvent cost and minimized the environmental damage. In addition, this stability-indicated and validated method can be used in routine stability analyses in quality control laboratories. The results demonstrated the development and validation of a short-term RP-HPLC method for the simultaneous, stability-indicated quantitative analysis of pharmaceutical dosage forms containing AMB, IND, and PRE.

The developed method was compared with previously published methods, and it was observed that some of these methods involved analyses in binary combinations (Khan et al., 2023; Al-Tannak, 2018; Zaazaa et al., 2013). Some previously published methods for the same combination are not stability-indicating methods (El-Bagary, 2017; Metwally et al., 2020; Patel et al., 2020). Since the purpose of these methods (El-Bagary, 2017; Metwally et al., 2020; Patel, et al., 2020) is only to determine the amount of a substance, it is not appropriate to compare them with the proposed stability indicator method. When we compared the proposed method with the stability-indicating HPLC method previously reported by Chaudhary et al., for the combination of AMB, IND, and PRE, the analysis time of the developed method was 45 min shorter. In routine analyses, this period provides considerable advantages in terms of time and cost. Additionally, in the proposed study, acid and base decompositions were tested in stronger environments using 1 N HCl and 1N NaOH. In addition, in the photostability study, the sample was exposed to all wavelengths in the range of 300-800 nm in the photostability study.

As a result, the proposed method is a fast, selective, precise, accurate, and stable RP-HPLC method with a shorter analysis time than the previously developed stability-indicating RP-HPLC method (Chaudhary & Dave, 2020).

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