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ORIGINAL ARTICLE

Developed and Validated for the Estimation of Bupropion and Dextromethorphan in a Fixed Dose Combination of the Tablet

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ABSTRACT

Objectives: The aim of this study was to develop a simple, accurate, and precise method for the estimation of bupropion and dextromethorphan in a fixed-dose combination of tablets and robust high-performance liquid chromatography for assay analysis of such a fixed combination.

Materials and Methods: Chromatographic analysis was performed and separations were achieved on a Denali C18 150 × 4.6 mm, 5 micron using a mobile phase composition of *ortho-phosphoric* acid and acetonitrile in the ratio of 600:400 (*v/v*), flow rate of 1.0 mL/min, injection volume is 10 µL and run time of 6 min in isocratic elution. Ultraviolet (UV) detection was performed at a wavelength of 221 nm. The temperature was maintained at 30 ˚C. Well-resolved peaks were observed with a high number of theoretical plates, lower tailing factor, and reproducible relative retention time. The method was validated, and all validation parameters were found to be within the acceptance limits.

Results: A simple, accurate, and precise method has been developed for estimating bupropion and dextromethorphan in a fixed dose combination of tablets. The optimized method included the following parameters: column temperature of 30 ˚C, 40% acetonitrile as the mobile phase, and flow rate of 1.0 mL/min. Retention times were 2.25 min and 3.12 min for bupropion and dextromethorphan, respectively. The method was found to be linear in the range of 17.5-105 µg/mL [for R^2 < 0.999) and 7.5-45 µg/mL (for R^2 > 0.999] for bupropion and dextromethorphan, respectively. Both active pharmaceutical ingredients dissolved more than 90% within 5 min.

Conclusion: The current study describes a new, simple, reliable, and economical elution reversed-phase high performance liquid chromatography method for estimating bupropion and dextromethorphan in a fixed combination tablet dosage form. The forced degradation studies were conducted using several degradation conditions such as acidic, alkali, oxidation, thermal, UV, and neutral conditions; the proposed method was effectively employed from the resolution of sample peaks. To the best of our knowledge, no such detailed and stability-indicating method has been reported for a fixed tablet dosage form.

Keywords: Bupropion, dextromethorphan, stress degradation, RP-HPLC method development and validation

INTRODUCTION

AUVELITY is a combination of dextromethorphan hydrobromide, an uncompetitive *n*-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, and bupropion hydrochloride, an aminoketone and CYP450 2D6 inhibitor.[1]

Dextromethorphan is an uncompetitive antagonist of the NMDA receptor (an ionotropic glutamate receptor) and a sigma-1 receptor agonist. The mechanism of action of dextromethorphan for treating major depressive disorder (MDD) is unclear. The mechanism of action of bupropion for treating MDD is also unclear; however, it may be related to noradrenergic and/or dopaminergic mechanisms. Bupropion increases the plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6, which catalyzes a major biotransformation pathway for dextromethorphan. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine and does not inhibit monoamine oxidase or the reuptake of serotonin.[1]

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Bupropion hydrochloride

Bupropion hydrochloride is an antidepressant of the aminoketone class. It is chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitors, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines and acts as a nicotinic acetylcholine receptor antagonist.[2-6]

Dextromethorphan hydrobromide

Dextromethorphan hydrobromide is an oral non-narcotic antitussive drug widely used in practical medicine. It was very well absorbed by the digestive system and did not bind to plasma proteins. A combination of pseudophedrine hydrochloride, chlorpheniramine maleate, and acetaminophen is used in pharmaceutical preparations to reduce symptoms usually associated with the common cold.[7-10]

Individual high-performance liquid chromatography (HPLC) methods reported for each drug were inappropriate for simultaneous determination because of interferences due to corresponding chromatographic peaks. However, these procedures require the use of more than one column, mobile phase, or flow rate, which can be time-consuming and uneconomical. Recently, a method has been reported for the simultaneous estimation of bupropion and dextromethorphan. However, the chromatogram revealed that the bupropion peak was eluted in the void volume where the interference was observed with the blank peak, and the placebo chromatogram was not recorded to identify the interference at bupropion and dextromethorphan. The reported method showed degradation of more than 10% for bupropion and dextromethorphan in acid, base, and peroxide, but degradation chromatograms were not shown.[11] The main aim of this method is to determine and validate bupropion and dextromethorphan in a fixed combination of tablet dosage forms based on the International Conference on Harmonization (ICH) guidelines.[12] This method was developed for use as a reproducible procedure for the quantitative analysis of drug samples. The designed method can be considered advisable for developing a precise, accurate, and simple reversed-phase high performance liquid chromatography (RP-HPLC) method.

The chemical name for bupropion is (±)-1-(3chlorophenyl)-2-[(1,1-dimethylethyl) amino]-1-propranone hydrochloride. The molecular formula is $C_{13}H_{18}ClNO•HCl$ and the molecular weight is 276.2 g/mol. The chemical structure of bupropion is shown in Figure 1.

The chemical name for dextromethorphan is (9S,13S,14S)-3-methoxy-17-methylmorphinan hydrobromide. The molecular formula is $C_{18}H_{26}BrNO$ and the molecular weight is 352.3 g/mol. The chemical structure of dextromethorphan is shown in Figure 2.

MATERIALS AND METHODS

Chemicals, reagents, and instruments

Bupropion, dextromethorphan, *ortho-phosphoric* acid (H_3PO_4), acetonitrile, and Milli-Q water. Denali C18 150 × 4.6 mm, 5-micron column, HPLC instrument equipped with ultraviolet-visible spectrophotometer and photo diode array (PDA) detector.

Chromatographic conditions

Flow rate: 1.0 mL, injection volume: 10 µL, detector: 221 nm, column temperature: 30 ˚C, column: Denali C18 150 × 4.6 mm, 5 m, and run time: 6 min.

Mobile phase and solution preparation

Preparation of the buffer

One milliliter of *ortho-phosphoric* acid solution was diluted to 1000 mL with Milli-Q water.

Preparation of the mobile phase

Mix 600 mL of buffer and 400 mL of acetonitrile and sonicate to degas.

Preparation of the diluent

Mix 500 mL of water and 500 mL of acetonitrile and sonicate to degas.

Standard preparation

As much as 35 mg of bupropion and 15 mg of dextromethorphan were accurately weighed and transferred according to working standards into a 50 mL clean, dry volumetric flask; 10 mL of diluent was added and sonicated for 10 min, and the final volume was made up to the mark with diluent (700 µg/mL bupropion and 300 µg/mL of dextromethorphan).

From the above stock solution, 1 mL was taken into a 10 mL volumetric flask and made up to the mark with diluent (70 µg/mL bupropion and 30 µg/mL of dextromethorphan).

Sample preparation

An equivalent weight of 70 mg of bupropion fixed dose combination tablet powder was accurately weighed and transferred into a 100 mL volumetric flask; 75 mL of diluent was added and sonicated for 25 min. The volume was made up to the mark with diluent and filtered using a Milli-Q filter (700

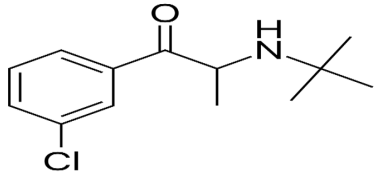

Figure 1. Chemical structure of bupropion

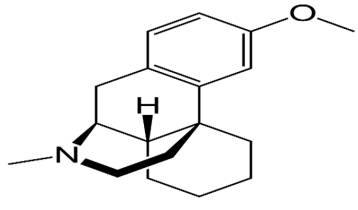

Figure 2. Chemical structure of dextromethorphan

µg/mL bupropion and 300 µg/mL of dextromethorphan). Then, 1 mL of filtered sample stock solution was transferred to a 10 mL volumetric flask and made up to the mark with diluent (70 µg/mL bupropion and 30 µg/mL of dextromethorphan).

Degradation studies

Oxidation

From a stock solution of 700 µg/mL bupropion and 300 µg/mL dextromethorphan, 1 mL was pipetted and 1 mL of 20% hydrogen peroxide (H_2O_2) was added separately. The resultant solution was maintained for 60 min at 30 ˚C. For the HPLC study, the resultant solution was diluted to obtain 70 µg/mL of bupropion and 30 µg/mL of dextromethorphan, then 10 µL injection volume was injected into the system, and the chromatogram was recorded to assess the stability of the sample.

Acid degradation studies

From a stock solution of 700 µg/mL bupropion and 300 µg/mL dextromethorphan, 1 mL was pipetted and 1 mL of 2 N hydrochloric acid was added separately. The resultant solution was refluxed for 30 min at 60 ˚C. The acid was then neutralized with an equivalent volume of sodium hydroxide solution. For the HPLC study, the resultant solution was diluted to obtain 70 µg/mL of bupropion and 30 µg/mL of dextromethorphan, then 10 µL injection volume was injected into the system, and the chromatogram was recorded to assess the stability of the sample.

Alkali degradation studies

From a stock solution of 700 µg/mL bupropion and 300 µg/mL dextromethorphan, 1 mL was pipetted and 1 mL of 2 N sodium hydroxide solution was added separately. The resultant solution was refluxed for 30 min at 60 ˚C. Next, the base was neutralized with an equivalent volume of hydrochloric acid solution. For the HPLC study, the resultant solution was diluted to obtain 70 µg/mL of bupropion and 30 µg/mL of dextromethorphan, then 10 µL injection volume was injected into the system, and the chromatogram was recorded to assess the stability of the sample.

Thermal degradation studies

The solution was exposed to heat at 105 ˚C for 6 h, and then 1 mL of the stock exposed solution of 700 µg/mL bupropion and 300 µg/mL dextromethorphan was pipetted. For the HPLC study, the resultant solution was diluted to obtain 70 µg/mL of bupropion and 30 µg/mL of dextromethorphan, then 10 µL injection volume was injected into the system, and the chromatogram was recorded to assess the stability of the sample.

Photostability studies

The solution was exposed to UV light at 1.2 million lux hours and 200 watt hour/m^2 for four days, and then 1 mL of stock exposed solution of 700 µg/mL bupropion and 300 µg/mL dextromethorphan was pipetted. For the HPLC study, the resultant solution was diluted to obtain 70 µg/mL of bupropion and 30 µg/mL of dextromethorphan, then 10 µL injection volume was injected into the system, and the chromatogram was recorded to assess the stability of the sample.

Neutral degradation studies

From the stock solution of 700 µg/mL bupropion and 300 µg/mL dextromethorphan, 1 mL of the solution was pipetted and 1 mL of water was added separately. The solution was refluxed for 6 h at 60 ˚C. For the HPLC study, the resultant solution was diluted to obtain 70 µg/mL of bupropion and 30 µg/mL of dextromethorphan, then 10 µL injection volume was injected into the system, and the chromatogram was recorded to assess the stability of the sample.

RESULTS

A simple, accurate, and precise method has been developed for estimating bupropion and dextromethorphan in a fixed dose combination of tablets. The optimized method included the following parameters: column temperature of 30 ˚C, 40% acetonitrile as the mobile phase, and flow rate of 1.0 mL/min. Retention times were 2.25 min and 3.12 min for bupropion and dextromethorphan, respectively.

DISCUSSION

With the progress of the ICH guidelines, the determination of a stability-indicating method has developed to be clearer and obligatory. The guidelines are necessary for handling forced degradation studies under different conditions, such as acid, base, photolytic, oxidation, heat, and neutral. Hence, the necessity of separation of several components through the study of stability samples is evident. HPLC has gained a reputation in stability studies due to its specificity, sensitivity, and high-resolution capacity. The work planned in this research was conducted to study the chromatographic actions of the samples of stress degradation of bupropion and dextromethorphan in the tablet dosage formulation. To the best of our knowledge, and motivated us to develop an RP-HPLC-PDA stability indicating test in which the degradation products were resolved from the integral drugs.

Method development

Initially, the analytical method was developed using *ortho-phosphoric* acid solution and acetonitrile in a ratio of 1:1, but the resultant chromatogram observed closed eluted peaks. The resultant chromatogram is shown in Figure 3.

Finally, the method was optimized with critical quality attributes such as standard preparation, sampling preparation, column,

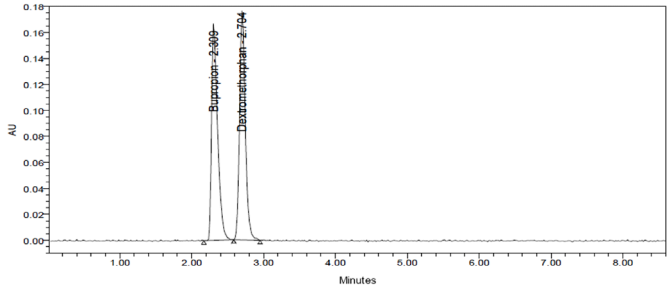

Figure 3. Standard chromatogram of bupropion and dextromethorphan
AU: Absorbance units

detector, resolution of peaks, and instrument. The optimized standard solution containing 70 µg/mL of bupropion and 30 µg/mL of dextromethorphan was used to validate the parameters. The resulting chromatograms are shown in Figures 4 and 5.

Method validation

The method was validated as *per* the ICH guidelines. The different validation parameters were performed as follows: linearity, precision, accuracy, specificity, limit of detection (LOD), limit of quantitation (LOQ), robustness, degradation studies, and stability-indicating capability.

System suitability test

System suitability was evaluated using freshly prepared standard solutions. Five replicate injections of standard solution were injected into the HPLC system, and the obtained areas, retention time, tailing factor, theoretical plates, and relative standard deviation % (RSD) were calculated. System suitability results are tabulated in Tables 1 and 2. % RSD values were within the limit of not more than 2%.

Specificity

Specificity tests were performed on freshly prepared blanks and placebos of bupropion and dextromethorphan tablets. The resultant chromatograms indicated that no interference was observed from blank and placebo at retention time of bupropion and dextromethorphan in the optimized method conditions. The resulting chromatograms are depicted in Figures 6 and 7.

Linearity

The linearity parameter was evaluated using standard drug solutions by preparing six different concentrations. Linearity levels were 25%, 50%, 75%, 100%, 125%, and 150%. All six linearity solutions were injected into the HPLC system, and the correlation coefficient values against drug concentrations versus peak areas were calculated. The results are presented in Table 3, and related graphs are depicted in Figures 8 and 9. The correlation coefficient values were within the limit of 0.999.

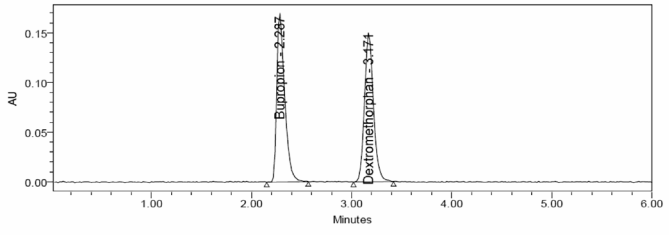

Figure 4. Standard chromatogram of bupropion and dextromethorphan
AU: Absorbance units

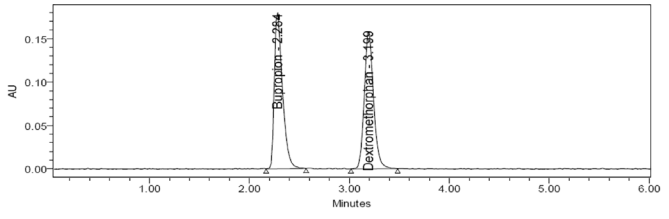

Figure 5. Sample chromatogram of bupropion and dextromethorphan
AU: Absorbance units

Precision

Precision was performed by preparing six replicate sample preparations from a homogeneous sample. Six replicate solutions were obtained as *per* the test procedure mentioned in the Materials and Methods section. % of RSD results were calculated for the areas and % assay. The obtained results are tabulated in Table 4. Precision results were found satisfactory, and the % RSD values were below 2%.

Intermediate precision

Intermediate precision was performed by preparing six replicate sample preparations from a homogeneous sample using different analysts, columns, and laboratories. Six replicate solutions were obtained as *per* the test procedure mentioned in the Materials and Methods section. % of RSD results were calculated for the areas and % assay. The obtained results are tabulated in Table 5. Intermediate precision results were found satisfactory, and the % RSD values were below 2%.

Table 1. System suitability results for bupropion

Injections	Retention time (min)	Area	USP plate count	USP tailing factor
1	2.265	939582	3409	1.63
2	2.284	941657	3650	1.50
3	2.287	944326	3791	1.47
4	2.290	946091	3827	1.46
5	2.291	948170	3946	1.47
Mean	2.283	943965	3724.6	1.506
SD	0.0106	3423.1	205.6	0.0709
% RSD	0.5	0.4	5.5	4.7

USP: United States Pharmacopeia, SD: Standard deviation, RSD: Relative standard deviation

Table 2. System suitability results for dextromethorphan

Injections	Retention time (min)	Area	USP plate count	USP tailing factor
1	3.138	763039	6037	1.14
2	3.142	765036	6148	1.16
3	3.150	763327	6085	1.16
4	3.165	767346	6141	1.15
5	3.171	755921	6194	1.15
Mean	3.153	762934	6121	1.152
SD	0.0143	4278.8	60.848	0.0084
% RSD	0.5	0.6	1.0	0.7

USP: United States Pharmacopeia, SD: Standard deviation, RSD: Relative standard deviation

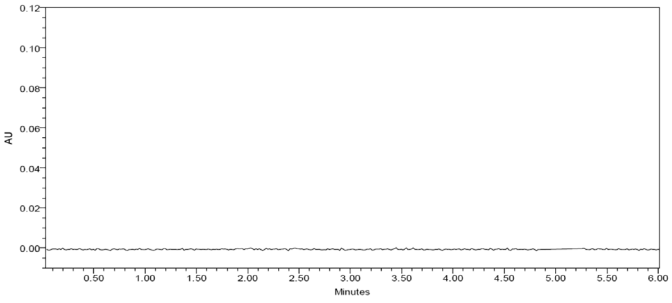

Figure 6. Blank chromatogram of bupropion and dextromethorphan
AU: Absorbance units

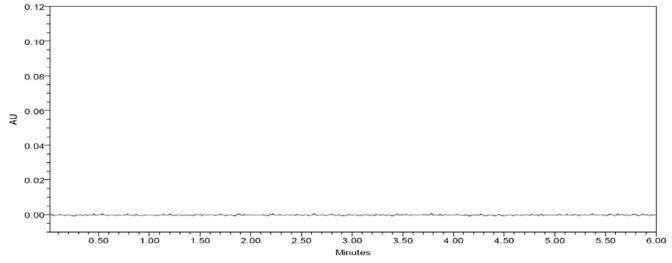

Figure 7. Placebo chromatogram of bupropion and dextromethorphan
AU: Absorbance units

Table 3. Linearity concentration

Linearity level	Bupropion		Dextromethorphan	
	Concentration (µg/mL)	Peak area	Concentration (µg/mL)	Peak area
25%	17.5	233642	7.5	189050
50%	35.0	477356	15.0	386094
75%	52.5	715373	22.5	573548
100%	70.0	946633	30.0	787591
125%	87.5	1178712	37.5	965859
150%	105.0	1413042	45.0	1145652
Correlation coefficient	0.999		0.999	

Accuracy

The accuracy of the method was determined at three concentration levels by performing recovery studies. The recovery studies were carried out by different concentrations of both drugs added to the placebo from 50%, 100%, and 150%. Recovery and percentage RSD were calculated. The obtained results are tabulated in Tables 6 and 7, and related graphs are depicted in Figures 10 and 11. % of recovery results were between 97 % and 103 %.

Robustness

The robustness of the method was evaluated by changing the flow rate, organic, and temperature. A system suitability test was conducted to check the variations, and the results were found to be satisfactory. The results are reported in Table 8.

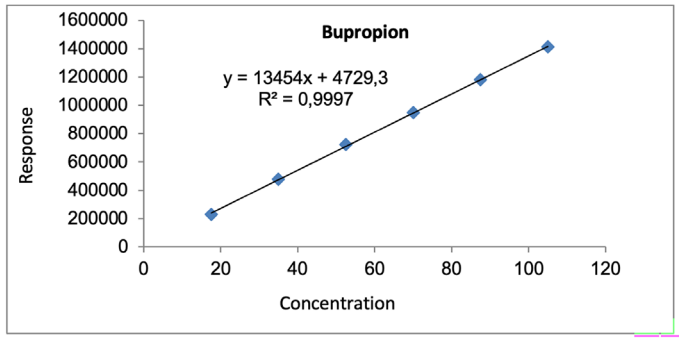

Figure 8. Linearity graph for bupropion
AU: Absorbance units

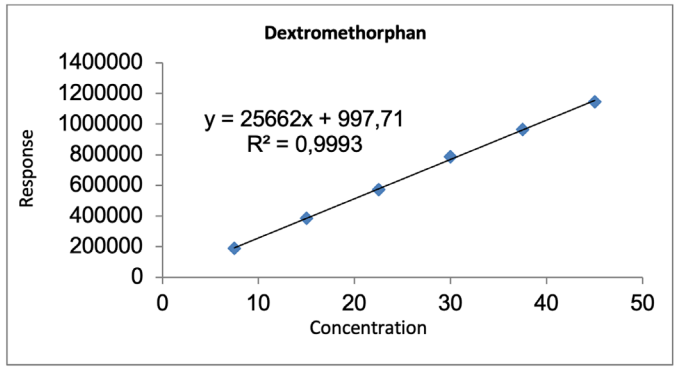

Figure 9. Linearity graph for dextromethorphan
AU: Absorbance units

Table 4. Precision results

S. no.	Bupropion		Dextromethorphan	
	Area	% Assay	Area	% Assay
1	946549	100.08	763992	99.96
2	946327	100.06	769671	100.70
3	947135	100.14	766504	100.29
4	942561	99.66	769536	100.68
5	950484	100.50	763402	99.88
6	949639	100.41	767899	100.47
Mean	947116	100.14	766834	100.33
SD	2807.2	0.30	2699.9	0.35
% RSD	0.3	0.3	0.4	0.4

SD: Standard deviation, RSD: Relative standard deviation, S. no.: Sample number

LOD and LOQ

LOD is the lowest concentration of analyte in a sample that can be identified but not quantified. LOQ is defined as the lowest concentration of analyte in a sample that can be estimated with tolerable precision, accuracy, and reliability by a specified method under affirmed experimental conditions. The LODs were found to be 0.15 µg/mL and 0.06 µg/mL for bupropion and dextromethorphan, respectively. The LOQs were found to be 2.91 µg/mL and 0.18 µg/mL for bupropion and dextromethorphan, respectively.

Degradation studies

Degradation studies involving acid, base, peroxide, thermal, UV, and neutral conditions were evaluated. Furthermore, all stress degradation results are tabulated in Tables 9 and 10, and the resultant chromatograms are shown in Figures 12 to 17.

Statistical analysis

The accuracy of the method was determined at three concentration levels by performing recovery studies. The recovery studies were carried out by different concentrations of both drugs added to the placebo from 50%, 100%, and 150%. The related graphs are depicted in Figures 10 and 11. % of recovery results were between 97% and 103%. The LODs were found to be 0.15 µg/mL and 0.06 µg/mL for bupropion and dextromethorphan, respectively. The LOQs were found to be 2.91 µg/mL and 0.18 µg/mL for bupropion and dextromethorphan, respectively.

Table 5. Intermediate precision results

S. no.	Bupropion		Dextromethorphan	
	Area	% Assay	Area	% Assay
1	945886	100.01	761882	99.68
2	939324	99.32	766487	100.29
3	939052	99.29	759040	99.31
4	945600	99.98	763144	99.85
5	939091	99.29	759107	99.32
6	946842	100.11	762823	99.81
Mean	942633	99.67	762081	99.71
SD	3832.0	0.41	2800.9	0.37
% RSD	0.4	0.4	0.4	0.4

SD: Standard deviation, RSD: Relative standard deviation, S. no.: Sample number

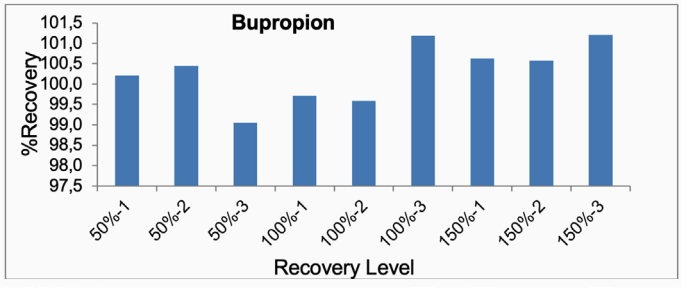

Figure 10. %recovery graph for bupropion

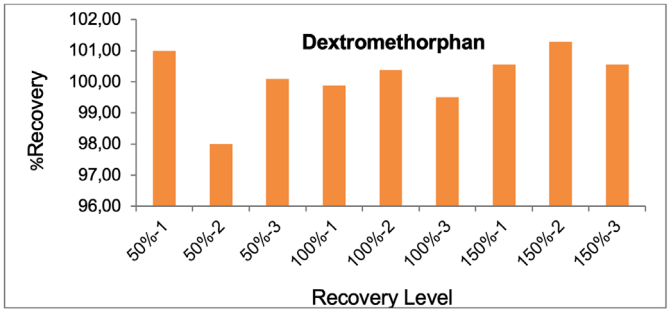

Figure 11. %recovery graph for dextromethorphan

Table 6. Accuracy results for bupropion

S. no.	Recovery level	% Assay	Average	SD	% RSD
1	50%-1	100.2			
2	50%-2	100.4	99.9	0.7462	0.7
3	50%-3	99.1			
4	100%-1	99.7			
5	100%-2	99.6	100.2	0.8907	0.9
6	100%-3	101.2			
7	150%-1	100.6			
8	150%-2	100.6	100.8	0.3504	0.3
9	150%-3	101.2			

SD: Standard deviation, RSD: Relative standard deviation, S. no.: Sample number

Table 7. Accuracy results for dextromethorphan

S. no.	Recovery level	% Assay	Average	SD	% RSD
1	50%-1	100.99			
2	50%-2	98.00	99.7	1.5357	1.5
3	50%-3	100.09			
4	100%-1	99.88			
5	100%-2	100.36	99.9	0.4321	0.4
6	100%-3	99.50			
7	150%-1	100.55			
8	150%-2	101.28	100.8	0.4211	0.4
9	150%-3	100.55			

SD: Standard deviation, RSD: Relative standard deviation, S. no.: Sample number

Table 8. Robustness results

S. no.	Condition	Bupropion	Dextromethorphan	Resolution between both peaks
		% RSD	% RSD	
1	Optimized condition	0.4	0.5	5.4
2	Low flow rate (0.9 mL/min)	0.6	0.8	6.1
3	High flow rate (1.1 mL/min)	0.3	0.7	5.9
4	Low column temperature (25 °C)	0.7	1.0	7.2
5	High column temperature (35 °C)	0.7	0.6	5.7
6	Low organicvolume (+4 mL)	0.8	0.8	7.5
7	High organicvolume (-4 mL)	0.4	0.7	5.2

S. no.: Sample number, RSD: Relative standard deviation

Table 9. Degradation results for bupropion

Stress condition	% Amount remaining	% Amount degraded	Peak purity	
			Purity angle	Purity threshold
Acid	94.40	5.60	0.635	0.745
Base	95.29	4.71	0.555	0.732
Oxidation	95.50	4.50	0.944	1.090
Thermal	97.60	2.40	0.725	0.917
UV	98.67	1.33	0.538	0.726
Neutral	99.60	0.40	0.552	0.753

UV: Ultraviolet

Table 10. Degradation results for dextromethorphan

Stress condition	% Amount remaining	% Amount degraded	Peak purity	
			Purity angle	Purity threshold
Acid	94.38	5.62	1.270	1.525
Base	95.87	4.13	1.201	1.523
Oxidation	95.65	4.35	1.730	2.167
Thermal	97.58	2.42	1.915	2.304
UV	98.52	1.48	1.175	1.459
Neutral	99.01	0.99	1.187	1.498

UV: Ultraviolet

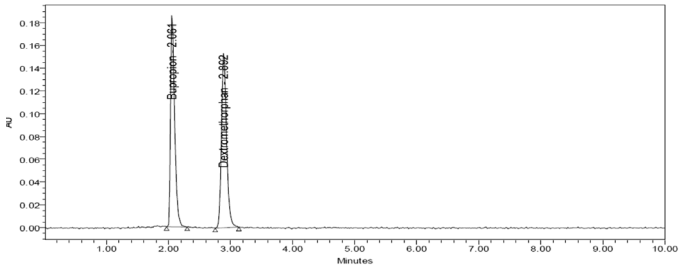

Figure 12. Acid degradation chromatogram
AU: Absorbance units

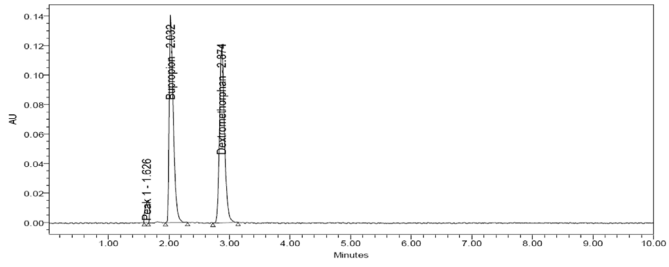

Figure 13. Base degradation chromatogram
AU: Absorbance units

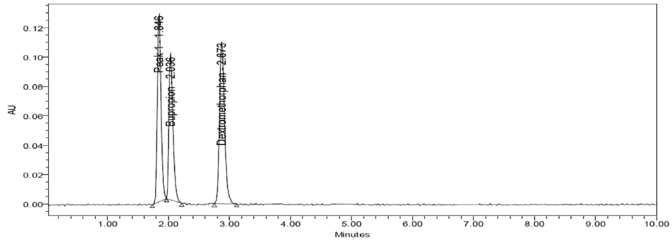

Figure 14. Oxidation degradation chromatogram
AU: Absorbance units

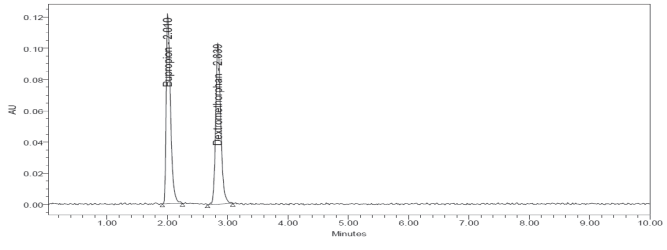

Figure 15: Thermal degradation chromatogram
AU: Absorbance units

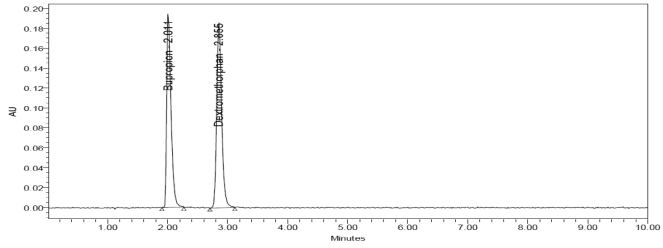

Figure 16: UV degradation chromatogram
AU: Absorbance units

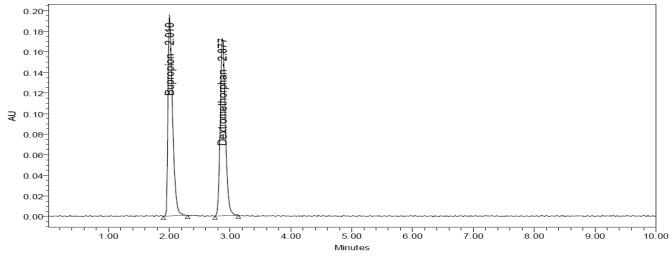

Figure 17: Water degradation chromatogram
AU: Absorbance units

CONCLUSION

The current study describes a new, simple, reliable, and economical elution RP-HPLC method for estimating bupropion and dextromethorphan in a fixed combination tablet dosage form. The forced degradation studies were conducted using several degradation conditions such as acidic, alkali, oxidation, thermal, UV, and neutral conditions; the proposed method was effectively employed from the resolution of sample peaks. To the best of our knowledge, no such detailed and stability-indicating method has been reported for a fixed tablet dosage form. The developed method was completed using a PDA as a tool for peak integrity and purity confirmation. Therefore, the proposed method can be used for the quantification of bupropion and dextromethorphan in a fixed tablet dosage form. Finally, this method was carefully validated; as a result, it can be suggested for routine analysis testing in a quality control laboratory.

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Ethics

Ethics Committee Approval: There is no requirement for ethical approval.

Informed Consent: Not necessary.

Conflict of Interest: No conflict of interest was declared by the authors.

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