

Development and Validation of a Method for Simultaneous Estimation of Bupropion and Dextromethorphan Using Reverse Phase High Performance Liquid Chromatography in Active Pharmaceutical Ingredient Form

ABSTRACT

Aims: New validated method for the simultaneous estimation of Bupropion and Dextromethorphan using HPLC.

Place and Duration of Study: Department of Chemistry, RVR & JC College of Engineering, Chowdavaram, Guntur, Andhra Pradesh, between July 2022 and August 2022.

Methodology: Using Inertsil ODS 250 x 4.6 mm, 5 μm column, acetonitrile and 0.1 percent formic acid (30:70 v/v) as a mobile phase, the proposed method successfully achieved effective chromatographic separation with a flow rate of 1 mL/min and a wave length of 240 nm. The Bupropion and Dextromethorphan peaks were resolved within 5 minutes of elution time, with the Bupropion peak eluting at 2.054 minutes and the Dextromethorphan peak eluting at 3.940 minutes.

Results: The proposed method displays excellent linearity in the concentration ranges of 52.5-315 $\mu\text{g/mL}$ for Bupropion and 22.5-135 $\mu\text{g/mL}$ for Dextromethorphan. The RSD of robustness levels has a maximum of just 2 percent.

Conclusion: The accuracy, specificity, and sensitivity of the method were all found to be in line with ICH guidelines, when the procedure was developed and tested.

Keywords: ICH Guide lines, RP-HPLC, Bupropion, Dextromethorphan, Validation.

1. INTRODUCTION

“**Dextromethorphan** is a medication most often used as a cough suppressant in over-the-counter cold and cough medicines. It is sold in syrup, tablet, spray, and lozenge forms. It is in the morphinan class of medications with sedative, dissociative, and stimulant properties” [1, 2] (at lower doses). “Dextromethorphan does not have a significant affinity for the mu-opioid receptor” [3, 4] “activity typical of morphinan compounds and exerts its therapeutic effects” [5, 6] through several other receptors [7]. “In its pure form, dextromethorphan occurs as a white powder. Dextromethorphan is also used recreationally. When exceeding approved dosages, dextromethorphan acts as a dissociative hallucinogen” [8, 9]. “It has multiple mechanisms of action, including actions as a nonselective serotonin reuptake inhibitor” [10, 11] and “a sigma-1 receptor agonist” [12, 13]. “Dextromethorphan and its major metabolite, dextrorphan, also block the NMDA receptor [14] at high doses, which produces effects similar to other dissociative anesthetics such as ketamine, nitrous oxide, and phencyclidine”.

“**Bupropion**, sold under the brand names Wellbutrin and Zyban among others, is an atypical antidepressant” [15] “primarily used to treat major depressive disorder” [16, 17] and “to support smoking cessation” [18, 19]. “ Bupropion has several features that distinguish it from other antidepressants: it does not usually cause sexual dysfunction [20]; it is not associated with weight gain and sleepiness” [21], “and it is more effective than SSRIs at improving symptoms of hypersomnia [22, 23] and fatigue”. “Bupropion does, however, carry a much higher risk of seizure than many other antidepressants and extreme caution must be taken in patients with a history of seizure disorder. Common adverse effects of bupropion with the greatest difference from placebo are dry mouth, nausea, constipation, insomnia, anxiety, tremor, and excessive sweating. Raised blood pressure is notable” [24] “Rare but serious side effects include seizure, liver toxicity” [25], psychosis [26] and “risk of overdose” [27]. “Bupropion use during pregnancy may be associated with increased odds of congenital heart defects” [28]. “Bupropion acts as a norepinephrine–dopamine reuptake inhibitor and a nicotinic receptor antagonist. However, its effects on dopamine are weak” [29, 30]. Chemically, bupropion is an aminoketone that belongs to the class of substituted cathinones and more generally that of substituted amphetamines and substituted phenethylamines. Chemical structures of Bupropion and Dextromethorphan were shown in figure 1.

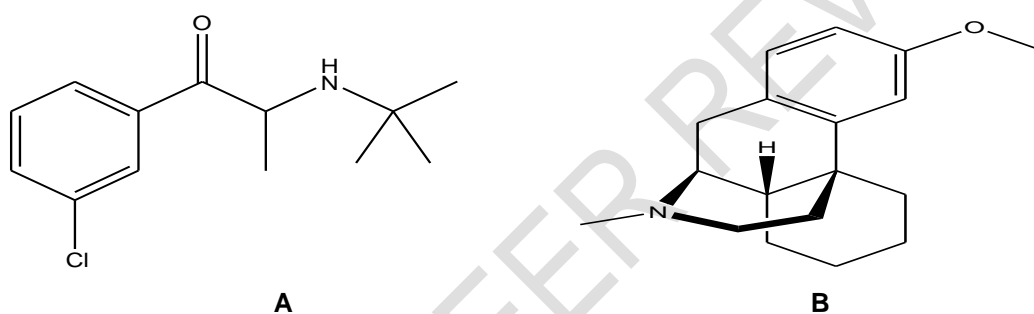


Fig. 1: Chemical structures of (A) Bupropion and (B) Dextromethorphan

To date, there have been no HPLC methods for Bupropion and Dextromethorphan estimation. Thus, the goal of the study is to predict Bupropion and Dextromethorphan, which is a pharmaceutical component, using RP-HPLC.

2. MATERIAL AND METHODS

2.1 Chemicals and Reagents

Merck (India) Ltd. provided acetonitrile, Formic acid, and water in Worli, Mumbai, India. Glenmark Pharmaceuticals in Mumbai provided the APIs that served as reference standards for both Bupropion and Dextromethorphan.

2.2 Equipment

HPLC makes: The chromatographic device used was the Waters acquity, which included a quaternary pump, a PDA (photo diode array) detector, and the chromatographic programme Empower-2.0.

2.3 Chromatographic Conditions

HPLC system instrumentation was used to develop and validate the technique (Waters Alliance e-2695 HPLC). Empower 2.0 software was used to process the data. Inertsil ODS column (250 x 4.6mm, 5 μ m) was selected for use in the experiment. The compound was purified by isocratic elution using a mobile phase of 0.1% formic acid buffer solution and acetonitrile in a 70:30 ratio. The pump was adjusted to pump 1.0 mL/min. UV detection was

conducted at a wavelength of 240nm. The injection volume was 10 microliters, and the diluent was the same as the mobile process.

2.4 Preparation of Standard solution

Standard stock solution of Bupropion and Dextromethorphan was prepared in 100 mL volumetric flask. It was filtered through a 0.45 micron nylon syringe filter. Standard stock solution concentrations of Bupropion (2100 µg/mL) and Dextromethorphan (900 µg/mL) were obtained.

2.5 Preparation of Sample solution

Five Bupropion and Dextromethorphan tablets (Each tablet contains 105 mg of Bupropion and 45 mg of Dextromethorphan) were accurately weighed and triturated to get a fine powder. A 210 mg Bupropion and 90 mg Dextromethorphan equivalent weight tablet powder was transferred into a 100 mL volumetric flask and dissolved in diluent. The solution was ultra-sonicated for 10 min and made the volume with diluent. The tablet sample stock solution was then filtered through 0.45 micron syringe filter and utilized for preparing sample solution for the assay.

3. RESULTS AND DISCUSSION

The purpose of this study was to develop a simple, accurate, and rapid RP-HPLC method for simultaneous estimation of Bupropion and Dextromethorphan. To optimize the chromatographic conditions, different ratios of buffers (phosphate buffer, 0.1% Ortho phosphoric acid and 0.1% tri ethyl amine) and the acetonitrile in the mobile phase with isocratic and gradient mode was tested. By using Acetonitrile and 0.1% formic acid (70:30) as mobile phase, the trial gave USP tailing of 1.05, 1.69 and USP resolution of 3.59 and USP plate count of 4257, 3521. The trial chromatogram was shown in figure 2.

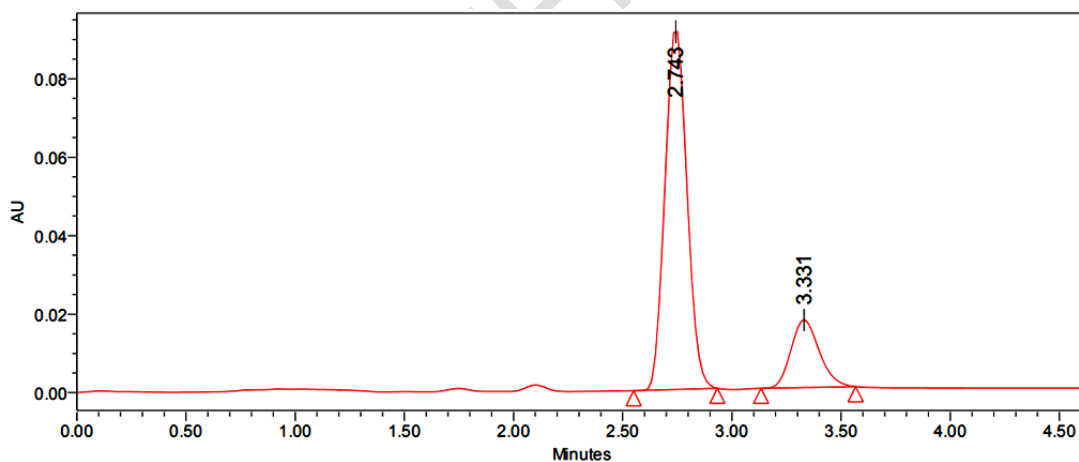


Fig. 2. Chromatogram of trial-1

Finally 0.1% formic acid buffer and acetonitrile with isocratic elution was selected because it results in a greater response of active pharmacy ingredients. During the optimization of the method various stationary phases such as C₈, C₁₈ and amino, phenyl columns were tested. From these trials the peak shapes were relatively good with Inertsil ODS column of 250 x 4.6 mm, 5 µ with a PDA detector. A buffer and acetonitrile mixture is part of the mobile process (70:30), the flow rate is 1.0 mL/min and the column temperature is room temperature. Recovery data and peak sharpness are calculated based on finalization of diluent and standard solution concentrations, as well as injection volumes that are greater than the quantification maximum (LOQ). An isocratic concentration was used to achieve better resolution. Finally by using Inertsil ODS (250 x 4.6mm, 5 µm) column, 0.1% formic acid :

ACN 70:30 as mobile phase we got the optimized chromatogram by satisfying all the suitability conditions.

3.1 Method validation

The optimized RP-HPLC method was validated as per the ICH guidelines with respect to system suitability, linearity and range, precision, accuracy, and robustness. As seen in Table 1, the optimized conditions for the defined and validated HPLC process are listed.

Table 1. Optimized chromatographic conditions

S. No.	Parameter	Method Conditions
1	Column	Inertsil ODS 250 x 4.6mm, 5 μ m
2	Flow rate	1 mL/min
3	Wave length	240nm
4	Injection Volume	10 μ L
5	Run time	5 min
6	Mobile phase	0.1% Formic acid : ACN 70:30

3.1.1 Specificity

Figure 3 is completely blank. No chromatographic interference was observed for placebo and blank samples at the retention times of Bupropion and Dextromethorphan.

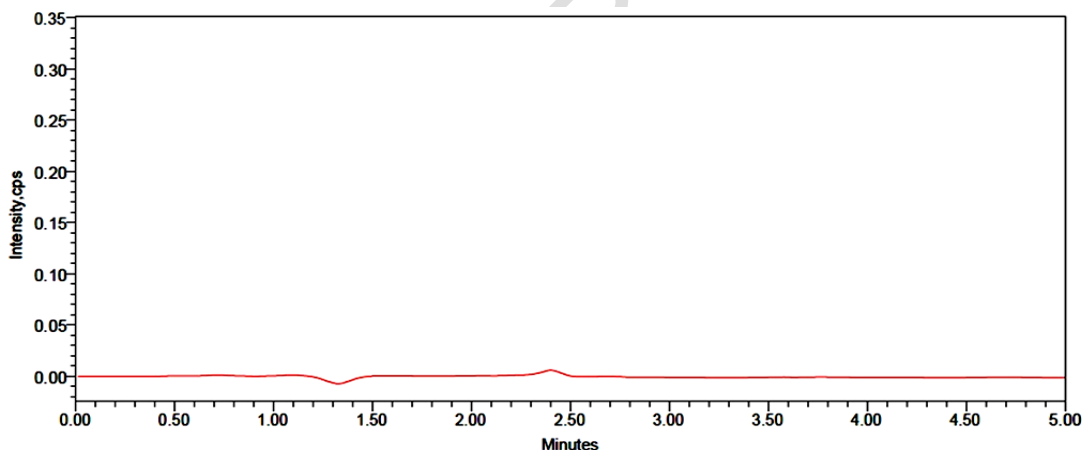


Fig. 3. Chromatogram of blank

3.1.2 System suitability

To run the HPLC, the standard solution was added to the system, and it was found that the system suitability parameters were in an acceptable range. The RSD percentage was determined using the average RSD (relative standard deviation) peak areas. The percentage of identical injections from the RSD fell within the recommended range. Table 2 and figure 4 show the obtained results.

Table 2: Results of system suitability

S. No	System suitability parameter	Acceptance criteria	Drug Name	
			Bupropion	Dextromethorphan
1	% RSD	Not more than	0.3	0.52

		2.0		
2	USP Tailing	Not more than 2.0	1.06	1.15
3	USP Plate count	Not less than 3000	2058	3856

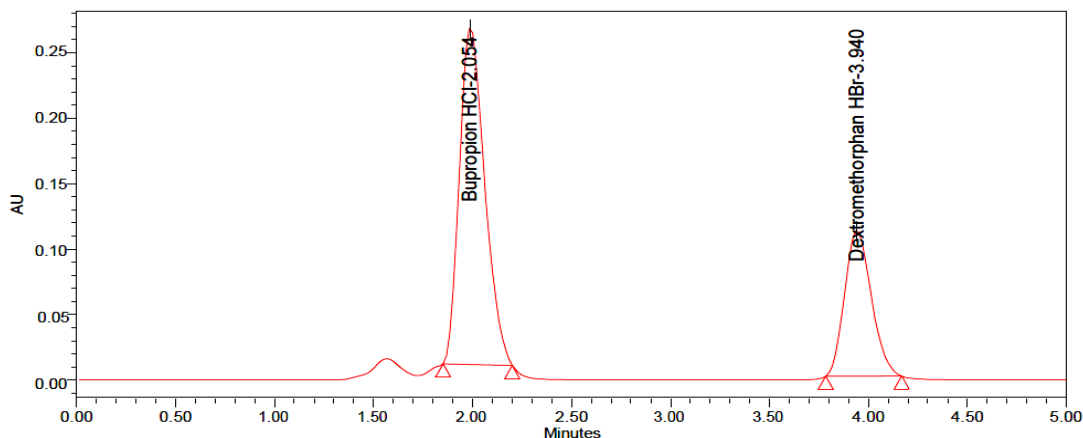


Fig. 4. Chromatogram of standard

3.1.3 Linearity

For Bupropion, linearity concentrations of 52.5 µg/mL to 315 µg/mL were prepared, while for Dextromethorphan, ranged from 22.5 µg/mL to 135 µg/mL. The regression equations for Bupropion (CC-0.9998) and Dextromethorphan (CC-0.9994) were $Y=12072.84x+17032.14$ and $Y=14859.64x+14789.5$ respectively. Table 3 showed the results, and Figure 5 depicted the linearity map.

Table 3: Results of linearity

S. No.	Bupropion		Dextromethorphan	
	Conc. (µg/mL)	Area	Conc. (µg/mL)	Area
Linearity-1	52.50	687392	22.50	368414
Linearity-2	105.00	1273025	45.00	679383
Linearity-3	157.50	1921134	67.50	1039478
Linearity-4	210.00	2544502	90.00	1311917
Linearity-5	262.50	3160044	112.50	1710677
Linearity-6	315.00	3843429	135.00	2014838
Slope	12072.84		14859.64	
Intercept	17032.14		14789.50	
CC	0.9998		0.9994	

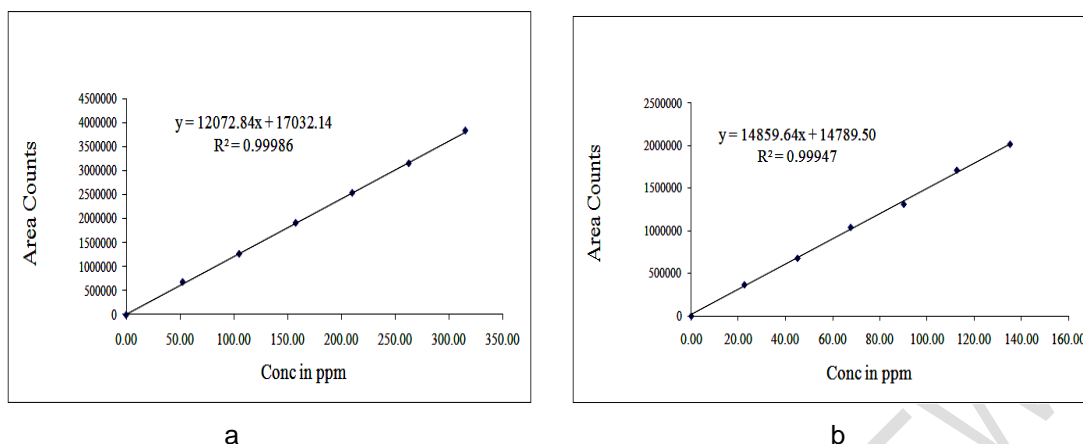


Fig. 5 Calibration plots of (a) Bupropion and (b) Dextromethorphan

3.1.4 Limit of detection and quantification

LOD and LOQ were calculated with the calibration curve method. A known RP-HPLC procedure was used to calculate the compound's LOD and LOQ by injecting standard solutions in increasing concentrations. In order to determine LOD and LOQ, the slope approach was employed, with LOQ being calculated as $10x/S$ and LOD as $3.3x/S$, where S is the calibration curve slope and is the response standard deviation. Bupropion's LOD and LOQ concentrations were $0.315\mu\text{g/mL}$ and $1.05\mu\text{g/mL}$ and Dextromethorphan's were $0.135\mu\text{g/mL}$ and $0.45\mu\text{g/mL}$ respectively.

3.1.5 Precision

To pinpoint the accuracy of the procedure, the entire analytical process was put to the test by evaluating standard solution preparation and the end results. At least six different determinations were employed to establish repeatability, and the relative standard deviation was established using this information. Based on the data found in Table 4 the following points are made, sample chromatogram was shown in figure 6.

Table 4: Results of method precision

Analyte	Std Conc. ($\mu\text{g/mL}$)	%RSD
Bupropion	210	1.34
Dextromethorphan	90	0.84

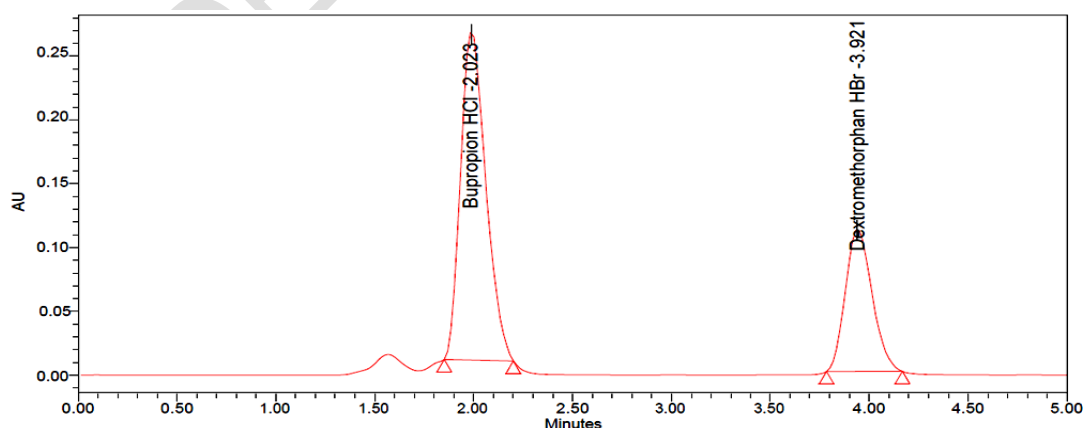


Fig. 6. Chromatogram of sample

3.1.6 Accuracy

The method's accuracy was confirmed through the recovery experiments on three different levels (50 percent, 100 percent and 150 percent). Preparations containing Bupropion concentrations of 105, 210, and 315 micrograms per millilitre and Dextromethorphan concentrations of 45, 90, and 135 micrograms per millilitre were created. The 98 to 102 percent recovery percentages were found. The accuracy findings for Bupropion and Dextromethorphan were presented in table 5.

Table 5: Results of accuracy

Accuracy	% Recovery	
	Bupropion	Dextromethorphan
50*	100.6	100.9
100*	100.1	100.9
150*	100.5	101.0

* Results are mean recovery of three sample preparations

3.1.7 Ruggedness

Six duplicates of a standard solution were sampled on a separate day, using a different analyst and device. Means and % RSD values were obtained for locations of maximum peaks. Findings found in Table 6 are shown in the chart below.

Table 6: Results of intermediate precision

Analyte	Std. Conc. ($\mu\text{g/mL}$)	%RSD
Bupropion	210	0.98
Dextromethorphan	90	0.98

3.1.8 Robustness

Despite a small flow rate variance (0.1 mL) and organic solvent (10 percent) in its chromatographic condition, no significant difference in RSD is made in robustness. Findings are shown in Table 7.

Table 7: Results of robustness

S.No	Parameter name	% RSD for purity	
		Bupropion	Dextromethorphan
1	Flow (0.9 mL/min)	1.06	0.9
2	Flow (1.1 mL/min)	0.93	1.25
3	Organic solvent (+10%) (77:23)	0.84	1.05
4	Organic solvent (-10%) (63:37)	1.39	0.91

3.1.9 Forced degradation

This proposed method is effective for both release and stability studies, and as such, can be seen as a better technique for stability. Acid, base, oxidation, reduction, and thermal degradation are all part of the forced degradation study required by the ICH requirements. Dependent on the type of chromatography used, it is apparent that the drugs under consideration were stable during the stress testing even though degraded peaks were observed (Table 8).

3.1.9.1 Acid degradation

The acid degradation method involves introducing 1ml of 1N HCl to a 50mL volumetric flask, heating the flask for 30 minutes at 60°C, then marking the flask with diluent before adding 1mL of 1N NaOH. The final product is obtained after filtering the solution using a 0.45 nylon syringe filter.

3.1.9.2 Alkali degradation

The alkali degradation process begins with the measurement of 50mL of standard solution, followed by the addition of 1mL of 1N NaOH, which is then heated at 60°C for 30 minutes. This is followed by the addition of 1mL of 1N HCl, and the process is ended by diluting the mixture. The final product is obtained after filtering the solution using a 0.45 nylon syringe filter.

3.1.9.3 Peroxide degradation

The following procedure was used to decompose the materials. The solutions, 5 mL of normal solution and 1 mL of 30% H₂O₂, are placed in volumetric flasks, then warmed for 30 minutes at 60°C and allowed to cool before combining with diluent. The solution can be filtered using a 0.45 nylon syringe filter.

3.9.4 Reduction degradation

The degrading protocol was as follows: In a 50 mL volumetric flask, 5 mL of normal solution is put in, followed by 1 mL of 30% sodium bicarbonate solution. The entire contents are then heated to 60°C for 15 minutes, and then cooled down to 40°C. To filter the solution, use a 0.45-micron nylon syringe filter.

3.1.9.5 Thermal degradation

The test product was put in an oven heated to 105°C for six hours and then refluxed for 30 min at 60°C. The solution was injected into the HPLC system as a result.

3.1.9.6 Hydrolysis degradation

Standard solution of 5 mL is placed in to a 50 mL volumetric flask, and 2 mL of HPLC water is added. The flask is then heated to 60°C for 15 minutes before chilling with diluent. To filter the solution, use a 0.45-micron nylon syringe filter.

3.1.9.6 Photo degradation

A technique was performed where the standard solution was exposed to the sun for 12 hours, and then 60°C refluxed for 30 minutes. The HPLC technique requires normal water injection.

Table 8: Results of forced degradation

Degradation Condition	% Degradation of Bupropion	% Degradation of Dextromethorphan
Acid Degradation	15.1	11.2
Alkali Degradation	13.9	12.3
Peroxide Degradation	17.7	14.7
Reduction Degradation	12.3	10.1
Thermal Degradation	2.7	4.2
Photolytic Degradation	3.8	4.6
Hydrolysis Degradation	1.2	0.8

4. CONCLUSION

To develop a simple, rapid and specific RP-HPLC method for the estimation of Bupropion and Dextromethorphan in active pharmaceutical ingredient form. The drug's behaviour when subjected to acid, basic, and neutral environments, as well as oxidation, reduction, photo and heat stress was researched. The drugs were remained stable when exposed to neutral, thermal and photo conditions, but it was unstable in the remaining conditions of degradation.

A technique with good selectivity and precision for measuring Bupropion and Dextromethorphan using isocratic RP-HPLC has been developed. According to the regression line equations found in the peak area, the concentration of drugs in the range of 52.5-315 µg/mL for Bupropion and 22.5-135 µg/mL for Dextromethorphan may be accurately predicted. A method that effectively proved itself was able to identify the drugs Bupropion and Dextromethorphan accurately, promptly, and precisely.

REFERENCES

1. Malhi GS, Byrow Y, Bassett D, Boyce P, Hopwood M, Lyndon W, Mulder R, Porter R, Singh A, Murray G. Stimulants for depression: On the up and up?, *Aust N Z J Psychiatry*. 2016; 50 (3): 203–7. doi:10.1177/0004867416634208
2. Bahji A, Mesbah-Oskui L. Comparative efficacy and safety of stimulant-type medications for depression: A systematic review and network meta-analysis, *J Affect Disord*. 2021; 292: 416–423. doi:10.1016/j.jad.2021.05.119
3. Huang W, Manglik A, Venkatakrisnan AJ, Laeremans T, Feinberg EN, Sanborn AL, et al. Structural insights into μ -opioid receptor activation, *Nature*. 2015; 524 (7565): 315–321. doi:10.1038/nature14886
4. Koehl A, Hu H, Maeda S, Zhang Y, Qu Q, Paggi JM, et al. Structure of the μ -opioid receptor-G_i protein complex, *Nature*. 2018; 558 (7711): 547–552. doi:10.1038/s41586-018-0219-7
5. Morra Mostafa Ebraheem, Elgebaly Ahmed, Elmaraezy Ahmed, Khalil Adham M, Altibi Ahmed M A, et al. Therapeutic efficacy and safety of Botulinum Toxin A Therapy in Trigeminal Neuralgia: a systematic review and meta-analysis of randomized controlled trials, *The Journal of Headache and Pain*. 2016; 17 (1): 63. doi:10.1186/s10194-016-0651-8
6. Akyurekli Celine, Le Yevgeniya, Richardson Richard B, Fergusson Dean, Tay Jason, Allan David S. A Systematic Review of Preclinical Studies on the Therapeutic Potential of Mesenchymal Stromal Cell-Derived Microvesicles, *Stem Cell Reviews and Reports*. 2014; 11 (1): 150–160. doi:10.1007/s12015-014-9545-9
7. Taylor CP, Traynelis SF, Siffert J, Pope LE, Matsumoto RR. Pharmacology of dextromethorphan: Relevance to dextromethorphan/quinidine (Nuedexta®) clinical use, *Pharmacology & Therapeutics*. 2016; 164: 170–182. doi:10.1016/j.pharmthera.2016.04.010
8. Volgin Andrey D, Yakovlev Oleg A, Demin Constantin A, Alekseeva Polina A, Kyzar Evan J, Collins Christopher, Nichols David E, Kalueff Allan V. Understanding Central Nervous System Effects of Deliriant Hallucinogenic Drugs through Experimental Animal Models, *ACS Chemical Neuroscience*. 2019; 10 (1): 143–154. doi:10.1021/acchemneuro.8b00433
9. Sherwood Alexander M, Prisinzano Thomas E. Novel psychotherapeutics – a cautiously optimistic focus on Hallucinogens, *Expert Review of Clinical Pharmacology*. 2018; 11 (1): 1–3. doi:10.1080/17512433.2018.1415755
10. Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity, *Br J Anaesth*. 2005; 95 (4): 434–41. doi:10.1093/bja/aei210
11. Li C, Shan L, Li X, Wei L, Li D. Mifepristone modulates serotonin transporter function, *Neural Regen Res*. 2014; 9 (6): 646–52. doi:10.4103/1673-5374.130112

12. Brimson JM, Brimson S, Chomchoei C, Tencomnao T. Using sigma-ligands as part of a multi-receptor approach to target diseases of the brain, *Expert Opinion on Therapeutic Targets*. 2020; 24 (10): 1009–1028. doi:10.1080/14728222.2020.1805435
13. Hong W, Werling LL. Evidence that the sigma(1) receptor is not directly coupled to G proteins, *European Journal of Pharmacology*. 2000; 408 (2): 117–125. doi:10.1016/S0014-2999(00)00774-3
14. Bading H. Therapeutic targeting of the pathological triad of extrasynaptic NMDA receptor signaling in neurodegenerations, *The Journal of Experimental Medicine*. 2017; 214 (3): 569–578. doi:10.1084/jem.20161673
15. Garay RP, Zarate CA, Charpeaud T, Citrome L, Correll CU, Hameg A, Llorca PM. Investigational drugs in recent clinical trials for treatment-resistant depression, *Expert Rev Neurother*. 2017; 17 (6): 593–609. doi:10.1080/14737175.2017.1283217
16. Karrassi R, Hammani Z, Benjelloun R, Otheman Y. Major depressive disorder: Validated treatments and future challenges, *World J Clin Cases (Review)*. 2021; 9 (31): 9350–9367. doi:10.12998/wjcc.v9.i31.9350
17. Swardfager W, Herrmann N, Marzolini S, et al. Major depressive disorder predicts completion, adherence, and outcomes in cardiac rehabilitation: a prospective cohort study of 195 patients with coronary artery disease, *The Journal of Clinical Psychiatry*. 2011; 72 (9): 1181–88. doi:10.4088/jcp.09m05810blu
18. Coughlin LN, Tegge AN, Sheffer CE, Bickel WK. A machine-learning approach to predicting smoking cessation treatment outcomes, *Nicotine & Tobacco Research*. 2018; 22 (3): 415–422. doi:10.1093/ntr/nty259
19. Halpern SD, French B, Small DS, Saulsgiver K, Harhay MO, Audrain-McGovern J, et al. Randomized trial of four financial-incentive programs for smoking cessation, *The New England Journal of Medicine*. 2015; 372 (22): 2108–17. doi:10.1056/NEJMoa1414293. PMC 4471993.
20. Patel K, Allen S, Haque MN, Angelescu I, Baumeister D, Tracy DK. Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant, *Therapeutic Advances in Psychopharmacology*. 2016; 6 (2): 99–144. doi:10.1177/2045125316629071
21. Kushida Clea A, Sullivan Shannon S. Multiple Sleep Latency Test and Maintenance of Wakefulness Test, *Chest*. 2008; 134 (4): 854–861. doi:10.1378/chest.08-0822.
22. Billiard M, & Podesta C. Recurrent hypersomnia following traumatic brain injury, *Sleep Medicine*. 2013; 14(5), 462-465. <https://doi.org/10.1016/j.sleep.2013.01.009>
23. Billiard M, Dauvilliers Y. Idiopathic Hypersomnia, *Sleep Med Rev*. 2001; 5 (5): 349–358. doi:10.1053/smr.2001.0168
24. Wilens TE, Hammerness PG, Biederman J, Kwon A, Spencer TJ, Clark S, et al. Blood pressure changes associated with medication treatment of adults with attention-deficit/hyperactivity disorder, *The Journal of Clinical Psychiatry*. 2005; 66 (2): 253–259. doi:10.4088/jcp.v66n0215
25. Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians, *The American Journal of Psychiatry*. 2014; 171 (4): 404–415. doi:10.1176/appi.ajp.2013.13050709

26. Kumar S, Kodela S, Detweiler JG, Kim KY, Detweiler MB. Bupropion-induced psychosis: folklore or a fact? A systematic review of the literature, *General Hospital Psychiatry*. 2011; 33 (6): 612–617. doi:10.1016/j.genhosppsych.2011.07.001
27. Nelson JC, Spyker DA. Morbidity and Mortality Associated With Medications Used in the Treatment of Depression: An Analysis of Cases Reported to U.S. Poison Control Centers, 2000-2014, *The American Journal of Psychiatry*. 2017; 174 (5): 438–450. doi:10.1176/appi.ajp.2016.16050523
28. De Vries C, Gadzhanova S, Sykes MJ, Ward M, Roughead E. A Systematic Review and Meta-Analysis Considering the Risk for Congenital Heart Defects of Antidepressant Classes and Individual Antidepressants, *Drug Safety*. 2021; 44 (3): 291–312. doi:10.1007/s40264-020-01027-x
29. Eap CB, Gründer G, Baumann P, Ansermot N, Conca A, Corruble E, et al. Tools for optimising pharmacotherapy in psychiatry (therapeutic drug monitoring, molecular brain imaging and pharmacogenetic tests): focus on antidepressants, *The World Journal of Biological Psychiatry*. 2021; 22 (8): 561–628. doi:10.1080/15622975.2021.1878427
30. Gautam M, Patel S, Zarkowski P. Practice patterns of bupropion co-prescription with antipsychotic medications, *J Addict Dis*: 2022; 1–8. doi:10.1080/10550887.2022.2028531