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Research Article

Simultaneous Estimation Of Dextromethorphan Hydrobromide And Bupropion Hydrochloride In Pharmaceutical Formulation By Uv Spectroscopic Method Using Simultaneous Equation Method (Vierodt's Method)

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ABSTRACT

A simple, accurate and reliable UV-visible spectrophotometric method was developed and validated for Dextromethorphan hydrobromide (DXM)and bupropion hydrochloride (BUP) by simultaneous equation method in bulk drug samples and pharmaceutical dosage forms. 0.1N Hcl was selected as the solvent based on the solubility studies of both drugs. Dextromethorphan hydrobromide showed maximum absorbance at 224nm, while bupropion hydrochloride showed maximum absorbance at 250nm. The linearity range for both drugs was found to be 2-10µg/ml with correlation coefficients of 0.991 for DXM and 0.9991 for BUP, indicating excellent linearity. Various analytical validation parameters i.e., Accuracy, Precision, LOD and LOQ were calculated using standards. In order to check the performance assay was carried for the marketed formulation was found to be 100.3% and 99.48% respectively, LOD and LOQ for DXM were found to be 0.07955 and 0.24106 µg/ml and for BUP it was found to be 0.09191 and 0.27852µg/ml. The results %recovery for DXM and BUP were observed in the range of 98% and 101%. %RSD for the precision study was found to be less than 2% for both the drugs. The developed method can be used for estimation of dextromethorphan hydrobromide (DXM) and bupropion hydrochloride (BUP) from tablet formulation.

1. INTRODUCTION

Anti-depressant is considered to be first line drugs for the treatment of neuropathic pain.

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Antidepressants are analgesic in patients with chronic pain and no concomitant depression, indicating that the analgesic and antidepressant effects occur independently. The analgesic induced by these drugs seems to be centrally mediated but consistent evidence also indicates a peripheral site of action. Pain is a common symptom of depression, and depression is frequent in chronic pain patients, supporting the hypothesis that pain and depression share some common biochemical mechanisms. The antidepressants have a genuine analgesic effect and that research into their mechanism of action will help to facilitate the development of new drugs. [1]

Dextromethorphan hydrobromide it is cough suppressant used in many cough and cold medicines. In 2022, US FDA approved the combination dextromethorphan and bupropion to serve as a rapid acting antidepressant in people with Major Depressive Disorder [2]. In the morphine class of medications with sedative, dissociative, and stimulant properties (low dose). Dextromethorphan does not have a significant affinity for the non-opioid activity typical of morphine compounds and exerts its therapeutic effects through several other receptors. In its pure form, practically white crystals or crystalline powder, having a faint odour. Melts at about 126º, with decomposition. Sparingly soluble in water, freely soluble in alcohol and in chloroform; insoluble in ether [3].

The Chemical name (1S,9S,10S)-4-methoxy-17-methyl-17-azatetracyclo (7.5.3.1.10.2.7) heptadeca-2(7),3,5-triene; hydrobromide

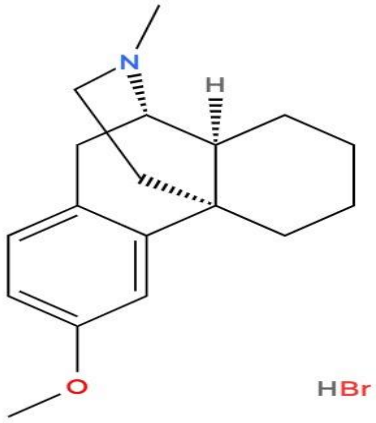

Figure 1: Structure of DXM [4]

Bupropion hydrochloride was originally classified as an "atypical" antidepressant because it does not exert the same effects as the classical antidepressants such as Monoamine Oxidase Inhibitors (MAOIs), Tricyclic antidepressants (TCAs), or Selective Serotonin Reuptake Inhibitors (SSRIs), bupropion is a unique option for the treatment of MDD as it lacks any clinically relevant serotonergic effects, typical of other mood medications, or any effects on histamine or adrenaline receptors. Lack of activity at these receptors results in a more tolerable side effect profile; bupropion is less likely to cause sexual side effects, sedation, or weight gain as compared to SSRIs or TCSs, for example. Bupropion sometimes used as an add on agent to first-line treatments of depression such as selective serotonin reuptake inhibitor (SSRI) medications when there is a treatment-failure or only partial response [5].

The chemical name 2-(tert-butyl amino)-1-(3-chlorophenyl) propane-1-one; hydrochlorides [6]

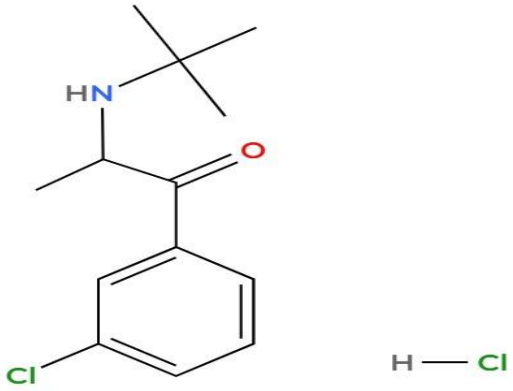

Figure 2: Structure of BUP [7]

The literature survey revealed that several analytical methods including HPLC, HPTLC, LC/MS, and UV spectroscopy were reported on individual drugs and along with other drug combinations. Since Dextromethorphan and bupropion is a fixed dose combination, there is only one HPLC method has been reported for the estimation of these drugs. So, in the present research work, the aim is to develop and validate analytical method for the estimation of dextromethorphan and bupropion hydrochloride.

Validation of the developed method will be carried out in accordance with international conference for harmonization ICH Q2 (R1) guidelines.

Conference for harmonization ICH Q2(R1) guidelines.

Method validation is an integral part of method development; it is the process by which a method is tested by the developer for its specificity, accuracy, and precision. Validation demonstrates that analytical methods are suitable for their intended use and that they support the identity, quality, purity and potency of the drug substances and drug products [8].

2.MATERIALS AND METHOD

2.1 Materials: The glassware used in the research were made of borosilicate and were properly calibrated before use. A calibrated digital weighing balance (Sartorious TE-214S) with maximum capacity of 200g was used to weigh the required chemicals in the range of 10mg to 700mg. UV-Visible spectrophotometric analysis was carried out using a Shimadzu UV-1700 pharma spec double-beam spectrophotometric with a spectral bandwidth of 2nm, wavelength accuracy of 0.5nm, and matched quartz cells. FT-IR analysis was performed using a Shimadzu FTIR-8400S instrument with potassium bromide (AR grade) by palletisation technique for the characterization API. An ultrasonic bath (RC system MU 1700) was used to obtain a mixture of the solvent and sample.

2.2 Chemicals:

Dextromethorphan hydrobromide API was procured as a gift sample from CTX life sciences Pvt.Ltd, Surat, Gujarat, India and bupropion hydrochloride API was procured from SM Pharma Pvt.Ltd, Mumbai India. Marketed formulation

DEXBE ™ is manufactured by Exemed pharmaceutical Ltd.

2.3 Solubility

Solubility of dextromethorphan hydrobromide: 10mg of dextromethorphan hydrobromide was weighed and added to 4 different 10ml volumetric flasks and add the small quantity of water, Methanol,0.1N NaOH, 0.1N Hcl respectively to each flask and shaken for 1-2 min and then made up the volume with respective solvents and the results were found that, the drug DXM was very slightly soluble in water, soluble in methanol and very freely soluble in 0.1 N Hcl.

Solubility of bupropion hydrochloride: 10mg of bupropion hydrochloride was weighed and added to 4 different 10ml volumetric flasks and add the small quantity of Water, Methanol, 0.1N NaOH and 0.1N Hcl respectively to each flask and shaken for 1-2 min and then made up the volume with respective solvents where results were found that the drug BUP was very soluble in water, Methanol and very freely soluble in 0.1 Hcl.

2.4 Selection of Solvent: From the above studies DXM and BUP both were found to be soluble in 0.1N Hcl. Hence 0.1 N Hcl was selected as solvent to carry the research work.

2.5 Preparation of Standard Stock Solutions

I. Standard Stock Solution of DXM

10mg of standard DXM was weighed and transferred to a10ml volumetric flask. DXM was dissolved in 0.1N HCL by gentle shaking, and the volume was made up to the mark with 0.1N HCL to obtain a final concentration of 1000 µg/ml and labelled as 'Std Stock DXM -A'. From this solution, 1ml of an aliquot was pipetted out in 10ml volumetric flask and the volume was made up to the mark with water to obtain a final concentration of 100 µg/ml and labelled as 'Std Stock DXM-B'.

II. Standard Stock Solution of BUP

10 mg of standard BUP was weighed and transferred to a 10 ml volumetric flask. BUP was dissolved in 5 ml of 0.1N HCL of by gently shaking, and the volume was made up to the mark with 0.1N HCL to obtain a final concentration of 1000 µg/ml and labelled as 'Std Stock BUP-A'. From this solution, 1.0 ml of an aliquot was transferred to a 10 ml volumetric flask, and the volume was made up to the mark using Distilled water. This solution was labelled as 'Std Stock BUP-B (100 µg/ml).

2.5.1 Selection of Analytical Wavelength

The standard stock solution-A of DXM and BUP (1000µg/ml) was prepared by dissolving 10mg of pure drug in 10ml of 0.1NHcl. from this, 1ml was transferred to a 10ml volumetric flask and the volume was made up with water to obtain stock solution- B(100µg/ml). Further, working solution in the range of 2-10µg/ml was prepared by pipetting 0.2-1ml from stock solution -B into separate 10ml volumetric flask and diluting up to volume with water. These solutions were scanned in the wavelength range of 200-400nm, and 224nm and 250nm was selected as the analytical wavelength based on maximum absorbance.

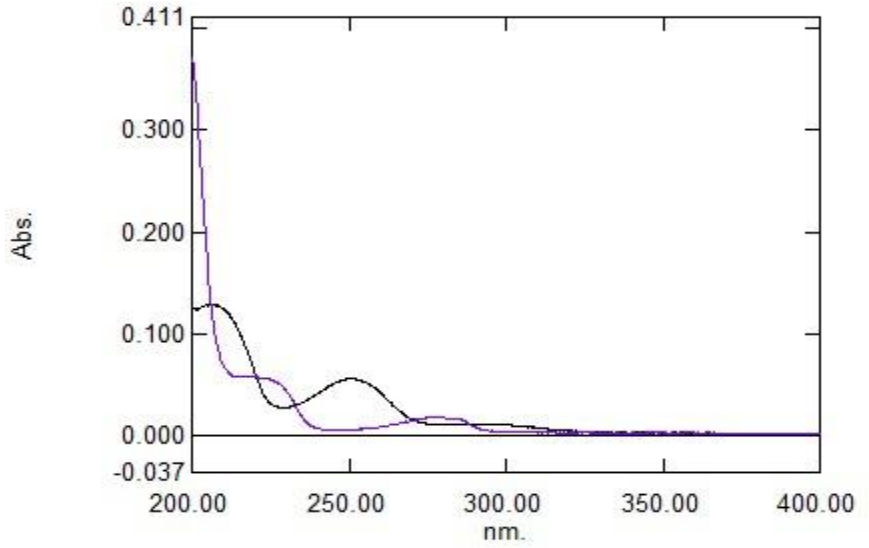

Figure 3: Overlay spectra of DXM (4µg/ml) and BUP (4µg/ml)

2.5.2 Analytical Linearity Concentration Range

Calibration curve for DXM and BUP: The stock solutions of DXM were diluted to get concentration range of 2-10 µg/ml absorbance o these solutions were measured at 224nm and 250nm respectively. While for Bup the stock solution was diluted to get the concentration range of 2-10 µg/ml and absorbance of these solutions were measured at 250 nm and 224nm respectively. Curves were plotted for these drugs as shown in the Figure 4,5,6,7.

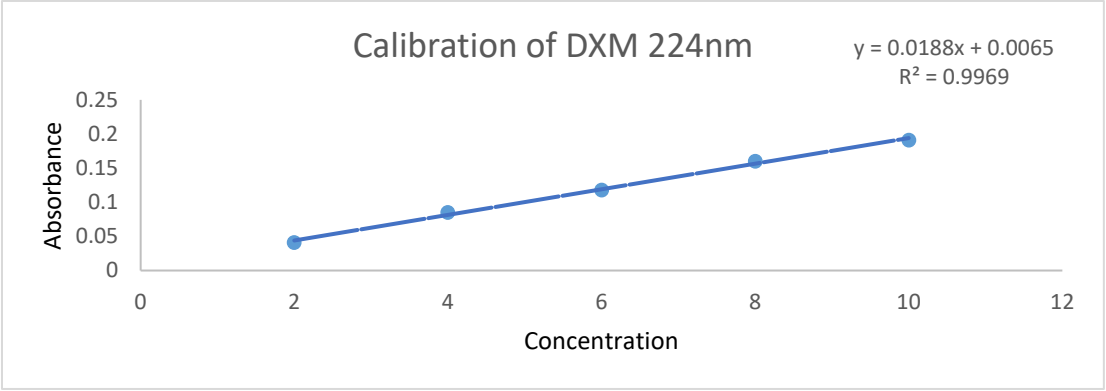

Figure: 4. Calibration Curve of DXM 224nm

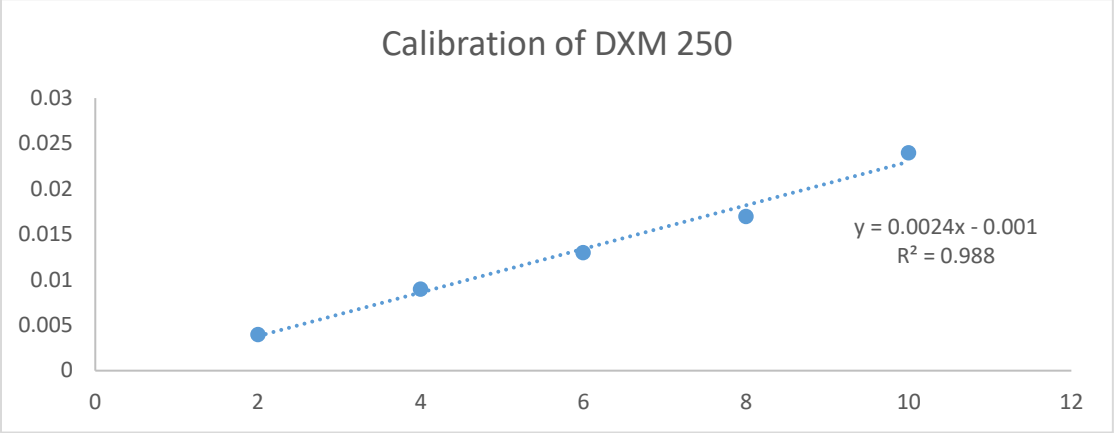

Figure: 5. Calibration Curve of DXM 250nm

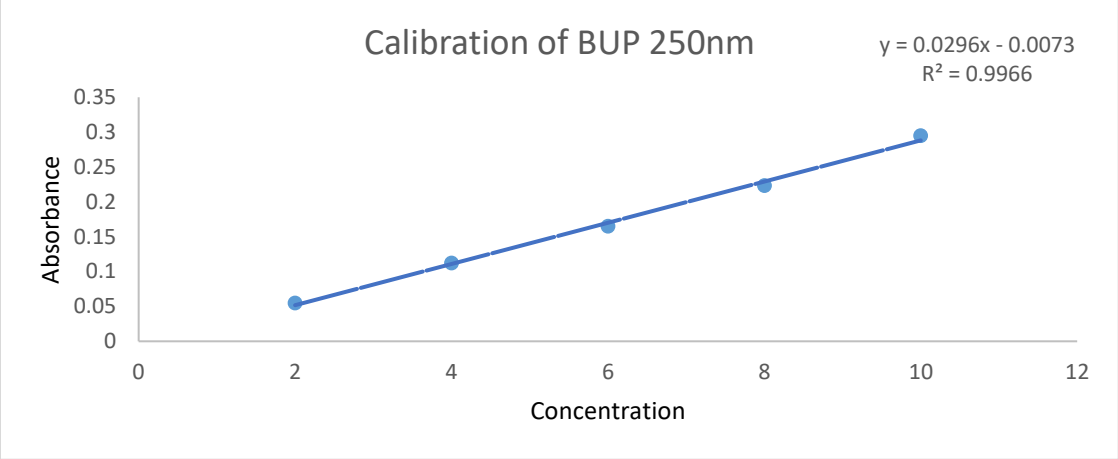

Figure: 6. Calibration Curve of BUP 250nm

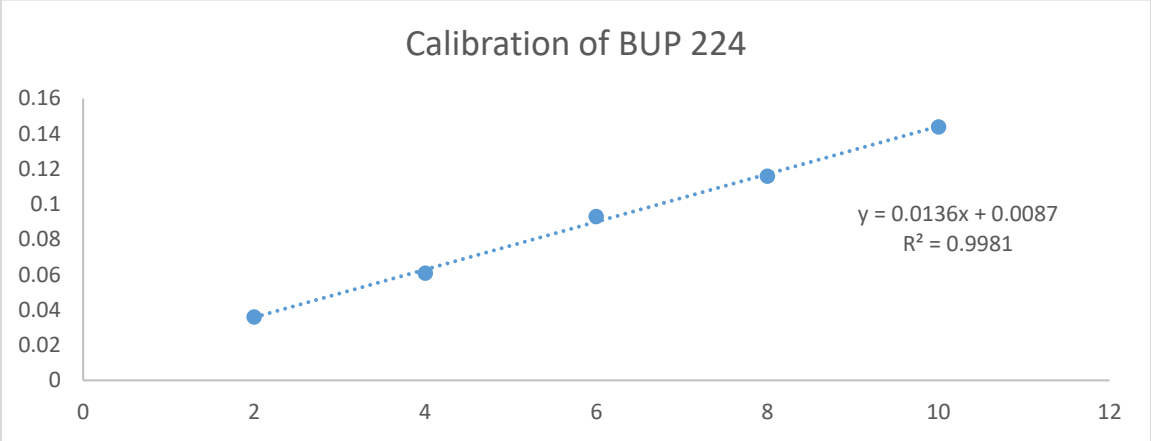

Figure: 7. Calibration Curve of BUP 224nm

2.5.3 Analysis of Tablet Formulation

Twenty tablets of DXM and BUP (DEXBE ™) were weighed and crushed to obtain fine powder. An accurately weighed 10mg tablet powder equivalent to about 45 mg of DXM and 105mg of BUP was transferred to 10ml volumetric flask and

sonicated for 10 minutes in 5ml of 0.1N HCL and made up to the volume with 0.1N HCL to get the concentration of 4500 µg/ml DXM and 10500 µg/ml BUP. The resulting solution was filtered through Whatman filter paper no.41 and this solution was used as 'Sample Stock A'. From the 'Sample Stock A' solution 0.5 ml of the aliquot was pipetted out and transferred in to a 10 ml volumetric flask. The volume was made up to the mark with distilled water to obtain a solution with concentration of 450 µg/ml of DXM and 1050 µg/ml of BUP and this solution was labelled as 'Sample Stock B'. From the "Sample Stock-B" solution 1ml of aliquot was pipetted out and transferred into 10ml volumetric flask. The volume was made up to the mark with distilled water to obtain the working sample solution containing 45µg/ml of DXM and 105µg/ml of BUP and this solution was labelled as 'Sample Solution-C'. The sample solution was scanned at 224 nm and 250 nm. The resultant absorbance was recorded was and noted. Results are given in Table No:5.

The concentration of two drugs (X and Y) in sample solution was calculated by using following equations:

$$C_x = A_2ay_1\text{-}A_1ay_2 / ax_2ay_1\text{-}ax_1ay_2$$

$$C_y = A_1ax_2\text{-}A_2ax_1 / ax_2ay_1\text{-}ax_1ay_2$$

Where, ax1, ax2, ay1 and ay2 are the absorptivity of X and Y at λ1 and λ2 respectively.

A1 and A2 are the absorbance of diluted sample λ1 and λ2 respectively.

3. VALIDATION OF SPECTROPHOTOMETRIC METHOD

3.1 Accuracy Study for DXM and BUP

To determine the accuracy of the method, recovery study by standard addition method at 80%, 100%, and 120% level of the assay concentration. For this study, 1 ml of the pre-analysed 'Sample Stock-A' solution (4500 µg/ml of DXM and 10500µg/ml of BUP) was transferred to the three separate clean 10 ml volumetric flask which was already containing 0.8 ml, 1 ml and 1.2 ml of DXM and BUP (100µg/ml) respectively and made up to the mark with water. These solutions were analysed in UV-spectroscopy mode same as that of the sample solution analysis. Results are given in Table No:6,7.

3.2 Precision

The precision of an analytical method was studied by performing intermediate precision.

1. Intermediate Precision

A. Intra-day Precision

Variation of results within the same day was analysed. Intra-day precision was determined by analysing the standard solutions of 2, 4, 6µg/ml DXM and 2, 4, 6 µg/ml of BUP at three different time intervals on same day (0hr,2hr, and 4hr). The %RSD was calculated to assess precision using the following formula: Results are given in Table No:8,9.

$$\%RSD = (SD/mean) \times 100$$

B. Inter-day Precision

Variation of results between the days was analysed. Inter-day precision was determined by analysing the standard solutions of 2 ,4, 6 µg/ml DXM and 2, 4, 6 µg/ml of BUP on three consecutive days. The %RSD was calculated to assess the reproducibility of the method using the following formula: Results are given in Table No:10,1

$$\%RSD = (SD/mean) \times 100$$

3.3 Limit of Detection (LOD) and Limit of Quantification (LOQ)

Detection limit and quantification limit were determined from the standard deviation of

y- intercepts of six calibration curves and average slope of six calibration curves.

The formula is as follows: -

$$LOD=3.3\times\frac{standard\ deviation\ of\ y-intercepts\ of\ six\ calibration\ curves}{Average\ slope\ of\ six\ Calibration\ Curves}$$

$$LOQ=10\times\frac{standard\ Deviation\ of\ y-Intercepts\ of\ Six\ \ calibration\ curves}{Average\ slope\ of\ Six\ Calibration\ Curves}$$

Results are given in Table No:12.

4. RESULTS

4.1 Linearity studies of Dextromethorphan hydrobromide

Table No:1. Results of Calibration Curve of DXM at 224nm

Conc (µg/ml)	Mean Absorbance	±SD	%RSD
2	0.041167	0.000687	1.669274
4	0.084	0.000816	0.97202
6	0.118167	0.001067	0.90312
8	0.160167	0.001167	0.66629
10	0.190333	0.001599	0.8399

Table No: 2. Results of Calibration Curve of DXM at 250nm

Conc (µg/ml)	Mean Absorbance	±SD	%RSD
2	0.004	0.00037	0.66639
4	0.009	0.00037	0.9983
6	0.013	0.00037	1.83047
8	0.017	0.00039	1.17094
10	0.024	0.00040	1.54212

4.2 Linearity studies of Bupropion hydrochloride:

Table No:3. Results of Calibration Curve of BUP at 250nm

Conc(µg/ml)	Mean Absorbance	±SD	%RSD
2	0.045	0.00096	1.75675
4	0.11183	0.00107	0.95427
6	0.16333	0.00137	0.84145

8	0.22133	0.00149	0.67351
10	0.27333	0.00221	0.80893

Table No:4. Results of Calibration Curve of BUP at 224nm

Conc(µg/ml)	Mean Absorbance	±SD	%RSD
2	0.036	0.00037	1.03045
4	0.061	0.00075	1.20869
6	0.093	0.00096	1.03506
8	0.116	0.000153	1.30558
10	0.144	0.00195	1.34382

Table No:5. Assay Results of Tablet Formulation

Sr. No.	Amount present (mg/tab)		Amount Found (mg/tab)		%Assay	
	DXM	BUP	DXM	BUP	DXM	BUP
1	45	105	44.32	104.59	98.50	99.61
2	45	105	45.17	104.47	98.29	99.50
3	45	105	46.31	104.51	102.93	99.54
4	45	105	46.31	104.51	102.93	99.54
5	45	105	45.02	103.8	100.0	99.95
6	45	105	44.72	104.7	99.39	99.74
Mean			45.31	104.7	100.3	99.48
SD			0.829	0.262	0.019	0.002
%RSD			1.831	0.251	1.907	0.250

Table No:6. Results of Accuracy Study

Level of % Recovery	Sr. No	Amount of Standard Drug Added (µg/ml)		Total Amount Found (µg/ml)		Total Amount Recovered (µg/ml)		%Recovery	
		DXM	BUP	DXM	BUP	DXM	BUP	DXM	BUP
80%	1	36	84	81.46	190.6	36.46	85.64	101.2	101.9
	2	36	84	81.25	188.8	36.25	83.83	100.7	99.79
	3	36	84	81.46	189.2	36.46	84.28	101.2	100.3
100%	1	45	105	90.56	210.4	45.56	105.4	101.2	100.4
	2	45	105	90.45	210.7	45.45	105.7	101.0	100.6
	3	45	105	90.22	210.2	45.22	105.2	100.5	100.2
120%	1	54	126	98.55	231.2	53.55	126.2	99.17	100.1
	2	54	126	98.79	230.9	53.79	125.9	99.62	99.9

	3	54	126	99.04	230.4	54.04	125.4	100.0	99.5

Table No: 7. Statistical Validation Data for Accuracy Study

Level of % Recovery	Mean *(% Recovery)		±SD		% RSD	
	DXM	BUP	DXM	BUP	DXM	BUP
80%	101.09	100.69	0.32991	1.12219	0.3263	1.1144
100%	100.92	100.46	0.38380	0.23201	0.3802	0.2309
120%	99.626	99.90	0.44843	0.30010	0.4501	0.3003

Table No: 8. Results of Intra-day Precision of DXM at 224 nm

Time (hr)	Absorbance of DXM at following Concentration (µg/ml)		
	2	4	6
0	0.038	0.077	0.126
2	0.039	0.078	0.127
4	0.038	0.077	0.129
Mean	0.038	0.077	0.127
±SD	0.000471	0.000471	0.001247
%RSD	1.229751	0.609575	0.979491

Table No: 9. Results of Intra-day Precision of BUP at 250 nm

Time(hr)	Absorbance of BUP at following Concentration (µg/ml)		
	2	4	6
0	0.186	0.265	0.355
2	0.187	0.263	0.359
4	0.189	0.264	0.357
Mean	0.188	0.264	0.357
±SD	0.001247	0.00816	0.001633
%RSD	0.665775	0.309279	0.457421

Table No: 10. Results of Inter-day precision of DXM at 224 nm

DAY	Absorbance of DXM at following Concentration(µg/ml)

	2	4	6
1	0.173	0.254	0.321
2	0.171	0.259	0.323
3	0.17	0.259	0.323
Mean	0.171	0.257	0.322
±SD	0.001247	0.002357	0.001155
%RSD	0.727949	0.915941	0.358232

Table No: 11. Results of Inter-day precision of BUP at 250 nm

DAY	Absorbance of BUP at following Concentration(µg/ml)		
	2	4	6
1	0.186	0.265	0.355
2	0.189	0.262	0.359
3	0.186	0.263	0.357
Mean	0.187	0.263	0.357
±SD	0.001414	0.001414	0.001886
%RSD	0.756264	0.537724	0.5272

Table No: 12. Summary of UV-Visible spectrophotometric Method

Parameters	DXM	BUP
Wavelength (nm)	**224nm**	**250nm**
Linearity Range (µg/ml)	2-10µg/ml	2-10µg/ml
Regression Equation (y = mx+c)	y = 0.0188x+0.0065	y =0.0539x+0.0021
Correlation Coefficient (R^2)	0.999	0.9998
LOD (µg/ml)	0.07955	0.09191
LOQ (µg/ml)	0.24106	0.27852
Analysis of Tablets (Mean % Assay)	100.35	99.48
%Recovery	100.3	99.48
Intra Day Precision (%RSD)	1.22975	0.66578
Inter Day Precision (%RSD)	0.91594	0.75626

5. CONCLUSION

A simple, precise, and sensitive UV-spectrophotometric method utilizing the Simultaneous equation method has been developed for the estimation of dextromethorphan hydrobromide and bupropion hydrochloride.

The developed method was validated according to ICH guidelines, and the results of the assay studies were satisfactory. Therefore, this method can be successfully applied for routine analysis of Dextromethorphan hydrobromide and Bupropion

hydrochloride in marketed formulations of the pharmaceutical dosage form.

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