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DEVELOPMENT AND VALIDATION OF A RP-HPLC METHOD FOR SIMULTANEOUS DETERMINATION OF BUPROPION AND NALTREXONE IN PURE FORM AND ITS PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

A Rapid and Precise Reverse Phase High Performance Liquid Chromatographic method has been developed for the validated of Bupropion and Naltrexone, in its pure form as well as in tablet dosage form. Chromatography was carried out on X-Terra C18 (4.6 x 150mm, 5µm) column using a mixture of Methanol: TEA Buffer pH 4.5: Acetonitrile (65:15:20) as the mobile phase at a flow rate of 1.0ml/min, the detection was carried out at 212 nm. The retention time of the Bupropion and Naltrexone was 2.090, 5.289 ±0.02min respectively. The method produce linear responses in the concentration range of 5-25mg/ml of Bupropion and 45-225mg/ml of Naltrexone. The method precision for the determination of assay was below 2.0%RSD. The method is useful in the quality control of bulk and pharmaceutical formulations.

Keywords: *Bupropion, Naltrexone, RP-HPLC, validation.*

INTRODUCTION[1-3]

Analytical chemistry is the branch of chemistry involved in separating, identifying and determining the relative amounts of the components making up a sample of matter. It is mainly involved in the qualitative identification or detection of compounds and the quantitative measurement of the substances present in bulk and pharmaceutical preparation.

Measurements of physical properties of analytes such as conductivity, electrode potential, light absorption or emission, mass to charge ratio, and fluorescence, began to be used for quantitative analysis of variety of inorganic and biochemical analytes. Highly efficient chromatographic and electrophoretic techniques began to replace distillation, extraction and precipitation for the separation of components of complex mixtures prior to their qualitative or quantitative determination. These newer methods for separating and determining chemical species are known collectively as instrumental methods of analysis. Most of the instrumental methods fit into one of the three following categories viz spectroscopy, electrochemistry and chromatography

Advantages of instrumental methods

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- Small samples can be used
- High sensitivity is obtained
- Measurements obtained are reliable
- Determination is very fast
- Even complex samples can be handled easily

Limitations of instrumental methods

- An initial or continuous calibration is required
- Sensitivity and accuracy depends on the instrument
- Cost of equipment is large
- Concentration range is limited
- Specialized training is needed
- Sizable space is required

High Performance Liquid Chromatography

HPLC is a type of liquid chromatography that employs a liquid mobile phase and a very finely divided stationary phase. In order to obtain satisfactory flow rate liquid must be pressurized to a few thousands of pounds per square inch.

The rate of distribution of drugs between Stationary and mobile phase is controlled by diffusion process. If diffusion is

minimized faster and effective separation can be achieved .The techniques of high performance liquid chromatography are so called because of its improved performance when compared to classical column chromatography advances in column chromatography into high speed,efficient ,accurate and highly resolved method of separation.

For the recent study metformin and Sitagliptin was selected for estimation of amount of analyte present in formulation and bulk drug. The HPLC method is selected in the field of analytical chemistry, since this method is specific, robust, linear, precise and accurate and the limit of detection is low and also it offers the following advantages

• Speed many analysis can be accomplished in 20min (or) less.

• Greater sensitivity (various detectors can be employed).

• Improved resolution (wide variety of stationary phases).

• Re usable columns (expensive columns but can be used for many analysis).

• Ideal for the substances of low viscosity.

• Easy sample recovery, handling and maintenance.

• Instrumentation leads itself to automation and quantification (less time and less labour).

• Precise and reproducible.

• Integrator itself does calculations.

• Suitable for preparative liquid chromatography on a much larger scale.

MATERIALS AND METHODS

Bupropion Provided by Sura labs, Naltrexone Provided by Sura labs, Water and Methanol for HPLC from LICHROSOLV (MERCK), Acetonitrile for HPLC from Merck.

HPLC METHOD DEVELOPMENT:

TRAILS

Preparation of standard solution:

Accurately weigh and transfer 10 mg of Bupropion and Naltrexone working standard into a 10ml of clean dry volumetric flasks add about 7ml of Methanol and sonicate to dissolve and removal of air completely and make volume up to the mark with the same Methanol.

Further pipette 0.15ml of the above Bupropion and 0.1.35ml of Naltrexone stock solutions into a 10ml volumetric flask and dilute up to the mark with Methanol.

Procedure:

Inject the samples by changing the chromatographic conditions and record the chromatograms, note the conditions of proper peak elution for performing validation parameters as per ICH guidelines.

Mobile Phase Optimization:

Initially the mobile phase tried was Methanol: Water and Water: Acetonitrile and Methanol: TEA Buffer: ACN with varying proportions. Finally, the mobile phase was optimized to Methanol: TEA Buffer: ACN in proportion 50:25:25 v/v respectively.

Optimization of Column:

The method was performed with various columns like C18 column, Symmetry and Zodiac column. X-Terra C18 (4.6×150mm, 5µ) was found to be ideal as it gave good peak shape and resolution at 1ml/min flow.

VALIDATION

PREPARATION OF BUFFER AND MOBILE PHASE:

Preparation of Triethylamine (TEA) buffer (pH-4.5):

Dissolve 1.5ml of Ttiethyl amine in 250 ml HPLC water and adjust the pH 4.5. Fliter and sonicate the solution by vaccum filtration and ultra sonication.

Preparation of mobile phase:

Accurately measured 650 ml (65%) of Methanol, 150 ml of Triethylamine buffer (15%) and 200 ml of Acetonitrile (20%) were mixed and degassed in digital ultrasonicater for 10 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation:

The Mobile phase was used as the diluent.

VALIDATION PARAMETERS

SYSTEM SUITABILITY

Accurately weigh and transfer 10 mg of Bupropion and 10mg of Naltrexone working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.15ml of the above Bupropion and 1.35ml of Naltrexone stock solutions into a 10ml volumetric flask and dilute up to the mark with Diluent.

Procedure:

The standard solution was injected for five times and measured the area for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits.

SPECIFICITY STUDY OF DRUG:

Preparation of Standard Solution:

Accurately weigh and transfer 10 mg of Bupropion and 10mg of Naltrexone working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it

completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.15ml of the above Bupropion and 1.35ml of Naltrexone stock solutions into a 10ml volumetric flask and dilute up to the mark with Diluent.

Preparation of Sample Solution:

Take average weight of Tablet and crush in a mortor by using pestle and weight 10 mg equivalent weight of Bupropion and Naltrexone sample into a 10mL clean dry volumetric flask and add about 7mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent.

Further pipette 1.35ml of Sample stock solution into a 10ml volumetric flask and dilute up to the mark with Diluent.

Procedure:

Inject the three replicate injections of standard and sample solutions and calculate the assay by using formula:

$$\%ASSAY = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \text{Weight of tablet} \times 100$$

PREPARATION OF DRUG SOLUTIONS FOR LINEARITY:

Accurately weigh and transfer 10 mg of Bupropion and 10mg of Naltrexone working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Procedure:

Inject each level into the chromatographic system and measure the peak area.

Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.

PRECISION

REPEATABILITY

Preparation of Bupropion and Naltrexone Product Solution for Precision:

Accurately weigh and transfer 10 mg of Bupropion and 10mg of Naltrexone working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.15ml of the above Bupropion and 1.35ml of Naltrexone stock solutions into a 10ml volumetric flask and dilute up to the mark with Diluent.

The standard solution was injected for five times and measured the area for all five injections in HPLC. The %RSD for the area of five replicate injections was found to be within the specified limits.

INTERMEDIATE PRECISION:

To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different days by maintaining same conditions.

Procedure:

DAY 1:

The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

DAY 2:

The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Accuracy:

Procedure:

Inject the Three replicate injections of individual concentrations (50%, 100%, 150%) were made under the optimized conditions. Recorded the chromatograms and measured the peak responses. Calculate the Amount found and Amount added for Bupropion and Naltrexone and calculate the individual recovery and mean recovery values.

ROBUSTNESS:

The analysis was performed in different conditions to find the variability of test results. The following conditions are checked for variation of results. .

For preparation of Standard solution:

Accurately weigh and transfer 10 mg of Bupropion and 10mg of Naltrexone working standard into a 10ml of clean dry volumetric flasks add about 7mL of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.15ml of the above Bupropion and 1.35ml of Naltrexone stock solutions into a 10ml volumetric flask and dilute up to the mark with Diluent.

Effect of Variation of flow conditions:

The sample was analyzed at 0.9 ml/min and 1.1 ml/min instead of 1ml/min, remaining conditions are same. 10µl of the above sample was injected and chromatograms were recorded.

Effect of Variation of mobile phase organic composition:

The sample was analyzed by variation of mobile phase i.e. Methanol: TEA Buffer: Acetonitrile was taken in the ratio and 70:5:25, 60:30:10 instead (65:15:20), remaining conditions are same. 10µl of the above sample was injected and chromatograms were recorded.

RESULTS AND DISCUSSION

Optimized Chromatogram (Standard)

Mobile phase: Methanol: TEA Buffer pH 4.5: Acetonitrile (65:15:20)

Column: X-Terra C18 (4.6×150mm, 5.0 µm)

Flow rate: 1 ml/min

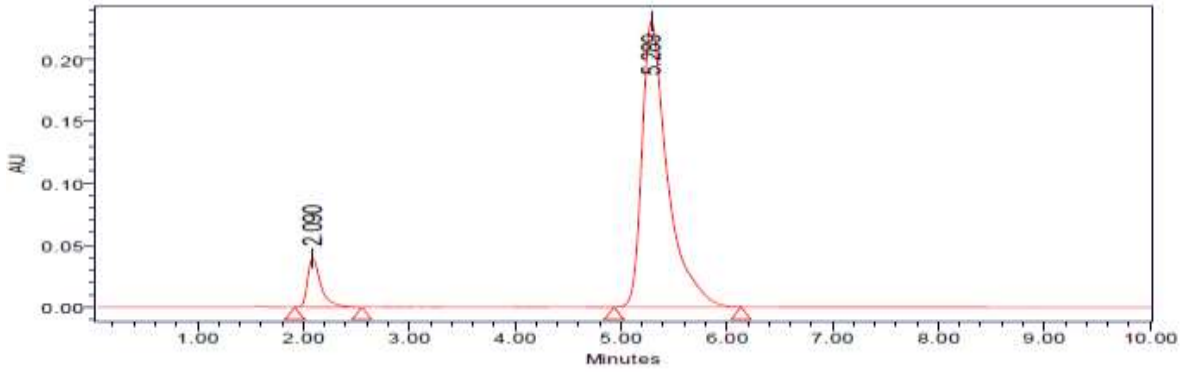
Wavelength: 212 nm

Column temp: Ambient

Injection Volume: 10 µl

Run time: 10 minutes

Fig 1: Optimized Chromatogram



S. No	Peak name	R_t	Area	Height	USP Resolution	USP Tailing	USP plate count
1	Bupropion	2.090	372126	39690		1.70	5587
2	Naltrexone	5.289	3864998	231194	9.80	1.77	5698

Observation: From the above chromatogram it was observed that the Bupropion and Naltrexone peaks are well separated and they shows proper retention time, resolution, peak tail and plate count. So it's optimized trial.

Optimized Chromatogram (Sample)

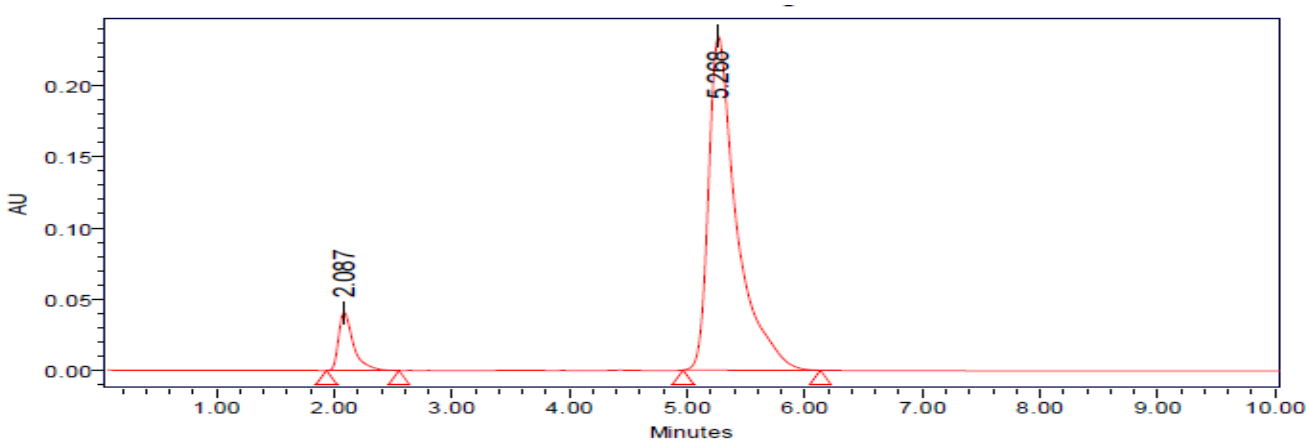


Table 2: Optimized Chromatogram (Sample)

S. No	Peak name	R_t	Area	Height	USP Resolution	USP Tailing	USP plate count
1	Bupropion	2.087	356547	41157		1.72	5557
2	Naltrexone	5.268	3896493	234961	9.82	1.91	5804

VALIDATION

System suitability:

Table 3: Results of system suitability for Bupropion

S no	Name	Rt	Area	Height	USP plate count	USP Tailing
1	Bupropion	2.090	342126	39690	5463	1.42
2	Bupropion	2.090	342426	39690	5576	1.42
3	Bupropion	2.089	342564	39990	5098	1.44
4	Bupropion	2.089	347976	40396	5143	1.43
5	Bupropion	2.085	352914	40963	5674	1.47
Mean			345601.2			
Std. Dev			4756.58			
% RSD			1.3			

Table 4: Results of system suitability for Bupropion

S no	Name	Rt	Area	Height	USP plate count	USP Tailing	USP Resolution
1	Naltrexone	5.289	3864998	231194	5786	1.46	9.80
2	Naltrexone	5.289	3864998	232184	5908	1.47	9.81
3	Naltrexone	5.338	3881443	231044	5487	1.48	9.81
4	Naltrexone	5.327	3896952	231969	5032	1.40	9.83
5	Naltrexone	5.262	3900103	233541	5389	1.43	9.82
Mean			3881699				
Std. Dev			16802.33				
% RSD			0.4				

Assay (Standard):

Table 5: Peak results for assay standard

S no	Name	Rt	Area	Height	USP Resolution	USP Tailing	USP plate count	Injection
1	Bupropion	2.090	348126	39690		1.70	5587	1
2	Naltrexone	5.289	3864998	231194	9.80	1.77	5628	1
3	Bupropion	2.089	352564	39990		1.66	5571	2
4	Naltrexone	5.338	3881443	231044	9.93	1.83	5688	2
5	Bupropion	2.089	357976	40396		1.68	5530	3
6	Naltrexone	5.327	3896952	231969	9.91	1.86	5712	3

Assay (Sample):

Table 6: Peak results for Assay sample

S no	Name	Rt	Area	Height	USP Resolution	USP Tailing	USP plate count	Injection
1	Bupropion	2.088	352290	40269		1.69	5516	1
2	Naltrexone	5.276	3883794	231354	9.75	1.89	5677	1
3	Bupropion	2.087	356547	41157		1.72	5557	2
4	Naltrexone	5.268	3896493	234961	9.82	1.91	5804	2
5	Bupropion	2.085	358914	40963		1.75	5489	3
6	Naltrexone	5.262	3900103	233541	9.78	1.95	5790	3

$$\%ASSAY = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Weight of standard}}{\text{Dilution of standard}} \times \frac{\text{Dilution of sample}}{\text{Weight of sample}} \times \frac{\text{Purity}}{100} \times \frac{\text{Weight of tablet}}{\text{Label claim}} \times 100$$

The % purity of Bupropion and Naltrexone in pharmaceutical dosage form was found to be100.5%.

LINEARITY

Table 7: Chromatographic Data for Linearity Study Bupropion:

Concentration Level (%)	Concentration µg/ml	Average Peak Area
33.3	5	134436
66.6	10	245571
100	15	371548
133.3	20	499024
166.6	25	619830

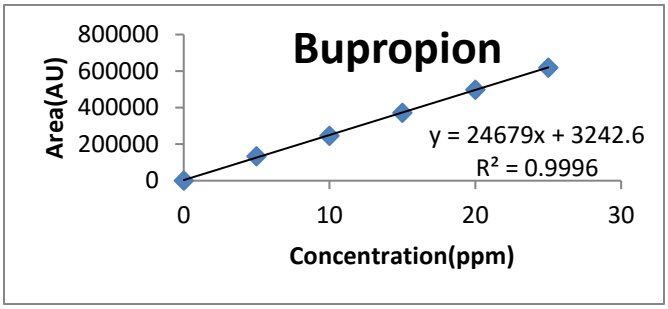


Figure 3: calibration graph for Bupropion

Table 8: Chromatographic Data for Linearity Study Naltrexone

Concentration Level (%)	Concentration µg/ml	Average Peak Area
33	45	1330054
66	90	2728974
100	135	3917063
133	180	5300022
166	225	6412695

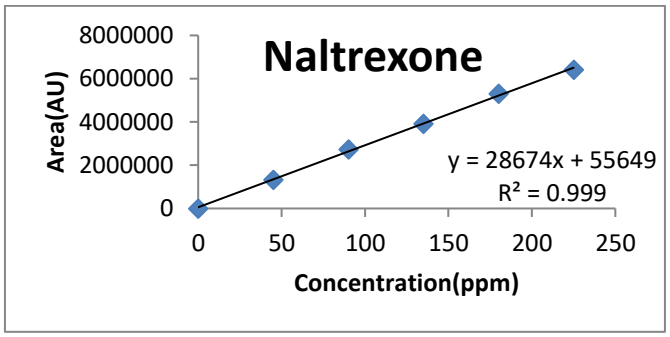


Figure 4: calibration graph for Naltrexone

REPEATABILITY

Table 9: Results of repeatability for Bupropion:

S no	Name	Rt	Area	Height	USP plate count	USP Tailing
1	Bupropion	2.086	362266	41697	5081.3	1.8
2	Bupropion	2.083	364902	41402	5144.1	1.8
3	Bupropion	2.083	366870	41540	5118.1	1.8
4	Bupropion	2.081	367273	42256	5147.3	1.8
5	Bupropion	2.081	368101	42143	5101.8	1.8
Mean			365882.4			
Std. Dev			2338.4			
% RSD			0.6			

Acceptance criteria:

- %RSD for sample should be NMT 2
- The %RSD for the standard solution is below 1, which is within the limits hence method is precise.

Table 10: Results of method precession for Naltrexone:

S no	Name	Rt	Area	Height	USP plate count	USP Tailing	USP Resolution
1	Naltrexone	5.178	3903548	240181	5988.3	2.0	9.8
2	Naltrexone	5.199	3905819	235523	5856.3	2.0	9.7
3	Naltrexone	5.235	3916120	238578	5930.2	2.0	9.9
4	Naltrexone	5.202	3916542	238814	5936.9	2.0	9.8
5	Naltrexone	5.206	3920943	241006	5040.0	2.0	9.5
Mean			3912594.4				
Std. Dev			7507.6				
% RSD			0.2				

Acceptance criteria:

- %RSD for sample should be NMT 2
- The %RSD for the standard solution is below 1, which is within the limits hence method is precise.

Intermediate precision:

Table 11: Results of Intermediate precision Day 1for Bupropion

S no	Name	Rt	Area	Height	USP plate count	USP Tailing
1	Bupropion	2.083	369246	42277	5537.8	1.6
2	Bupropion	2.083	370766	42708	5561.8	1.6
3	Bupropion	2.089	370840	42065	5489.3	1.6
4	Bupropion	2.083	370840	42065	5489.3	1.6
5	Bupropion	2.082	371041	42568	5583.2	1.8
6	Bupropion	2.080	371386	42211	5533.2	1.8
Mean			370686.5			
Std. Dev			740.7369			
% RSD			0.19			

Acceptance criteria:

- %RSD of six different sample solutions should not more than 2

Table 12: Results of Intermediate precision Day 1 for Naltrexone

S no	Name	Rt	Area	Height	USP plate count	USP Tailing	USP Resolution
1	Naltrexone	5.229	3743003	242955	5269.7	2.2	10.2
2	Naltrexone	5.203	3845359	242255	5100.5	2.1	10.0
3	Naltrexone	5.133	3885014	242854	5127.6	2.1	10.0
4	Naltrexone	5.229	3743003	242955	5269.7	2.2	10.2
5	Naltrexone	5.151	3722513	240346	5048.8	1.5	9.9
6	Naltrexone	5.112	3728789	237638	5997.2	1.6	9.9
Mean			3777947				
Std. Dev			69194.4				
% RSD			1.8				

Table 13: Results of Intermediate precision Day 2 for Bupropion

S no	Name	Rt	Area	Height	USP plate count	USP Tailing
1	Bupropion	2.078	370979	42978	7083.0	1.9
2	Bupropion	2.082	371041	42568	8583.2	1.8
3	Bupropion	2.080	371386	42211	7533.2	1.8
4	Bupropion	2.089	369246	42277	6537.8	1.6
5	Bupropion	2.083	370840	42065	5489.3	1.6
6	Bupropion	2.089	369246	42277	6537.8	1.6
Mean			370456.3			
Std. Dev			954.6004			
% RSD			0.25			

Acceptance criteria: %RSD of six different sample solutions should not more than 2

Table 14: Results of Intermediate precision for Naltrexone

S no	Name	Rt	Area	Height	USP plate count	USP Tailing	USP Resolution
1	Naltrexone	5.077	3841404	246818	5208.0	1.5	10.1
2	Naltrexone	5.151	3885014	242854	5127.6	1.3	10.0
3	Naltrexone	5.112	3743003	242955	5269.7	1.5	10.2
4	Naltrexone	5.133	3743003	242955	5269.7	1.6	10.2
5	Naltrexone	5.203	3885014	242854	5127.6	1.5	10.0
6	Naltrexone	5.133	3743003	242955	5269.7	1.6	10.2
Mean			3806740				
Std. Dev			71613.47				
% RSD			1.8				

ACCURACY: Table 15: The accuracy results for Bupropion

%Concentration (at specification Level)	**Area**	**Amount Added (ppm)**	**Amount Found (ppm)**	**% Recovery**	**Mean Recovery**
50%	192446.6	7.5	7.4	98.6	98.7%
100%	374222	15	14.8	98.66	
150%	555891.3	22.5	22.3	99.1	

Table 16: The accuracy results for Naltrexone

%Concentration (at specification Level)	**Area**	**Amount Added (ppm)**	**Amount Found (ppm)**	**% Recovery**	**Mean Recovery**
50%	2001752	67.5	67.3	99.7	99.7%
100%	3927797	135	134.8	99.8	
150%	5858665	202.5	202.1	99.8	

Acceptance Criteria:

• The percentage recovery was found to be within the limit (98-102%).

The results obtained for recovery at 50%, 100%, 150% are within the limits. Hence method is accurate.

LIMIT OF DETECTION

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

LOD= 3.3 × σ / s

Where

σ = Standard deviation of the response

S = Slope of the calibration curve

Result:

Bupropion:

=3.3 × 5088/24679

=0.6µg/ml

Naltrexone:

=9.7µg/ml

=3.3 × 84406/28674

LIMIT OF QUANTITATION

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined.

LOQ=10×σ/S

Where

σ = Standard deviation of the response

S = Slope of the calibration curve

Result:

Bupropion:

=10×5088/24679

= 2.0µg/ml

Naltrexone:

=10 × 84406/28674

= 29.4µg/ml

Robustness

Table 17: Results for Robustness Bupropion:

Parameter used for sample analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flow rate of 1.0 mL/min	372126	2.090	5587	1.70
Less Flow rate of 0.9 mL/min	356765	2.736	5432	1.82
More Flow rate of 1.1 mL/min	342356	1.673	5644	1.91
Less organic phase	312434	2.736	5098	1.82
More organic phase	305623	1.673	5123	1.91

Acceptance criteria:

The tailing factor should be less than 2.0 and the number of theoretical plates (N) should be more than 2000.

Table 18: Results for Robustness Naltrexone:

Parameter used for sample analysis	Peak Area	Retention Time	Theoretical plates	Tailing factor
Actual Flow rate of 1.0 mL/min	3864998	5.289	5698	1.77
Less Flow rate of 0.9 mL/min	3546737	6.746	5546	1.88
More Flow rate of 1.1 mL/min	3857216	4.032	5124	1.91
Less organic phase	3810347	6.746	5034	1.88

Acceptance criteria:

The tailing factor should be less than 2.0 and the number of theoretical plates (N) should be more than 2000.

SUMMARY

The analytical method was developed by studying different parameters.

First of all, maximum absorbance was found to be at 212 nm and the peak purity was excellent.

Injection volume was selected to be 10µl which gave a good peak area.

The column used for study was X-Terra C18 because it was giving good peak.

Ambient temperature was found to be suitable for the nature of drug solution. The flow rate was fixed at 1.0ml/min because of good peak area and satisfactory retention time.

Mobile phase is Methanol: TEA Buffer pH 4.5: Acetonitrile (65:15:20) was fixed due to good symmetrical peak. So this mobile phase was used for the proposed study.

Run time was selected to be 10 min because analyze gave peak around 2.090, 5.289 ±0.02min respectively and also to reduce the total run time.

The percent recovery was found to be 98.0-102 was linear and precise over the same range. Both system and method precision was found to be accurate and well within range.

The analytical method was found linearity over the range 5-25mg/ml of Bupropion and 45-225 mg/ml of Naltrexone of the target concentration.

The analytical passed both robustness and ruggedness tests. On both cases, relative standard deviation was well satisfactory.

CONCLUSION

In the present investigation, a simple, sensitive, precise and accurate RP-HPLC method was developed for the quantitative estimation of Bupropion and Naltrexone in bulk drug and pharmaceutical dosage forms.

This method was simple, since diluted samples are directly used without any preliminary chemical derivatisation or purification steps.

Bupropion and Naltrexone was freely soluble in ethanol, methanol and sparingly soluble in water.

Methanol: TEA Buffer pH 4.5: Acetonitrile (65:15:20) was chosen as the mobile phase. The solvent system used in this method was economical.

The %RSD values were within 2 and the method was found to be precise.

The results expressed in Tables for RP-HPLC method was promising. The RP-HPLC method is more sensitive, accurate and precise compared to the Spectrophotometric methods.

This method can be used for the routine determination of Bupropion and Naltrexone in bulk drug and in Pharmaceutical dosage forms.

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