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DEVELOPMENT AND VALIDATION OF RP-HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF VENLAFAXINE HYDROCHLORIDE AND BUPROPION HYDROCHLORIDE

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ABSTRACT

In the present research work, a simple and precise method was developed for simultaneous estimation of Venlafaxine HCl and Bupropion HCl in bulk and tablet dosage form was developed and validated.A new RP-HPLC method was developed using RP C-18 column (Zodiac10µm, 250mmX4.6mm) asstationaryphaseandmethanol:phosphatebuffer(Potassiumdihydrogenorthophosphate)(70:30v/v)asmobilephase.Theflowrateofmobilephasewas1ml/min.The analysis was performed at ambient temperature with UV detection at 231 nm. The retention time of Venlafaxine hydrochloride and Bupropion hydrochloride was found to be 4.7 min 8.5 min respectively. Both the drugs showed linear response between the concentration ranges from10-60µg/ml. The LOD was found to be 0.3 µg/ml and 0.5 µg/ml respectively and LOQ was found 1.1 µg/ml and 1.6 µg/ml respectively. The % recovery was found to be 100.1% and 100.05% respectively. So, the developed method was simple and conservative for bulk and tablet dosage form of Venlafaxine hydrochloride and Bupropion hydrochloride.

INTRODUCTION

Venlafaxine hydrochloride [1, 2] is a novel synthetic antidepressant derivative of ethyl cyclohexanol, metabolized into O-desmethylvenlafaxine and potentiates the activity of CNS. It is referred to as Serotonin norepinephrine reuptake inhibitor (SNRI), because it inhibits the uptake of both noradrenaline (NA) and 5-hydroxytryptamine (5-HT) but, in contrast to older tricyclic antidepressants (TCAs), does not interact with the cholinergic, adrenergic or histaminergic receptors or has sedative properly. Its trial shown to be effective antidepressants as TCAs and may work in some resistant cases. It's may improve the mood, energy level and help to restore the interest of daily living.

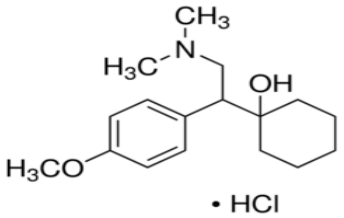

Fig 1: Structure of Venlafaxine hydrochloride

Bupropion hydrochloride [3,4] is the salt of an amino ketone showing antidepressant activity and potentially used in smoking cessation. The mechanism of the antidepressant effect of Bupropion hydrochloride is unknown. This antidepressant agent has different neurochemical properties from common

tricyclic antidepressant. Bupropion hydrochloride is also a selective inhibitor of the neuronal reuptake of nor adrenaline and dopamine (catecholamine's) with minimal effect on the reuptake of indolamine (serotonin) and there is no inhibitory effect on monoamine oxidase. It is a weak blocker of the neuronal uptake of serotonin, dopamine and norepinephrine as well as central nicotinic acetylcholine receptor antagonist.

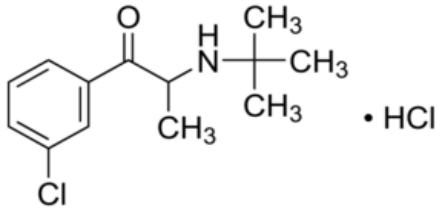

Fig 2: Structure of Bupropion hydrochloride

As compared to monotherapy of Venlafaxine hydrochloride and Bupropion hydrochloride, its combination therapy shows synergistic action on antidepressant activity. This combination shows some unique pharmacological profiles, which effects in the treatment of depression and converts partial response to full response in the patients with treatment-resistant depression. So, it's considered that this combination would reduce the depressive symptoms in the patients, who were unresponsive to various classes of psychotropic agents.On literature survey, it was found that several methods like UV Spectrophotometric method [5-7], Reverse Phase High Performance Chromatographic method (RP-HPLC) [8, 9] and High-Performance Thin Layer Chromatographic method (HPTLC) [10, 11] for individual drug has been established for Venlafaxine hydrochloride and Bupropion hydrochloride was estimated and validated by UV Spectrophotometric method [12-16], Potentiometric method, Conductometric method [15], Reverse Phase High Performance Liquid Chromatographicmethod (RP-HPLC) [16-21] for individual drug, RP-HPLC with other combination of drug has been established for Bupropion hydrochloride [22]. Hence, there is a need for the development of newer, simpler, rapid, accurate and reproducible analytical methods for simultaneous estimation of Venlafaxine hydrochloride and Bupropion hydrochloride in bulk and pharmaceutical dosage forms.

MATERIALS AND METHODS:

Preparation of Mobile Phase: Volume of 500 mL of HPLC grade methanol and 500 mL of phosphate buffer pH 4.8 wasused as mobile phase. The phosphate buffer was prepared by using dissolving 3.4 gm of potassium di-hydrogen ortho phosphate crystals in 500 mL of Millipore water. Both thesolvent systems were filtered by using 0.45µ filter papers and sonicate for 20 minutes. The gradient chromatographic mode was use.

Preparation of diluents: A solvent system composed of Methanol: Phosphate buffer with pH 4.8 (70:30 v/v) was used as diluents.

Preparation of standard stock solution of Venlafaxine hydrochloride and Bupropion hydrochloride (Stock I): Accurately 10 mg of Venlafaxine hydrochloride & 10 mg of Bupropion hydrochloride were weighed into a clean and dry 100 mL volumetric flask separately dissolved with sufficient volume of diluent. The final volume was made up to 100 mL with diluent to give the solution containing 100 µg/mL of Venlafaxine hydrochloride & Bupropion hydrochloride.

Preparation of working standard solutions of Venlafaxine hydrochloride and Bupropion hydrochloride:1 mL of standard stock solution of Venlafaxine hydrochloride and Bupropion hydrochloride was pipetted out into 10 mL volumetric flask and further diluted with diluent to 10mL to get concentration of 10µg/mL of Venlafaxine hydrochloride and Bupropion hydrochloride.

Procedure: 10µL of the blank, standard and sample were injected into the chromatographic system and areas for the Venlafaxine hydrochloride and Bupropion hydrochloride the peaks were used for calculating the % assay by using the formula.

Results:

Method validation: specificity, linearity range, accuracy, precision, repeatability, intermediate precision, limit of detection, limit of quantification, robustness, ruggedness, accuracy.

SPECIFICITY: 70 volumes of HPLC grade methanol and 30 volumes of phosphate buffer pH 4.8 was used as mobile phase as well as

diluent. Both the solvent systems were mixed well and filtered by using0.45 µ membrane filters and sonicated for 20 minutes. **(fig- 3,4)**

LINEARITY

Procedure for Determination of Linearity and Range:

Preparation of standard stock solution of Venlafaxine hydrochloride and Bupropion hydrochloride (STOCK I): Accurately 10 mg of Venlafaxine hydrochloride & of Bupropion hydrochloride were weighed into a clean and dry 100 mL volumetric flask separately dissolved with sufficient volume of diluent. The final volume was made up to 100 mL with diluent to give the solution containing 100 µg/mL of Venlafaxine hydrochloride & of Bupropion hydrochloride.

Preparation of working standard solution of Venlafaxine hydrochloride and Bupropion hydrochloride: The various concentration of working standard solutions of Venlafaxine hydrochloride & Bupropion hydrochloride was made by pipetting 1.0 mL, 2.0 mL, 3.0 mL, 4.0 mL and 5.0 mL from stock (I) separately into a series of 10 mL volumetric flask anddiluted to 10 mL to get the final concentration of 10 µg/mL, 20 µg/mL, 30µg/mL, 40µg/mL, 50 µg/ml 60µg/mL of Venlafaxine hydrochloride and Bupropion hydrochloride solutions respectively. **(Table- 1,2, Fig- 5,6)**

SYSTEM SUITABILITY: The system suitability parameter is the important validation parameter which deals with the concept that equipment, electronics, analytical operations and sample to be analysed constitute an integral system that can be evaluated as such. This test ensures that the analytical system is working properly and can give accurate and precise results**.(Fig 7, Table-3)**

PRECISION: The precision of an analytical procedure or method expresses the closeness of agreements between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be studied at three levels: repeatability, intermediate precision and reproducibility.

SYSTEM PRECISION: The system precision is checked by using standard substance to ensure that the analytical system is working properly. The peak area of six determinations is to be measured and percentage RSD should be calculated.**(Table 4)**

METHODPRECISION: Method precision is a validation parameter according to the ICH guidelines and used to indicate thatwhethermethodisgiving consistent resultsorasinglebatch,usuallytostandardization of methodology.**(Table 5)**

INTRA-DAY PRECISION: The Intra-day precision is checked by using standard substance to ensure that the analytical system is working properly. The peak area of six determinations in per hour is to be measured and percentage RSD should be calculated**. (Table 6)**

INTER-DAY PRECISION: The Inter-day precision is checked by using standard substance to ensure that the analytical system is working properly. The peak area of three days determinations is to be measured and percentage RSD should be calculated. **(Table 7)**

SENSITIVITY: Sensitivity of a method were studied in terms of Limit of Detection and Limit of Quantification. For the determination of LOD and LOQ, visualization method was followed. In visualization method lower dilutions of the standard drug Venlafaxine hydrochloride and Bupropion hydrochloride were successively prepared and injected into chromatograph and response was recorded.

ESTIMATION OF LOD AND LOQ:

Preparation of standard stock solution of Venlafaxine hydrochloride and Bupropion hydrochloride (Stock I): Accurately 10 mg of Venlafaxine hydrochloride and Bupropion hydrochloride were weighed separately and transferred into a clean and dry 100 mL volumetric flask and volume were made up to the mark using mobile phase diluent to get the concentration of 100 µg/mL of Venlafaxine hydrochloride and Bupropion hydrochloride respectively.

Preparation of standard stock solution of Venlafaxine hydrochloride and Bupropion hydrochloride (Stock III):1 mL of each stock solution (Stock II) was transferred separately into a clean and dry 10 mL volumetric flask and volume were made up to the mark using mobile phase diluent to get the concentration of 1 µg/mL of Venlafaxine hydrochloride and Bupropion hydrochloride respectively.

Preparation of working standard solution of Venlafaxine hydrochloride and Bupropion hydrochloride: From standard stock solution (Stock III), volume of 1 mL to 0.1 mL from standard stock IV were transferred into different 10 mL volumetric flasks and volume were made up to the mark using mobile phase diluent to get the concentration of 1 µg/mL to 0.01 µg/mL of Venlafaxine hydrochloride and Bupropion hydrochloride separately.**(Fig 8,9 Table-8)**

ROBUSTNESS: The robustness study was performed by using deliberate variations in method parameters :**(Table 9)** Variations in change in flow rate of mobile phase, Variations in wavelength of detection and Variations in change in composition of mobile phase.

RUGGEDNESS: The ruggedness parameter was performed for the developed RP-HPLC method by different analyst on same instrument and also on different instrument on different days using different lots of column. The % RSD for the same was calculated for intermediate precision.**(Table 10).**

ACCURACY: The accuracy was performed using marketed formulation. (Table 11, 12, 13)

Preparation of marketed sample stock solution: Twenty tablets of containing 150 mg of Venlafaxine hydrochloride and Bupropion hydrochloride respectively were weighed and finely powdered. Powder equivalent to 10 mg of Venlafaxine hydrochloride and Bupropion hydrochloride were accurately weighed and transferred together into 100 mL volumetric flask and volume were made up to the mark using mobile phase diluent to get the concentration of 100 µg/mL of Venlafaxine hydrochloride and Bupropion hydrochloride respectively. (Stock I). 1 mL of Stock I transferred into 10 mL of volumetric flask and make up the volume with diluent to get concentration of 10 µg/mL of Venlafaxine hydrochloride and Bupropion hydrochloride respectively (Stock II).

Preparation of standard stock solution: Accurately 10 mg of Venlafaxine hydrochloride and Bupropion hydrochloride were weighed separately and transferred together into a clean and dry 100 mL volumetric flask and volume were made up to the mark using mobile phase diluent to get the concentration of 100 µg/mL of Venlafaxine hydrochloride and Bupropion hydrochloride respectively. (stock I) 2 mL of Stock I transferred into 10 mL of volumetric flask and make up the volume with diluent to get concentration of 20 µg/mL of Venlafaxine hydrochloride and Bupropion hydrochloride respectively (Stock II).

Preparation of standard and sample mixture of Venlafaxine hydrochloride and Bupropion hydrochloride:

Level I (80%): Volume of 1 mL of sample stock solution II and 0.8 mL of standard stock II solutions of Venlafaxine hydrochloride and Bupropion hydrochloride was transferred to 10 mL of volumetric flask and volume was made up to the mark with mobile phase diluents (Three Replicates).

Level II (100%): Volume of 1 mL of sample stock solution and 1 mL of standard stock solutions of Venlafaxine hydrochloride and Bupropion hydrochloride was transferred to 10 mL of volumetric flask and volume was made up to the mark with mobile phase diluents. (Three Replicates).

Level III (120%): Volume of 1 mL of sample stock solution and 2.2 mL of standard stock solutions of Venlafaxine hydrochloride and Bupropion hydrochloride was transferred to 10 mL of volumetric flask and volume was made up to the mark with mobile phase diluents. (Three Replicates).

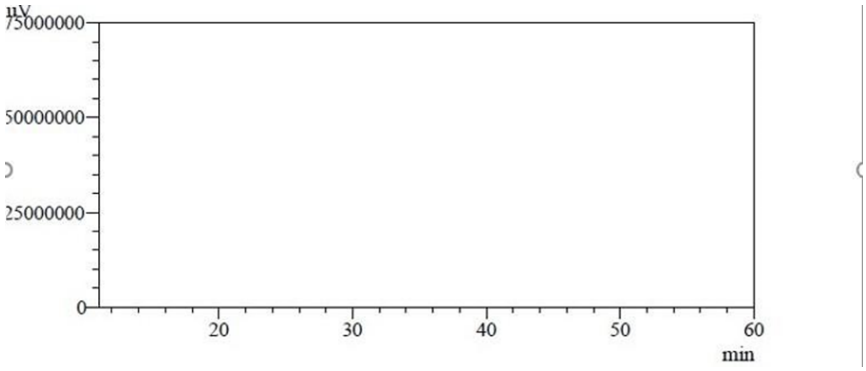

Fig 3: Chromatogram showing Blank

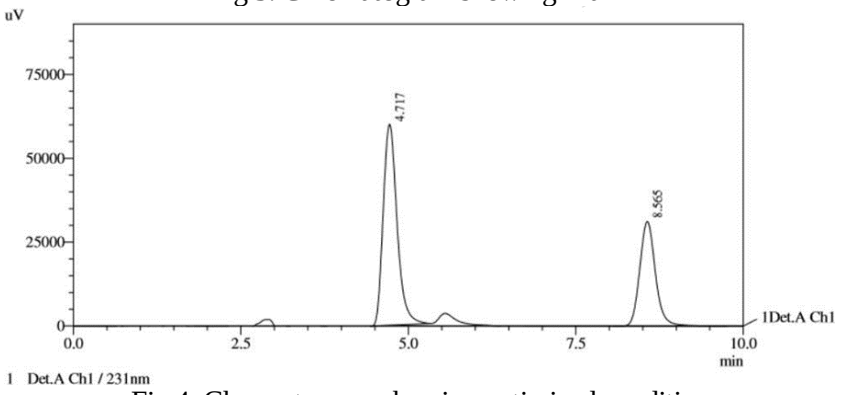

Fig 4: Chromatogram showing optimized condition

Table 1: Linearity and Range data of VENLA and BUPRO by RP-HPLC method

Sr. No.	Concentration (µg/ml)	Peak area for VENLA	Peak area for BUPRO
1	10 µg/ml	404925	241719
2	20 µg/ml	865216	510191
3	30 µg/ml	1214775	725157
4	40 µg/ml	1619700	967876
5	50 µg/ml	2024625	1208595
6	60 µg/ml	2429550	1460314

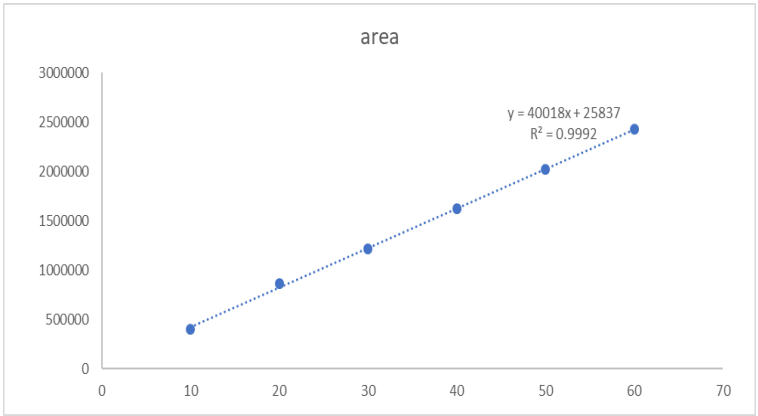

Fig: 5. Calibration curve of Venlafaxine hydrochloride

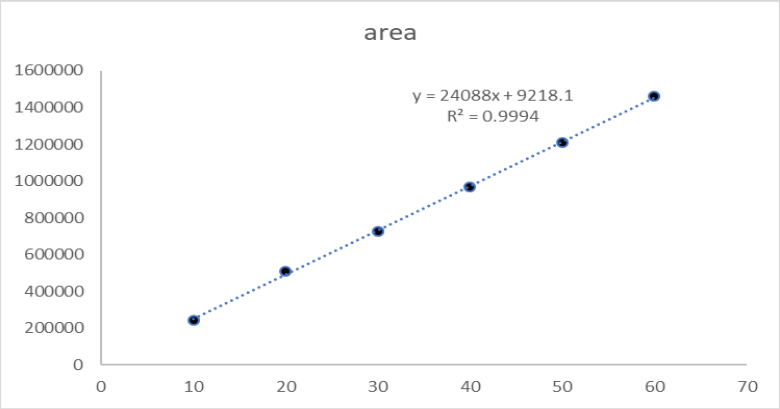

Fig: 6. Calibration curve of Bupropion hydrochloride

Table 2: Linearity and Range report of VENLA and BUPRO by RP-HPLC method

Parameters	**Venla**	**Bupro**	**Acceptance Criteria**
Linearity Range	10 -60 µg/ml	10 - 60 µg/ml	--
Regression Equation	y = 40018x +28837	y = 24088x +9218.1	--
Correlation Coefficient	0.9992	0.9994	More than 0.999
% Curve Fitting	99.92	99.94	-
Slope	40018	24088	-

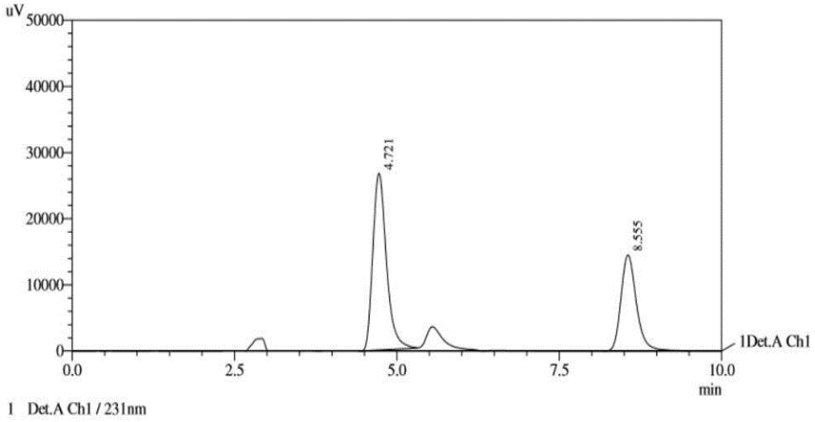

Fig 7. System suitability of VENLA and BUPRO

Table 3: System suitability parameter report of VENLA and BUPRO

S.No.	System Suitability Parameters	VENLA	BUPRO	Acceptance Criteria
1.	Resolution	0.00	9.690	More than 2
2.	Tailing Factor	1.317	1.167	Less than 2
3.	HETP	58.33 mm	22.77 mm	-
4.	Theoretical Plates	16847.59	44225.79	More than 2000

Table 4: System precision data of VENLA and BUPRO by RP-HPLC method

Replicate	Conc of VENLA and BUPRO	VENLA Peak Area*	BUPRO Peak Area*
1	20 µg/ml	865210	510188
2	20 µg/ml	865220	510190
3	20 µg/ml	865216	510098
4	20 µg/ml	865209	510186
5	20 µg/ml	865212	510191
6	20 µg/ml	865208	510191
Average		865212.5	510174.2
Standard Deviation		4.63	37.37
% RSD		0.000536	0.007326

Table 5: Method precision data of VENLA and BUPRO by RP-HPLC method

Replicate	VENLA Peak Area*	Conc of VENLA µg/ml	BUPRO Peak Area*	Conc of BUPRO µg/ml
1	865213	19.99	510189	19.99
2	865216	20.0	510191	20.0
3	865210	19.98	510194	20.01
4	865214	19.99	510210	20.02
5	865222	20.02	510190	20.0
6	865216	20.0	510292	20.0
	Average	19.99	Average	20.003
	Standard Deviation	0.0136	Standard Deviation	0.0103
	% RSD	0.068	% RSD	0.051

Table 6: Intraday precision data of VENLA and BUPRO by RP-HPLC method

Replicate	Time in Hour	VENLA		BUPRO	
		Peak Area	Conc obtained µg/ml	Peak Area	Conc obtained µg/ml
1	1 Hour	865214	19.99 µg/ml	510188	19.99 µg/ml
2	2 Hour	865212	19.99 µg/ml	510194	20.0 µg/ml
3	3 Hour	865216	20.0 µg/ml	510191	20.0 µg/ml
4	4 Hour	865218	20.0 µg/ml	510182	19.98 µg/ml
5	5 Hour	865216	20.0 µg/ml	510185	19.98 µg/ml
6	6 Hour	865211	19.98 µg/ml	510190	19.99 µg/ml
7	12 Hour	865217	20.0 µg/ml	510196	20.01 µg/ml
Mean			19.99		19.997
Standard Deviation			0.007868		0.008165
% RSD			0.0393		0.0488

Table 7: Inter day precision data of VENLA and BUPRO by RP-HPLC method

Day	VENLA		BUPRO	
	Peak Area	Conc obtained µg/ml	Peak Area	Conc obtained µg/ml
1 Day	865214	19.99	510198	20.02
2 Day	865216	20.0	510191	20.0
3 Day	865225	20.03	510188	19.99
Mean		20.01		20.01
Standard Deviation		0.0208		0.0152
% RSD		0.104		0.0763

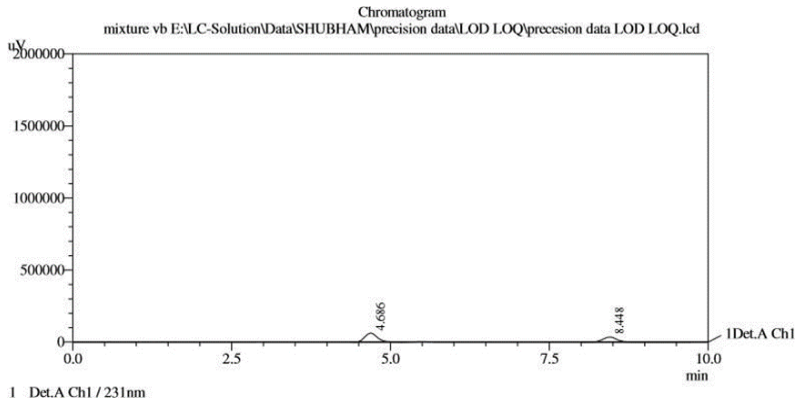

Fig 8. LOD of Venlafaxine hydrochloride and Bupropion hydrochloride

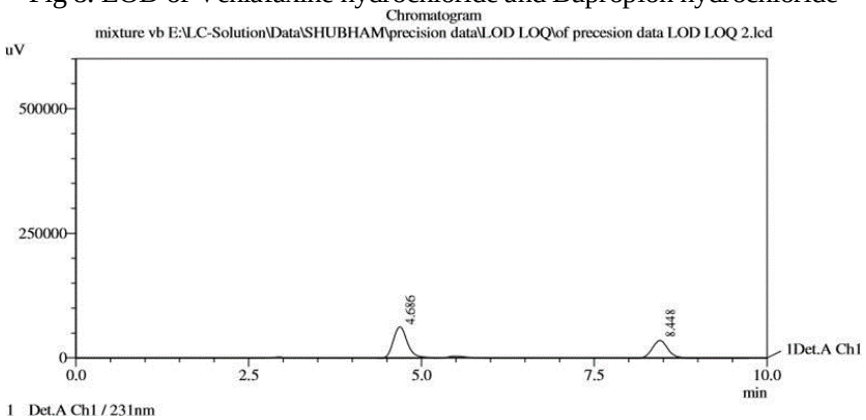

Fig 9. LOQ of Venlafaxine hydrochloride and Bupropion hydrochloride

Table 8: Data for LOD and LOQ of VENLA and BUPRO by RP-HPLC method

Drugs Name	Retention Time	LOD Concentration	LOQ Concentration
VENLA	4.6 Minute	0.3 µg/ml	1.1 µg/ml
BUPRO	8.4 Minute	0.5 µg/ml	µg/ml

Table 9: Robustness data of VENLA and BUPRO by RP- HPLC method

Robustness	VENLA	BUPRO
Change in the flow rate of mobile phase	99.95% to 100.1%	99.93% to 100.2%
Change in the wavelength of detection	99.96% to 100.01%	99.92% to 100.1%
Change in ratio of mobile phase	99.95% to 100.01%	99.95% to 100.01%

Table 10: Ruggedness data of VENLA and BUPRO by HPLC method

Drugs	Instrument-1 analyst-1	Instrument-1 analyst-2	Acceptance Criteria
VENLA	100.001 %	100.001 %	90%-110%
BUPRO	99.995 %	99.995 %	90%-110%

Table 11: Recovery study data for VENLA with marketed tablets by RP-HPLC

sLevel	Replica te	Std Conc. (µg/ml)	Sample Conc. (µg/ml)	Peak area	Total Conc found (µg/ml)	Amt of std. recovered (µg/ml)	% Recovery
80%	I	8	10	865198	18	8	100.0
	II	8	10	865192	17.99	7.99	99.87
	III	8	10	865210	18.01	8.01	100.13
100%	I	10	10	865214	19.99	9.99	99.9
	II	10	10	865217	20.0	10	100.0
	III	10	10	865226	20.01	10.01	100.1
120%	I	12	10	865246	22.0	12	100.0
	II	12	10	865254	22.02	12.02	100.17
	III	12	10	865298	22.04	12.04	100.33

Table 12: Recovery study data for BUPRO with marketed tablets by RP-HPLC

Level	Replica te	Std Conc. (µg/ml)	Sample Conc. (µg/ml)	Peak area	Total Conc found (µg/ml)	Amt of std. recovered (µg/ml)	% Recovery
80%	I	8	10	510058	17.99	7.99	99.87
	II	8	10	510065	18	8	100.0
	III	8	10	510098	18.01	8.01	100.3
100%	I	10	10	510191	20	10	100.0
	II	10	10	510256	20.02	10.02	100.2
	III	10	10	510238	20.01	10.01	100.1
120%	I	12	10	510297	22.01	12.01	100.08
	II	12	10	510294	22.0	12	100.0
	III	12	10	510312	22.02	12.02	100.16

Table 13: Report of recovery studies of VENLA and BUPRO by RP-HPLC

Levels	*Marketed Formulation*	
	Mean % Recovery of VENLA	Mean % Recovery of BUPRO
80 %	100.0	100.05
100 %	100.1	100.1
120 %	100.16	100.08
Acceptance criteria	90-110%	90-110%

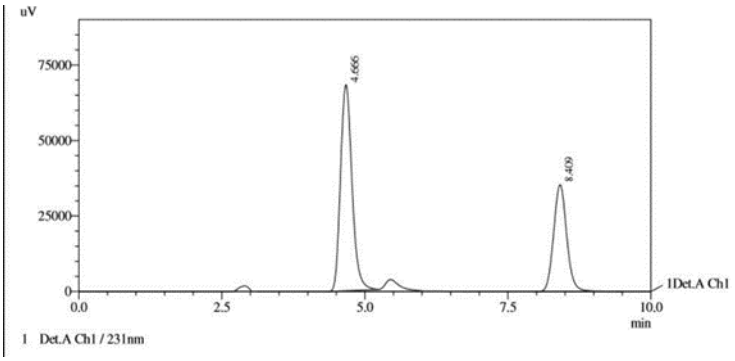

Fig 10. Application of Venlafaxine hydrochloride and Bupropion hydrochloride

Application of the RP-HPLC method for the simultaneous estimation of Venlafaxine hydrochloride and Bupropion hydrochloride in marketed formulation**(Figure 10).**

Table 13: Assay data of VENLA and BUPRO in marketed tablet by RP-HPLC method

Peak Area of VENLA	Peak Area of BUPRO	Conc. µg/ml		% Assay	
		VENLA	BUPRO	VENLA	BUPRO
347014	395416	20.02	20.01	100.1%	100.05%

RESULTS AND SUMMARY

Sr. No.	Parameters	Venla	Bupro	Acceptance Criteria
1	LINEARITY			
	Linearity Range	10-60µg/ml	10-60µg/ml	-
	Regression Equation	y = 40018x +25837	y = 24088x +9218.1	-
	Regression coefficient (r^2)	0.9992	0.9994	not less than 0.999
	Percentage fitting curve	99.92	99.94	should be more than 99.7 %
2	SPECIFICITY	Mobile phase used and excipients of tablets dosage forms not showed any peak at retention time of drugs.		No interference of placebo and blank in analysis and
3.	SYSTEM SUITABILITY			
	Theoretical plates	16847.59	44225.79	More than 2000
	Tailing factor	1.317	1.167	Less than 2
	Resolution	0.000	9.690	More than 2
4.	PRECISION			-
	System Precision	0.000536 %	0.007326 %	% RSD should be less than 2.0 %
	Method Precision	0.068 %	0.051 %	
	Intraday Precision	0.0393 %	0.0488 %	
	Interday Precision	0.104 %	0.0763 %	
5.	SENSITIVITY			
	LOD	0.3 µg/ml	1.1 µg/ml	-
	LOQ	0.5 µg/ml	1.6 µg/ml	-

6.	ROBUSTNESS			
	Change in Flow rate	99.95-100.1 %	99.93-100.2%	% Assay should be 90 – 110 %
	Change in Wave length	99.96-100.01%	99.92-100.1%	-
	Change in Mobile phase Ratio	99.95-100.01%	99.95-100.01%	-
7.	RUGGEDNESS			
	By Analyst-1 and Instrument-1	100.001%	99.995%	% Assay should be 90 – 110 %
	By Analyst-2 and Instrument-2	100.001%	99.995%	-
8.	ACCURACY			
	Accuracy with Marketed Tablet Formulation	100.0-100.16%	100.05-100.1%	Recovery range between 90-110%
9.	ASSAY			
	Marketed Formulation	100.1%	100.05%	% Assay should be 90 – 110 %

DISCUSSION

A RP-HPLC method was developed and validated for the simultaneous estimation of VENLA and BUPRO. The chromatography was carried out by using C-18 column (Zodiac 10µm, 250 mm X 4.6 mm) as stationary phase. An effective liquid chromatographic separation was achieved using mobile phase composed of Methanol and Phosphate buffer in the ratio 70:30 (pH 4.8) v/v. The flow rate of mobile phase was 1.0 ml/min. Estimation was performed at ambient temperature using UV detector and detection was performed at 231.The developed RP-HPLC method was then validated by using various parameters like linearity, specificity, system suitability, precision, LOD, LOQ, robustness, ruggedness and accuracy as per ICH guidelines.

CONCLUSION

On literature survey, it was found that analytical methods such as UV spectrophotometric, RP- HPLC, HPTLC, titrimetric methods have been developed and validated for the estimation of VENLA and BUPRO in bulk and tablet dosage form individually and combined with other drugs. However, no method has been developed for the simultaneous estimation of VENLA and BUPRO. Hence in present research work simultaneous estimation of VENLA and BUPRO have been developed and evaluated. So, in order to analyse these drugs in bulk as well as in marketed tablet formulations a new, simple, precise, robust, rapid and accurate RP-HPLC methods have been developed and validated. The developed RP-HPLC methods was suitable and valid for the simultaneous estimation of VENLA and BUPRO in pure and tablet dosage forms. The RP- HPLC method is more specific, sensitive, robust, and found to be precise than that of the UV Spectrophotometric as RP-HPLC method did not require the elaborate treatment and procedures compare to other method.

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