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Original Article

HPLC Method Development And Validation For The Estimation Of Lasmiditan Drug In Bulk And Tablet Dosage Form

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ABSTRACT

A simple, Précised, Accurate method was developed for the estimation of Lasmiditan by RP-HPLC technique. Chromatographic conditions used are stationary phase Agilent ECLPDS X DB 4.6mm x 250 mm, 5m ,Mobile phase Methanol : 0.1% Acetic acid in the ratio of 70:30 and flow rate was maintained at 1ml/min, detection wave length was 266nm, column temperature was set to 30^0C and diluent was mobile phase Conditions were finalized as optimized method. System suitability parameters were studied by injecting the standard six times and results were well under the acceptance criteria. The method demonstrated excellent linearity in concentration ranges of 5-25 (µg/ml) for Lasmiditan with correlation coefficients (R^2) 0.9999, confirming strong linearty.The regression equation obtained were Y= 137.9 X + 50.97 for Lasmiditan. The accuracy was studied through recovery studies and was found to be 99.41% to 100.74%.Method of precision showed %RSD value within acceptable limit (≤2%),ensuring reproducibility. LOD and LOQ are 0.006µg/ml and 0.0017µg/ml respectively. By using above method assay of marketed formulation was carried out 100.23% was present. Robustness studies further confirmed method reliability under small variations in method parameters.

Keywords: Lasmiditan, RP-HPLC, Method development, Validation.

INTRODUCTION

The common drug of choice for migraine include nonspecific analgesics, like NSAID and specific drug like triptains. Lasmiditans is the First and Only Medicine in New Class of Acute treatment for migraine[1] that received FDA approved Approval in 2019[2].The triptans have the risk of life threatening cardiovascular side effects because of their activation of 5-HT_{1B} receptor.[3,4] The high risk associated with triptans can be overcome by Lasmiditan with a newer oral 5-Hydroxy tryptamine receptor agonist with high affinity for 5-HT_{1F} and low affinity for 5 HT_{1B} receptors.[5,6]Lasmiditans and gepants that have no vasoconstrictive properties could theoretically be used for the treatment of acute migraine attacks in patients with TIA or stroke. The symptomatic relief from migraine with or without aura can be attained from Lasmiditan, sold under the brand name Migditan™.The drug is taken orally. Lasmiditan along with other nonspecific drug was found to be associated with significant pain reduction and mild adverse effects[7] the side effects caused by Lasmiditan can be over weighed due to its effectiveness in treating Acute Migraine[8].The main aim of present study is to estimation of Lasmiditan bulk drug by using simple and accurate RP-HPLC method.[9-16]

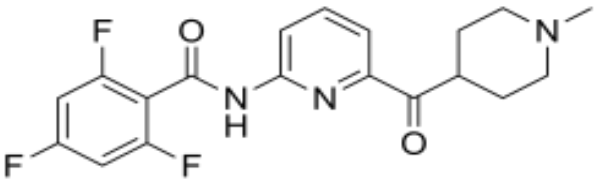

Figure No.1: Structure of Lasmiditan

Brand Name: Migditan™ 50

IUPAC Name: 2, 4, 6-Trifluoro-*N*-[6-[(1-methyl-4-piperidinyl)carbonyl]-2-pyridinyl]benzamide

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Chemical Formula: $C_{19}H_{18}F_3N_3O_2$

Molecular Weight: 377.367 $g \cdot mol^{-1}$

Method development for Lasmiditan refers to the scientific process of creating a standardized analytical technique, typically using a High Performance Liquid Chromatography (HPLC),to accurately measure the concentration of Lasmiditan in pharmaceutical sample like a tablets or solution, by optimizing parameters like mobile phase composition, column selection, detection of wavelength to ensure the reliable and precise quantification of the drug within a given formulation. Validation of Lasmiditan refers to the process of developing and testing of method to measure and quantify Lasmiditan.

Materials and Methods:

Lasmiditan (API), Lasmiditan tablets (Migditan™ 50), Methanol, 0.1% Acetic acid, Distilled water. All of solvents and chemicals were of HPLC quality grade.

Instrumentation:

The analysis of the drug was carried out on Agilent Gradient System with auto injector DAD Detector, Software chemstation, Analytical weighing Balance, Ultrasonicator.

Chromatographic Condition:

An Isocratic Elution carried out by using **Methanol: 0.1% Acetic acid (70:30) v/v** as the mobile phase. Equipped with Reverse Phase (Agilent) C_{18} column (4.6mm x 100mm; 2.5µm) and UV730D Absorbance detector and running chemstation. Column was used to determine the method at a flow rate 1ml/min by maintain the column temperature 30^0C.In addition, with an injection volume 20µL and the wavelength detected by 266nm.

API Formulation :(STOCK I)

Preparation of standard stock solution and working solution:

Accurately weighed 5 mg of Lasmiditan and transferred to 10mL volumetric flask.3/4 th of diluents **Methanol: 0.1% Acetic acid (7:3)** was added to the flask and sonicated for 15 minutes. Flasks were made up of with methanol mark upto 10mL volumetric flask and label them as a Standard stock solution of Lasmiditan (500 µg/ml of Lasmiditan).Moreover from this 0.1 ml from stock solution was pipette out, taken into 10mL volumetric flask and ,made up with Mobile Phase to make 5 µg/ml of Lasmiditan.

Sample Formulation: (STOCK II)

Preparation of Sample stock solution and working solution:

20 tablets were weighed and average weight of each tablet was calculated, then the weight equivalent to 5 tablets transferred into 10 mL volumetric flask. Add 10 ml of methanol and sonicate to dissolve completely upto the mark with diluents.futher the volume was made up with diluent and filter by HPLC filter to make 1000 µg/ml of Lasmiditan solution. From this 0.2 ml of filtered sample stock solution was transferred to 10 ml volumetric flask and made up with mobile phase to make 10 µg/ml of Lasmiditan.

Method Validation:

The established technique is validated in accordance with ICH criteria for the purpose of validation analytical methods. The validation matrics were: Linearity, Accuracy, Precision, limit of detection (LOD), limit of quantification (LOQ), Repeatability and robustness.

Linearity:

Linearity was conducted by preparing different standard solutions of Lasmiditan at different concentration levels. The standard solutions were prepared in the concentration range of 5-25µg/ml of Lasmiditan. Each concentration was injected into the HPLC system and record the areas obtained. Plot a graph between area taken on Y-axis and concentration on X-axis. Diluents were preparation as:

- Take 0.1 from stock I and make vol. with mobile phase 10 ML = 5 µg/ml Lasmiditan
- Take 0.2 from stock I and make vol. with mobile phase 10 ML = 10 µg/ml Lasmiditan
- Take 0.3 from stock I and make vol. with mobile phase 10 ML = 15 µg/ml Lasmiditan

- Take 0.4 from stock I and make vol. with mobile phase 10 ML=20 µg/ml Lasmiditan
- Take 0.5 from stock I and make vol. with mobile phase 10 ML =25 µg/ml Lasmiditan

Accuracy:

Recovery studies were performed to calculate the accuracy of developed method to preanalysed sample solution, a definite concentration of standard drug (80%, 100%, and 120%) was added and then its recovery was analyzed.

Precision:

In this method precision was evaluated as system precision, method precision and intermediate precision. In system precision six replicate standard solutions of Lasmiditan were analyzed and %RSD was calculated. In method precision six preparations with sample were injected and %RSD, % recovery was calculated. The intraday and inter-day precision study was conducted for Lasmiditan.

Repeatability:

The repeatability was performed for six replicate at six concentrations in linearity Conc.20 µg/ml, precision under the same operating condition over short interval time. Repeatability studies Etoricoxib was found to be, the %RSD was less than 2, which shows high percentage amount found in between 99% to 100% indicates the analytical method that concluded.

LOD and LOQ:

LOD was measured by diluting the standard solution of Lasmiditan and determining the concentration was response of sample peaks are three times the noise peak. LOQ was measured by diluting the standard solution of Lasmiditan and determining the concentration was response of sample peaks are ten times the noise peak.

$$DL = \frac{3.3\sigma}{S}$$

$$QL = \frac{10\sigma}{S}$$

Where,

σ = the S.D. of the y-intercepts of regression lines.

S = the slope of the calibration curve.

The slope S may be estimated from the calibration curve and S.D. was used should be calculated from the y-intercepts of regression line in calibration curve.

Robustness:

Small deliberate change in method like Flow rate, Mobile phase ratio and temperature are made but there were no recognized change in the result and are within range as per ICH guidelines.

Assay:

Assay and % purity were calculated for brand Migditan™ 50 with label claim 50 gm observed value compared with that of standard value without interference from excipient used in tablet dosage form.

RESULT DISCUSSION:

Method development and Optimization

Parameter	Condition
Mobile phase	Methanol : (0.1%)Acetic acid (70: 30% V/V)
Flow rate	1ml/min
Analytical column	Agilent C_{18} Column 100mm x 4.6mm,
Detection of wavelength	266nm

Column Temperature	30^0C
Injection volume	20µl
Run Time	7min

Table No.1: Optimized condition

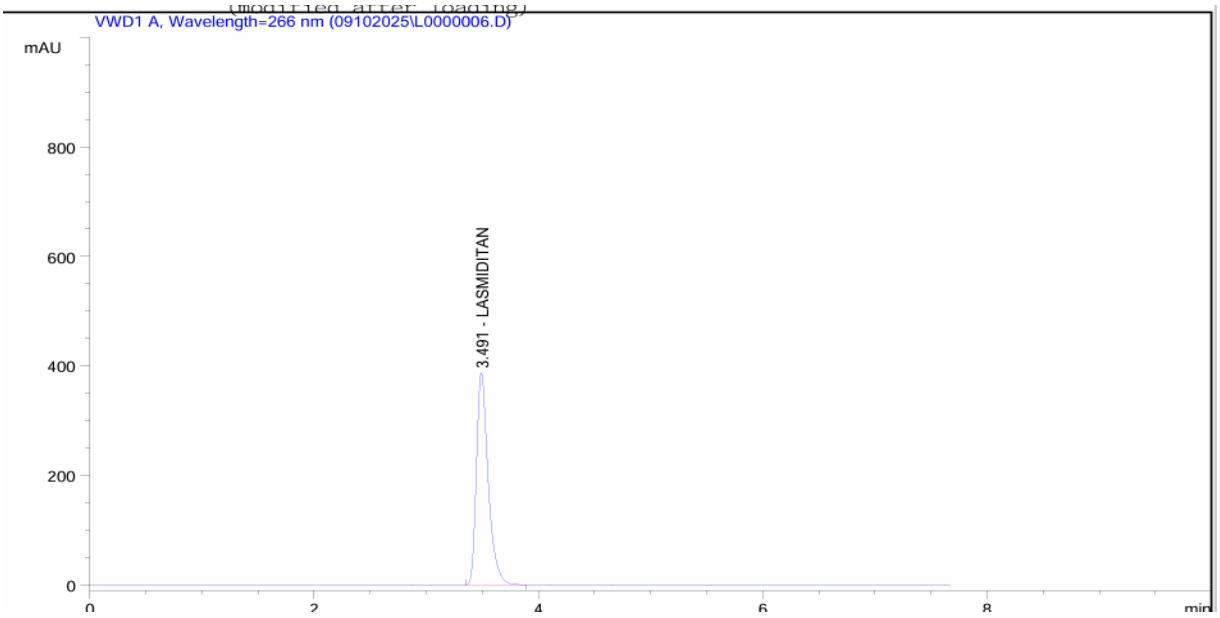

Figure No.2: Method development and optimization graph of Lasmiditan

Method Validation

Linearity-

Five concentration ranging 2-25 (µg/ml) were prepared and linearity were estimated in duplicate manner. The linearity equation for Lasmiditan was **Y= 137.95 X + 50.846**. For calibration curve over concentration range, and data has shown good correlation.

S. No	Lasmiditan	
	Concentration(µg/ml)	**Area**
Linearity-1	5	749.59
Linearity-2	10	1412.37
Linearity-3	15	2129.25
Linearity-4	20	2809.25
Linearity-5	25	3999.98
Slope	137.9	
Intercept	50.97	
C.C	0.999	

Table No.2: Linearity Data

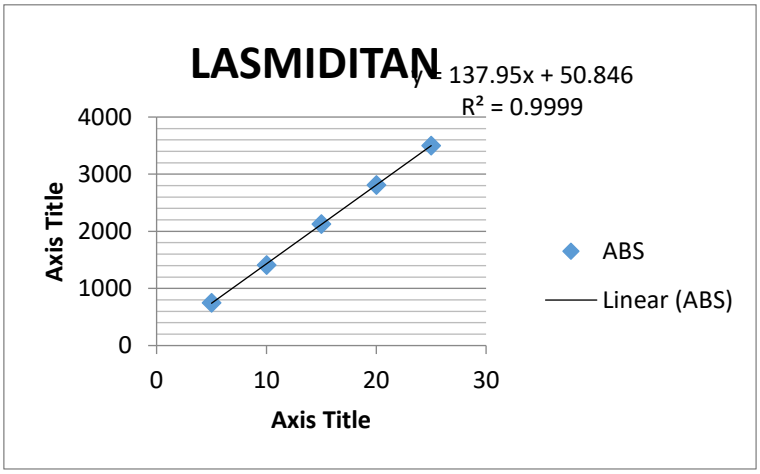

Figure No.3: Calibration Curve of Lasmiditan

Accuracy

Accuracy was determined by recovery studies which were carried out in three different concentration levels (80%, 100% and 120%). APIs with concentration 25, 50 and 75µg/ml of Lasmiditan were prepared. The percentage recovery values were found to be in the range of 98-102%.

Level of Recovery (%)	Amount spiked((µg/ml)	Amount recovered Mean (µg/ml)	% Recovery	SD	% RSD
80%	8	7.95	99.37	0.06	0.06
100%	10	10.07	100.76	0.02	0.02
120%	12	11.88	99.00	0.04	0.04

Table No.3: Accuracy data

***mean of each 3 reading.**

Precision

Precision of the method was established by injecting test preparation and tested through the complete analytical procedure from sample preparation to the final result.

Drug	Conc (µg/ml)	Intraday Precision			Interday Precision		
		Mean± SD	**%Amt Found**	**% RSD**	**Mean± SD**	**%Amt Found**	**% RSD**
LSD	10	1410.19±0.01	98.57	0.00	1241.65±0.45	86.34	0.04
	15	2154.80±0.03	101.71	0.00	3641.12±0.28	173.56	0.01

	20	2776.88±1.24	98.84	0.04	5934.25±0.57	213.32	0.01

Table No.4: Precision data

***Mean of each 3 reading**

Repeatability:

Six replicates of a sample solution was anlaysed on a different day, different analyst and different RSD values.

Analyte	Std. Concentration	Mean	%RSD
Lasmiditan	20	2797.42	0.02

Table No.5: Repeatability data

Robustness:

In robustness there is a small deviation in Wavelength and Mobile Phase (±10%) in their chromatographic condition and observed that there is no significant change in %RSD.

Parameters	Level	Conc. (µg/ml)	Area of detected (mean ±SD)	%RSD
Change in Mobile-phase composition	69:31	20	2746.2±5.69	0.21
	71:29	20	2732.81±1.47	0.05
Wavelength change	265nm	20	2723.7±2.76	0.10
	267nm	20	2824.3±23.19	0.82

Table No.6: Robustness data

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

The LOD concentrations of Lasmiditan were 0.006µg/ml and LOQ concentrations of Lasmiditan was 0.017µg/ml. Result of LOD and LOQ showed in table no 7.

Name	LOD(µg/ml)	LOQ(µg/ml)
Lasmiditan	0.006	0.017

Table No.7: LOD & LOQ data

Assay of Tablets:

The results of the analysis of synthetic mixture were reported. The assay value of drugs was close to 100, SD and % RSD are less than 2 indicate the no interference of excipient in the estimation of drug. Result of Assay of tablet showed in table no 8.

	LSD*
Label claim (mg)	50 mg
% found	100
% Assay	100.23
% RSD	0.059

Table No.8: % Assay purity data

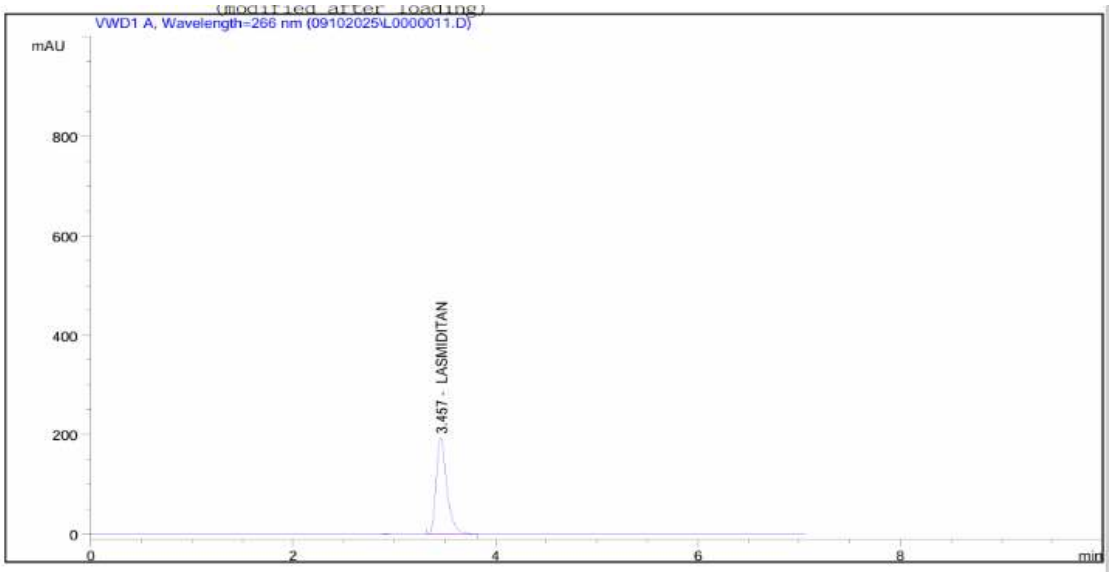

Figure No.4: Assay of Tablet (Migditan™ 50)

CONCLUSION

The proposed methods were found to be linear in the range of 5-25µg/ml with correlation coefficient close to one. Precision was determined by repeatability, Intermediate precision and reproducibility of the drugs. The robustness of developed method was checked by changing in the deliberate variation in solvent. The result obtained shows the developed methods to be Cost effective, Rapid (Short retention time), Simple, Accurate (the value of SD and %RSD less than 2), Precise and can be successfully employed in the routine. The Simplicity, Rapidly and Reproducibility of the proposed method completely fulfill the objective of this research work.

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