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DEVELOPMENT OF NOVEL UV SPECTROPHOTOMETRIC METHODS FOR THE ESTIMATION OF TASIMELTEON

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ABSTRACT

A simple, accurate, precise, rapid analytical methods for the estimation of Tasimelteon in bulk. The λmax of tasimelteon in acetonitrile and Double distill water (50:50) was found to be 225.0 nm. All five methods of UV-Spectrophotometry based upon Zero Order, First Order and Second Order derivative have been established considering amplitude and Area under curve of the spectrum. In all five method, Tasimelteon obeyed linearity in the concentration range of 4-20 µg/mL with correlation coefficient 0.999. All the methods were validated as per International conference on Harmonization (ICH) guidelines. All these proposed methods were proved to be linear, accurate, precise and rugged and also adequately sensitive.

KEYWORDS: Tasimelteon, Acetonitrile, UV-Visible spectroscopy.

1. INTRODUCTION

UV-Visible spectrophotometry is one of the most frequently employed techniques in pharmaceutical analysis. It involves measuring the amount of ultraviolet (190nm-380nm) or visible (380nm-800nm) radiation absorbed by a substance in solution. Absorption of light in both ultraviolet and visible region of the electromagnetic spectrum occurs when the energy of light matches that required to induce in the molecule an electronic, vibrational and rotational transition. Instrument which measure the ratio, or function of ratio, of the intensity of two beams of light in the UV-Visible region. In qualitative analysis, organic compounds are identified by use of spectrophotometer. If any recorded data is available, quantitative spectrophotometric analysis is used to as certain the identify of molecular species by its maximum absorbance (λmax) of the radiation. Spectrosphotometric technique is simple, rapid, moderately specific, and applicable to small quantites of compounds. The assay of an

absorbing substance may be quickly carried out by preparing a solution in a solvent and measuring its absorbance at a suitable wavelength.

Tasimelteon is chemically (1*R*,2*R*) -*N*- [2- (2,3-dihydrobenzofuran-4-yl)- cyclopropyl methyl] propanamide. Its molecular formula is C15H19NO2 and its molecular weight is 245.32. Tasimelteon is a selective dual melatonin receptor agonist indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (N24HSWD). Occurring commonly in blind individuals without light perception, this condition is often characterized by periods of night-time insomnia and day-time sleepiness. In blind individuals, a lack of light stimulation causes an extension of the 24-hour circadian cycle and can lead to progressively delayed sleep onset. By activating melatonin receptors MT1 and MT2 in the suprachiasmatic nucleus of the brain, tasimelteon has been shown to improve sleep by resynchronizing the circadian rhythm through its "non-photic" mechanism. Tasimelteon is currently the only drug available for the treatment of N24HSWD.

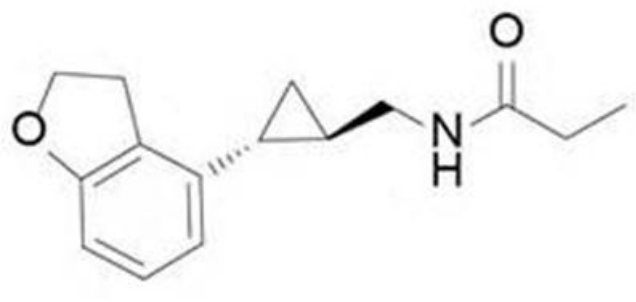

Figure 1: Chemical structure of tasimelteon.

There are several drugs and pharmaceutical formulation are introduced recently in pharma field all over the world. Literature survey was performed for all the recently launched drugs in the market. It has been found that researcher have documented analytical method development as well as stability indicating parameters for the most of the drug, however API & Dosage formulation of Tasimelteon has not been evaluated for above mentioned studies.

Hongkun Liang have been reported simultaneous determination of tasimelteon, M9, M11, M12, M13 and M14 in Human plasma by UPLC-MS/MS and its application.

2. MATERIALS AND METHODS

Tasimelteon standard was provided by Watson pharma-Ambernath East, Thane (India), All chemicals used were HPLC grade.

3. Instrument

UV-Visible Spectrophotometer

The wavelength of Tasimelteon was found to be 225.0 nm by using UV-Visible Spectrophotometer Jasco V-630 and Shimadzu-UV-1700.

4. RESULTS AND DISCUSSION

4.1 Preparation of standard stock solution

An accurately weighed (10mg) quantity of Tasimelteon (TASI) was transferred in a 100.0 mL volumetric flask, dissolved in Acetonitrile: Double distilled water (50:50) to prepare a standard stock solution having concentration 100 µg/mL of TASI.

4.2 Working standard solution

A 1.0 mL of above standard solution was diluted up to 10 mL with Acetonitrile: Double distilled water (50:50). (Concentration: 10 µg/mL of TASI).

4.3 Selection of wavelength

The working standard solution of TASI (10 µg/mL) was scanned in the range of 400-200 nm in 1.0 cm cell against solvent blank (ACN: DD Water) and spectrum was recorded. The spectrum so recorded is shown in Fig.No.1.

The study of spectra shows peak maxima for TASI at 225 nm.

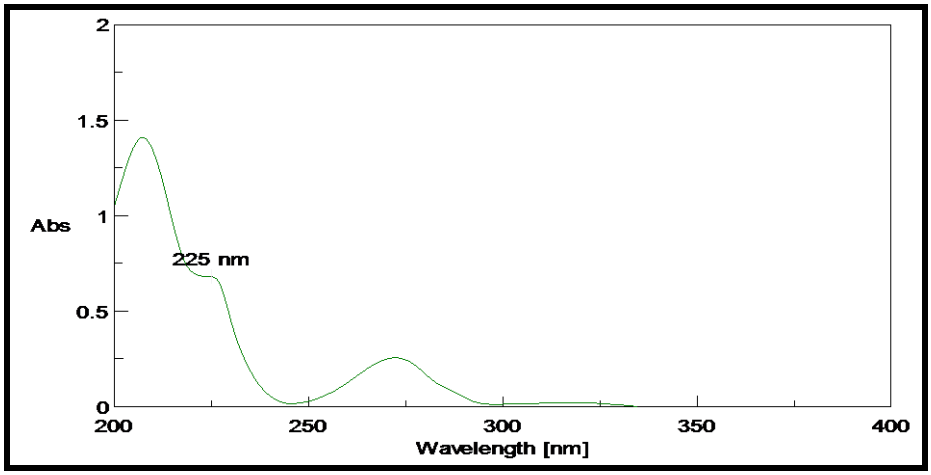

Fig. No. 1: Zero order spectra of TASI.

4.4 Study of Beer-Lamberts Law

Aliquots of standard stock solution were diluted with ACN:DD Water (50:50) to get a concentration of standard drug in the sequential series of 4, 8, 10, 12, 16, 20 µg/mL.

Absorbance of each solution was measured at λmax i.e., 225 nm. Result are shown in table No.1 while Calibration curve was plotted as absorbance Vs concentration and shown in Fig.No.2.

Table No 1: Observation for study of Beer-Lambert Law of TASI.

Sr. No	Concentration (µg/mL)	Absorbance
1	4	0.2420
2	8	0.4823
3	10	0.6006
4	12	0.7202
5	16	0.9612
6	20	1.2143
Coefficient of correlation		**0.9991**

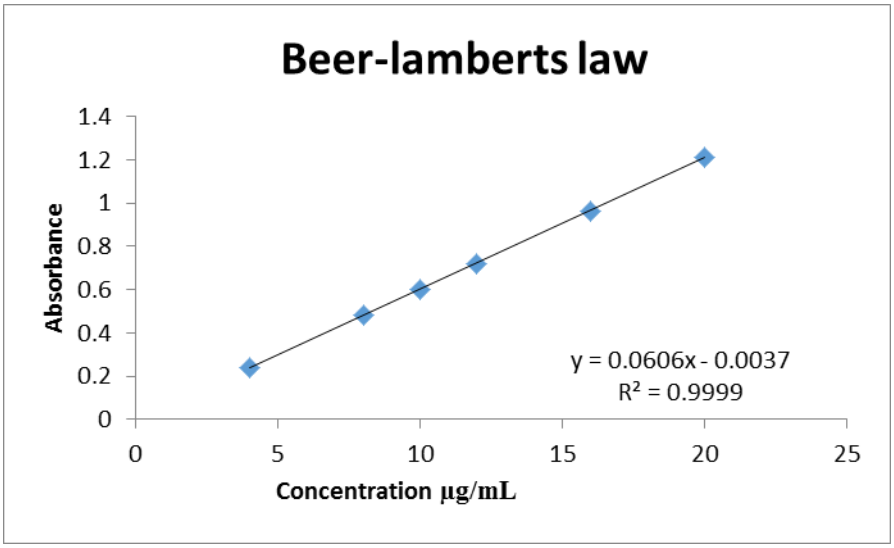

Fig. No. 2: Calibration curve of TASI.

4.5 Method Development

4.5.1. Method 1: Standard absorptivity value [A (1%, 1cm)]

Standard solution used for Beer-Lamberts law study and absorbance of TASI were used to calculate A (1%, 1cm) value, using formula as given below. The results are shown in table No.2.

$$A\ (1\%, 1cm) = \frac{Absorbance}{Concentration\ (\frac{g}{100}mL)}$$

Table No. 2: Absorptivity Value A (1%, 1cm).

Sr. No	Concentration (g/100mL)	Absorbance	A (1%, 1 cm)
1	0.004	0.2420	605.00
2	0.008	0.4823	602.87
3	0.01	0.6006	600.60
4	0.012	0.7202	600.16
5	0.016	0.9612	600.75
6	0.020	1.2143	607.15
MEAN			**602.75**

4.5.2. Method 2: First order derivative method

The working standard solution of TASI (10 µg/mL) was scanned in the range of 200-400 nm and first order derivative spectra was recorded shown in Fig.No.3 from the spectra 235 nm was selected for further study.

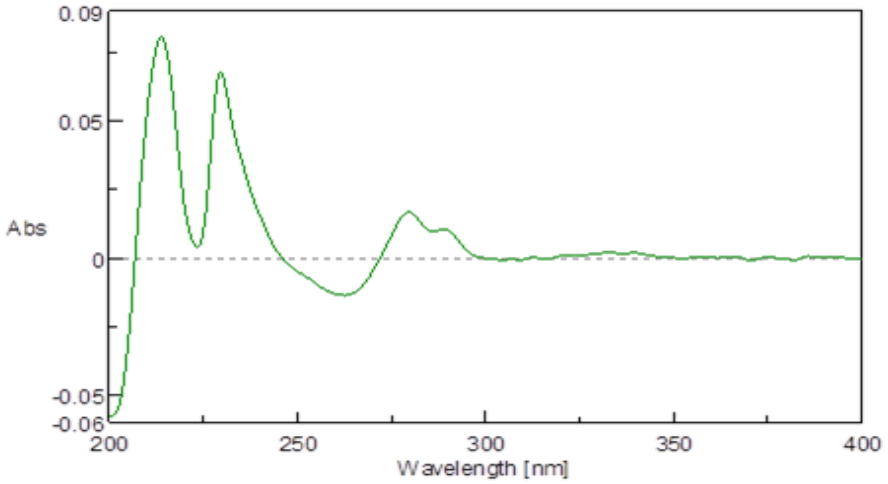

Fig. no. 3: First Order Derivative Spectra of TASI.

The results are shown in Table No.3 and calibration curve plotted as absorbance Vs concentration which is shown in Fig 4.

Table No. 3: Observation of TASI for Method 2.

Sr. No	Concentration (µg/mL)	Absorbance First order derivative method
1	4	0.014808
2	8	0.02741
3	10	0.033703
4	12	0.039649
5	16	0.052684
6	20	0.066082
Coefficient of Correlation		**0.9997**

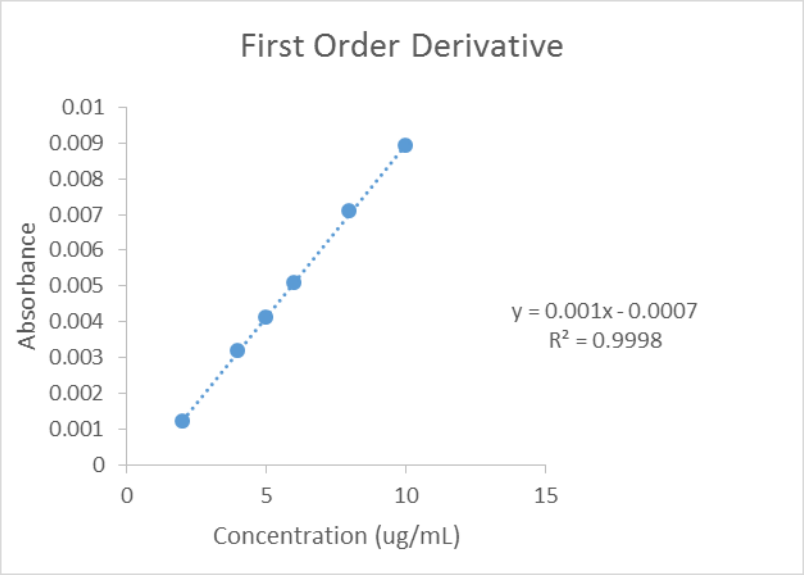

Fig. No. 4: Calibration curve for Method 2.

4.5.3. Method 3: Second order derivative method

The working standard solution of TASI (10 µg/mL) was scanned in range of 200-400 nm and second order derivative spectra was recorded shown in Fig.No.5. From the spectra 218 nm was selected for further study.

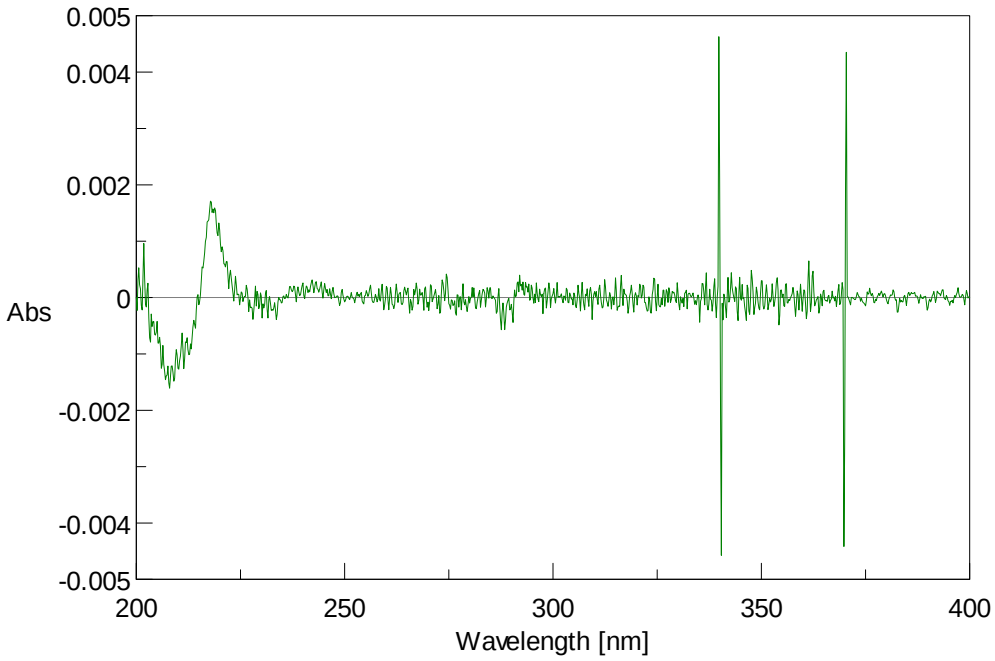

Fig. No. 5: Second Order Derivative Spectra of TASI.

The results are shown in the Table No.4 and calibration curve plotted as absorbance Vs concentration which is shown in Fig.No.6.

Table No. 4: Observation of TASI Method 3.

Sr.No.	Concentration (µg/mL)	Absorbance Second order derivative method
1	4	0.000629
2	8	0.002107
3	10	0.002893
4	12	0.003601
5	16	0.005231
6	20	0.006909
Coefficient of Correlation		**0.9991**

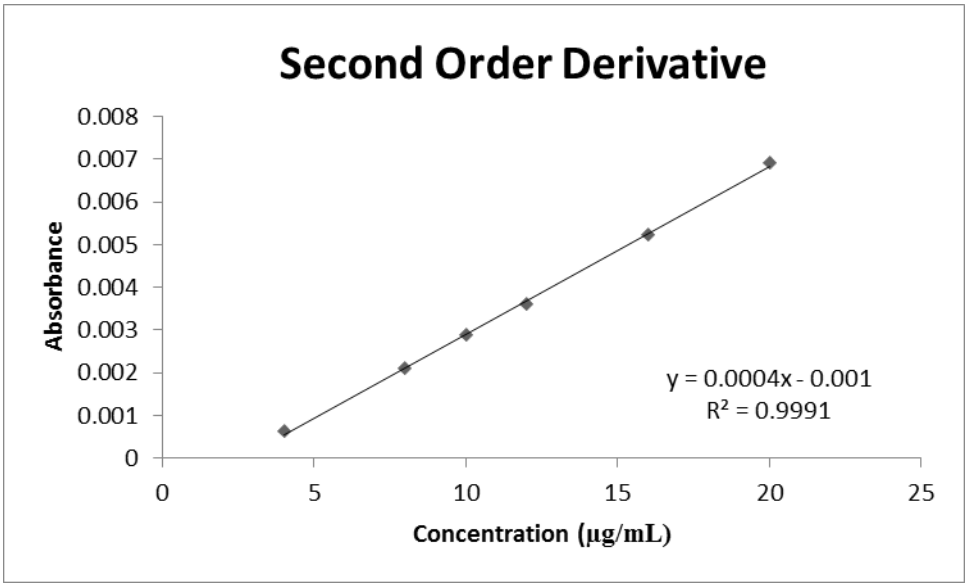

Fig. No. 6: Calibration curve for Method-3.

4.5.4. Method 4: Area under curve method

For the method wavelength selected was 277 nm (λ_1) and 267 nm (λ_2). The area under curve for solution concentration range 4-20 µg/mL of TASI was noted in the range 277 nm (λ_1) and 267 nm (λ_2). The AUC (Area under curve) involves the calculation of integrated valve of absorbance with respect to the wavelength λ_1 and λ_2. Area calculation processing item calculation the area bound by the curve the horizontal axis. The horizontal axis was selected by entering the wavelength range over which the area was selected by entering the wavelength range over which the area has to be calculated. The results are shown in Table No.5. The spectra displaying AUC was shown in Fig.No.7. Calibration curve plotted as area under curve against concentration and shown in Fig.No.8.

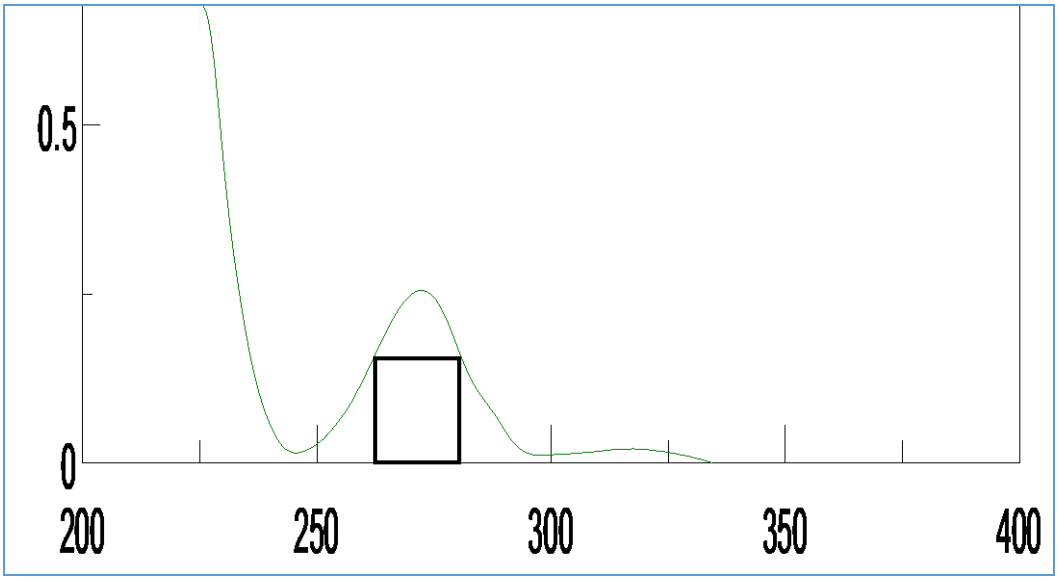

Fig. No. 7: Spectrum of TASI for area under curve.

Table No. 5: observation for method 4.

Sr.No	Concentration (µg/mL)	Area Under Curve (mV)
1	4	16.9
2	8	36.32
3	10	40.02
4	12	46.83
5	16	59.69
6	20	73.94
Coefficient of correlation		**0.9985**

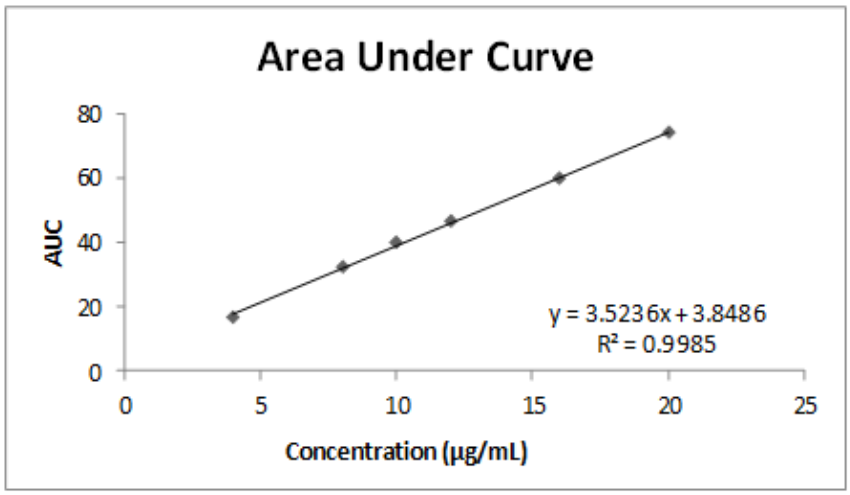

Fig. No. 8: Calibration curve for method 4.

4.6 VALIDATION

Validation of proposed method was carried out as per ICH guideline.

4.6.1. Linearity and Range

An accurately weighed (10mg) quantity of Tasimelteon was transferred in a 100.0 mL volumetric flask, dissolved in Acetonitrile:Double distilled water (50:50) to prepare a standard stock solution having concentration 100 µg/mL of TASI. A 1.0 mL of above standard solution was diluted up to 10 mL with Acetonitrile:Double distilled water (50:50). (Concentration: 10 µg/mL of TASI). The absorbance of each resulting solution was measured at 225.0 nm, 235.0 nm, 218.0 nm and 277.0-267.0 nm in 1.0 cm cell using solvent blank. The absorbance for linearity study are shown in Table No.6.

Table No. 6: Observation for linearity and range study.

Sr. No	Concentration (µg/mL)	Absorbance			
		225.0 nm	224.0 nm	226.0 nm	277.0-267.0 nm
1	10	0.6001	0.0231	0.0201	8.4778
2		0.6001	0.0237	0.0200	8.4627
3		0.6023	0.0230	0.0203	8.4523
Mean		**0.6008**	**0.0232**	**0.0201**	**8.4642**
±S.D.		**0.0012**	**0.0004**	**0.0001**	**0.0128**
%RSD		**0.21**	**1.74**	**0.75**	**0.15**

4.6.2. Ruggedness

The Tasimelteon was analyzed by proposed methods by two different analysts. Results are shown in Table.No.7 and 8.

Table No.7: Observation of Different Analyst Study.

Sr. No	Analyst	Concentration (µg/mL)	Absorbance			
			M-I	M-II	M-III	M-IV
1	Analyst 1	10	0.6033	0.03375	0.0028	38.22
2			0.6021	0.0334	0.0028	38.34
3			0.6012	0.0331	0.0028	38.75
Mean			**0.6022**	**0.0336**	**0.0027**	**38.43**
±S.D.			**0.0010**	**0.0001**	**3.49**	**0.277**
%RSD			**0.17**	**0.48**	**1.22**	**0.72**

Table No. 8: Observation of Different Analyst Study.

Sr. No	Analyst	Concentration (µg/mL)	Absorbance			
			M-I	M-II	M-III	M-IV
1	Analyst 2	10	0.6016	0.0337	0.0028	40.02
2			0.6004	0.0337	0.0028	40.12
3			0.6002	0.0331	0.0027	40.16
Mean			**0.6007**	**0.0335**	**0.028**	**40.10**
±S.D.			**0.0007**	**0.0003**	**1.18**	**0.07**
%RSD			**0.12**	**1.00**	**0.41**	**0.17**

4.6.3. Different Instrument

The Tasi was estimated by two different instrument. Results are shown in Table No.9 and 10.

Table No. 9: Observation of Different Instrument study.

Sr. No	Instrument	Concentration (µg/mL)	Absorbance			
			M-I	M-II	M-III	M-IV
1	Jasco V-630	10	0.6002	0.0332	0.0027	35.12
2			0.6023	0.0334	0.0027	35.45
3			0.6012	0.0316	0.0028	35.22
Mean			**0.6012**	**0.0332**	**0.0027**	**35.26**
±S.D.			**0.0010**	**9.87**	**3.51**	**0.16**
%RSD			**0.17**	**0.29**	**0.12**	**0.47**

Table No. 10: Observation of Different Instrument study.

Sr. No	Instrument	Concentration (µg/mL)	Absorbance			
			M-I	M-II	M-III	M-IV
1	Shimadzu-1600	10	0.6013	0.0334	0.0027	38.34
2			0.6023	0.0334	0.0026	38.33
3			0.6023	0.0334	0.0026	38.34
Mean			**0.6019**	**0.0334**	**0.0027**	**38.33**
±S.D.			**0.0005**	**1.80**	**6.80**	**0.005**
%RSD			**0.09**	**0.05**	**0.25**	**0.001**

4.6.4. Robustness

Deliberate changes made on the optimized UV-Spectrometric parameter. The Tasimelteon was analyzed by proposed methods by changing in the solvent concentration.

1. In acetonitrile
2. In acetonitrile and water (60:40)
3. In acetonitrile and water (40:60)

Results are shown in Table No.11, 12 and 13.

Table No. 11: Observation of TASI in Acetonitrile.

Sr. No	Concentration (µg/mL)	Absorbance			
		M-I	M-II	M-III	M-IV
1	10	0.8962	0.0041	0.0029	18.63
2		0.8966	0.0041	0.0029	18.66
3		0.8952	0.0041	0.0029	18.67
Mean		**0.8960**	**0.0041**	**0.0029**	**18.65**
±S.D.		**0.007**	**4.16**	**1.52**	**0.02**
%RSD		**0.08**	**1.00**	**0.52**	**0.11**

Table No. 12: Observation of TASI in Acetonitrile and water (60:40).

Sr. No	Concentration (µg/mL)	Absorbance			
		M-I	M-II	M-III	M-IV
1	10	0.8817	0.0044	0.0034	22.14
2		0.8856	0.0044	0.0034	22.36
3		0.8865	0.0044	0.0034	22.36
Mean		**0.8846**	**0.0044**	**0.0034**	**22.28**
±S.D.		**0.002**	**5.77**	**2.36**	**0.12**
%RSD		**0.28**	**0.13**	**0.68**	**0.56**

Table No. 13: Observation of TASI in Acetonitrile and water (40:60).

Sr. No	Concentration (µg/mL)	Absorbance			
		M-I	M-II	M-III	M-IV
1	10	0.5567	0.0333	0.0029	25.30
2		0.5518	0.0337	0.0029	25.15
3		0.5534	0.0332	0.0029	25.45
Mean		**0.5539**	**0.0334**	**0.0029**	**25.30**
±S.D.		**0.0024**	**0.0002**	**3.91**	**0.15**
%RSD		**0.45**	**0.81**	**1.32**	**0.59**

4.6.5. Interday and Intraday variation

An accurately measured quantity of Tasimelteon to about 10.0 mg transferred to 100.0 mL of volumetric flask, sufficient quantity of Acetonitrile:double distilled water (50:50) added, sonicated for 15 min. Add diluted up to the mark. The content in the flask were filtered through whatman filter paper. Form these filtrate 1.0 mL of the filtrate was diluted to 10 mL in volumetric flask to give 10 µg/mL of solution. The absorbance and AUC of the final solution was recorded after 0^{th} Hr, 3^{rd} Hr and 5^{th}Hr in 1.0 cm cell at selected wavelength (Table No.6.1.9a). similarly the absorbance of the same solution were measured on the 1^{st}, 3^{rd}, 5^{th} day and the standard deviation and percent relative standard deviation were calculated. The results are shown in Table No.14 and 15.

Table No. 14: Observation for Intraday study.

Sr.No	Intraday	Concentration (µg/mL)	Absorbance			
			M-I	M-II	M-III	M-IV
1	1^{st}Hr	10	0.6021	0.0334	0.00267	38.34
2	2^{nd}Hr		0.6023	0.0331	0.00265	38.23
3	3^{rd}Hr		0.6001	0.0328	0.00262	38.12
Mean			**0.6010**	**0.0331**	**0.00265**	**38.23**
±SD			**0.0012**	**0.0002**	**2.7682**	**0.11**
%RSD			**0.2022**	**0.8490**	**1.0431**	**0.2877**

Table No. 15: Observation of Interday study.

Sr. No	Day Interval	Concentration (µg/mL)	Absorbance			
			M-I	M-II	M-III	M-IV
1	1st day	10	0.6021	0.0334	0.00267	38.34
2	2nd day		0.6123	0.0341	0.00263	39.02
3	3rd day		0.6073	0.0342	0.00261	38.89
Mean			**0.6072**	**0.0339**	**0.00264**	**38.75**
±SD			**0.0051**	**0.0004**	**3.1069**	**0.3609**
%RSD			**0.8399**	**1.2339**	**1.1754**	**0.9315**

5. CONCLUSION

In the present research work attempts were made to develop simple, accurate, precise, rapid analytical methods for the estimation of Taimelteon in bulk.

The results obtained by UV method for estimation of Tasimelteon are reliable, accurate and precise. Hence, developed methods can be employed for routine quality control analysis of Tasimelteon in Bulk and in tablet, after further studies.

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