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DEVELOPMENT OF UV- SPECTROPHOTOMETRY METHODS FOR ESTIMATION OF AGOMELATINE IN BULK AND IN TABLET FORMULATION

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ABSTRACT

Four Simple, precise and economical UV-Spectrophotometric method has been established for the quantification of Agomelatine in bulk and Tablet Formulation. Method A is Zero order UV-Spectrophotometry using absorbance, Method B is zero order UV-Spectrophotometry using AUC, Method C is First order derivative UV-Spectrophotometry using amplitude and Method D is First order derivative UV-Spectrophotometry using AUC, The proposed methods were successfully applied for the determination of Agomelatine in bulk and tablet formulation. In methanol Agomelatine showed maximum absorbance at 276 nm. In Method A, absorbance was recorded at 276 nm while in Method B, AUC was selected in the wavelength range of 271.4 - 279.8 nm, In Method C, the amplitude was recorded at 279 nm while in Method D, AUC of the derivatized spectrum was studied at 276.2 – 282.6 nm. In all the Methods, Agomelatine followed linearity in the concentration range of 5 - 30 µg/mL with (R^2> 0.999). All these developed methods were applied for estimation of Agomelatine in tablet formulation. All these methods were validated for linearity and range, accuracy, precision, ruggedness and sensitivity.

KEYWORDS: Agomelatine, UV Spectrophotometry, Zero Order, AUC, First Order Derivative.

INTRODUCTION

Agomelatine is a white or almost off-whit to yellow coloured powder. Chemically it is N-[2-(7-methoxynaphthalen-1-yl) ethyl] acetamide, Soluble in methanol, practically insoluble in water with having molecular formula $C_{15}H_{17}NO_2$, (Figure 1) and having molecular weight is 243.301 g/mol.[1,2] Agomelatine has main pharmacology and pharmacokinetic property with high selective action at melatonin receptors (MT1 and MT2 receptors) and antagonist at serotonin- 2C (5-HT2C) receptors, binding studies indicate that it has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic, and benzodiazepine receptors.[3,4,5] The Spectrophotometry is the quantitative measurement of the reflection or transmission properties of a material as a function of wavelength. UV-Spectrophotometry methods gained a significant place in pharmacopoeia.[6] The prominent advantages of these methods include low time consumption and least calculations. The precision of these methods is also excellent. The use of UV Spectrophotometry especially applied in the analysis of pharmaceutical dosage form has increased rapidly over the last few years.[7,8] Derivative spectroscopy uses first or upper derivatives of absorbance with respect to wavelength for qualitative examinations and estimations. The use of derivative spectrometry is not limited to special cases, but may be of advantage whenever quantitative study of normal spectra is challenging. Few disadvantages are also associated with derivative methods; the major is the differential degrades the signal-to-noise ratio, so that some form of smoothing is required in conjunction with differentiation.[9,10] The Area under curve (AUC) technique involves integration of value of AUC with respect to the two selected wavelengths λ1 and λ2. Selection of wavelength range is on the basis of repeated observations so as to get the linearity between AUC and concentration.[11] Literature survey reveals that few UV-Spectrophotometric methodwere available for the estimation of Agomelatine in bulk and tablet dosage form. The current study it is designed to develop a new, simple, accurate, less time consuming method of analysis for the estimation of Agomelatine in bulk and tablet formulation form by UV-Spectrophotometry (Zero order, First order, AUC).

MATERIAL AND METHODS

Instruments

- SHIMADZU AUX – 120 (Weighing Balance)
- UV Shimadzu 2450 (PC Series)
- UV-visible double beam spectrophotometer
- Software UV Probe 2.21
- Matched quartz cells 1 cm
- Wavelength range 190-900 nm
- Lamp: 50 w, Deuterium Lamp

- Detector: Silicon Photodiode
- Cell holder: 1 mm wide, 12 mm high
- Resolution: 1 nm

Materials
All analytical grade chemicals and reagents were used from Merck chemicals, Mumbai, India.

Methods
Selection of Solvent
Methanol was selected as the solvent to dissolved the Agomelatine.

Preparation of Standard Stock Solution of Agomelatine
Standard stock solution was prepared by dissolving 10 mg of Agomelatine in 100 mL of methanol to obtain concentration 100 µg/mL.

Determination of λ max and Selection of area under curve (AUC)
From the stock solutions, 1 mL of Agomelatine solution was transferred to 10 mL volumetric flask and the volume was adjusted to the mark with same solvent to obtain concentration 10 µg/mL. The solution was scanned in the UV range of 400 - 200 nm. In Method A, absorbance was recorded at 276 nm while in Method B, area under curve was selected in the wavelength range of 271.4 - 279.8 nm. The UV-Spectra for 'Method A' and 'B', shown in Figure 2&3. In Method C, spectra of above solution derivatized into first order using software UV Probe 2.21 with delta lambda 4 and scaling factor 8. In 'Method C', the amplitude was recorded at 279 nm while in 'Method D'; AUC of the derivatized spectrum was studied at 276.2 – 282.6 nm. The spectra for 'Method C' and 'D', Shown in Figure 4 and 5.

Linearity Study
Appropriate volume in the range 0.5 – 4 mL of Agomelatine stock solution was transferred to eight separate 10 mL volumetric flasks. The volume was adjusted to the mark with Agomelatine to obtain concentrations of 5 - 40 µg/mL. In Method A, absorbance of these solutions were recorded at 276 nm and in Method B area under curve selected in 271.4 - 279.8 nm. The calibration curves were constructed by plotting concentration versus absorbance and AUC in 'Method A' and 'B', respectively. (Figure 6 and Figure 7) And In 'Method C' Amplitude of these solutions were recorded at 279 nm and in 'Method D', AUC was recorded in between 276.2-282.6 nm. The calibration curves were constructed by plotting concentration versus amplitude / AUC in 'Method C' and 'D', respectively. (Figure 8 and Figure 9) Linearity shown in Table 1.

Validation
The proposed method was validated as per ICH guideline for linearity, accuracy, precision, ruggedness. All Validation results are presented in **Table 2**.[12]

Accuracy
Accuracy of the method was studied by recovery experiment. To the pre-analysed sample solutions, known amounts of standard stock solution were added at three different levels i.e. 80, 100 and 120%.

Precision
Precision of the method was studied as intra-day and inter-day variations. Intra-day precision was determined by analyzing the 10, 15 and 20 µg/mL of Agomelatine solutions for three times in the same day. Inter-day precision was determined by analyzing the 10, 15 and 20µg/mL of Agomelatine solutions daily for three days. Repeatability was determined by analyzing 25 µg/mL concentration of Agomelatine solution for five times.

Sensitivity
Sensitivity of the proposed method was estimated in terms of limit of detection (LOD) and limit of quantification (LOQ). The LOD and LOQ were calculated by the use of the equation LOD= 3.3*S.D./S and LOQ =10*S.D./S; Where 'ASD' is average standard deviation of the peak area of the drug taken as a measure of noise and S is the slope of the corresponding calibration curve. Different volume of stock solution in the ranges 5 – 10 µg/mL was prepared. For determination of LOD and LOQ slope of corresponding calibration curve was considered.

Ruggedness
Ruggedness of the proposed method is determined by analysis of aliquots from homogenous slot by two analyst using same operational and environmental conditions.

Analysis of Bulk Material
From the Standard Stock Solutions of Agomelatine, an appropriate volume 2 mL was diluted to 10 mL mark to obtain 20 µg/mL, scanned in UV-spectrophotometer between **400 - 200 nm** against blank.

Analysis of Tablet Formulation
For the analysis of Marketed formulation; twenty tablets were weight, average weight was determined and crushed into fine powder. A quantity of drug equivalent to 10 µg/mL of Agomelatine was transferred into 100 mL of volumetric flaks containing 50 mL of Methanol shaken manually for 25 min and volume was made up to the mark with same solvent and filtered through Whatmann filter paper no 41. An appropriate volume 2 mL was diluted to 10 mL mark to obtain 20 µg/mL, scanned in UV- Spectrophotometer between 400 - 200 nm against blank. The result of analysis of Agomelatine tablet is reported in Table 3. The analysis was repeated for six times.

RESULTS AND DISCUSSION
In methanol, Agomelatine shows linearity in the concentration range of 5 - 30 µg/ml. The maximum absorbance (λ max)/wavelength range and correlation

coefficient for all methods given in Table 1. In all these methods, inter- and intra-day precision was studied (%RSD less than 2) and accuracy of all methods was determined by calculating mean % recovery at 80, 100 and 120% level. The results of accuracy, repeatability and ruggedness studies are represented in Table 2. Pharmaceutical formulation of Agomelatine was analyzed. The amounts of Agomelatine in formulation were determined by all methods; the results are shown in Table 3.

Figures:

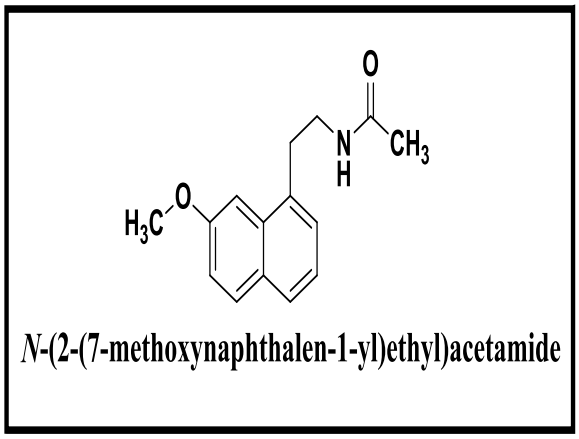

Figure 1: Chemical structure of Agomelatine.

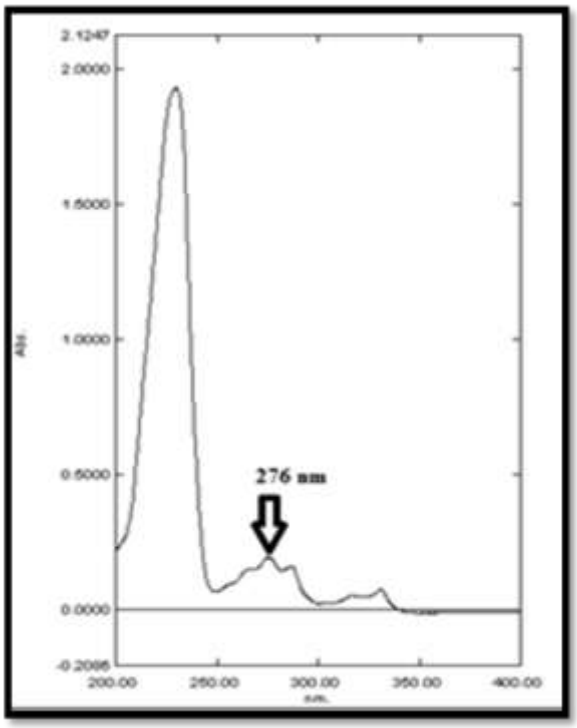

Figure 2: UV-Spectrum of Zero order spectroscopy.

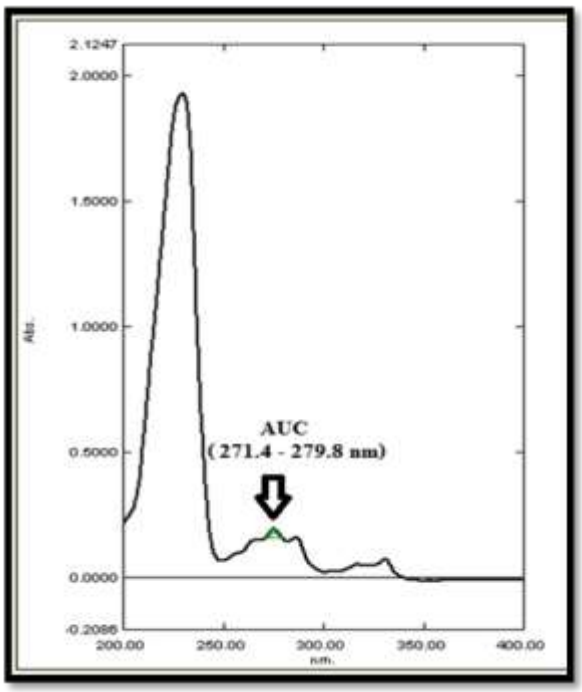

Figure 3: UV-Spectrum of Zero order AUC and selection of wavelength in the range 271.4 – 279.8 nm.

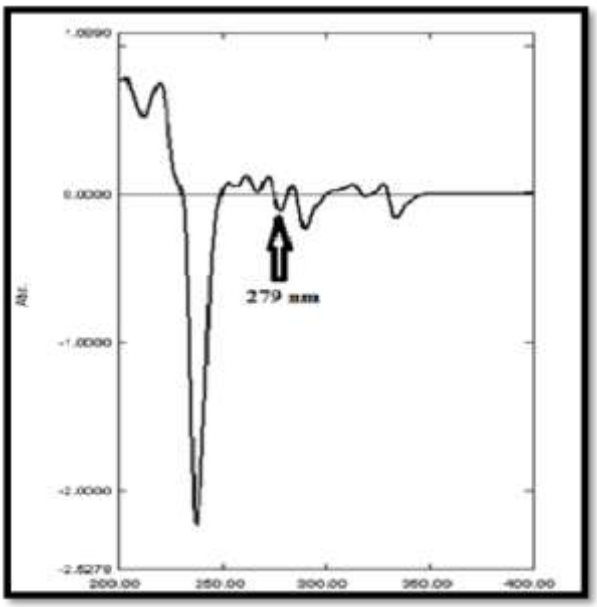

Figure 4: UV-Spectrum of First Order Derivative Spectroscopy.

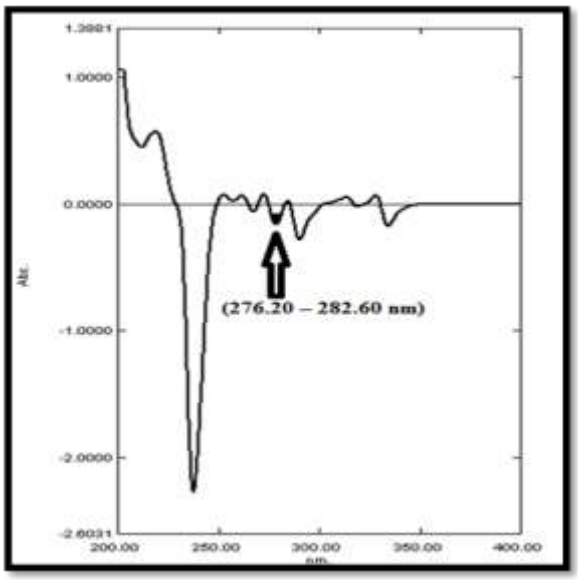

Figure 5: AUC of First Order Derivative Spectrum and selection of wavelength in the range 276.2 – 282.6 nm.

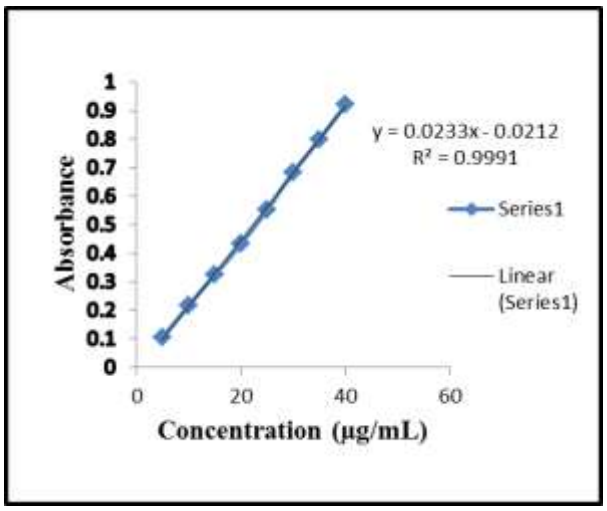

Figure 6: Calibration Curve of Zero order.

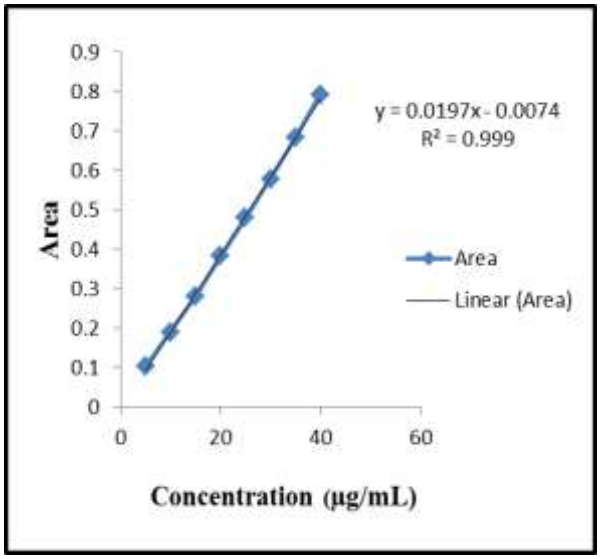

Figure 7: Calibration Curve of Zero order AUC.

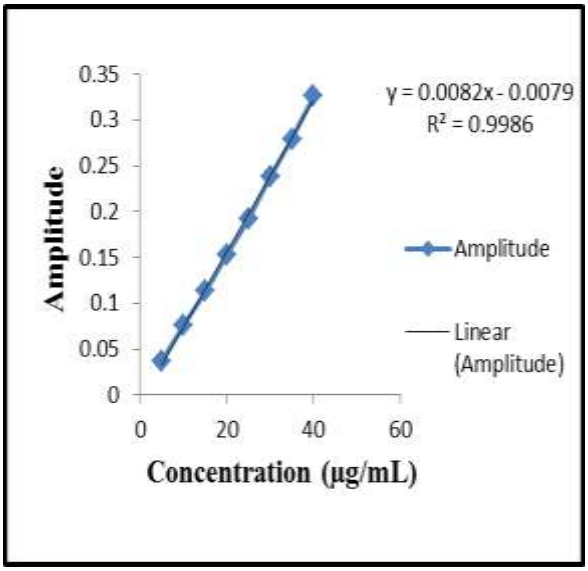

Figure 8: Calibration Curve of first order.

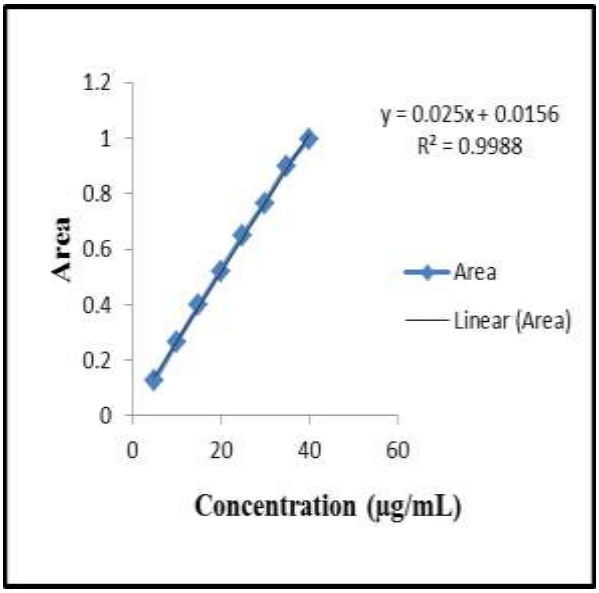

Figure 9: Calibration Curve of first order AUC.

Table 1: Details of UV spectrophotometric Methods.

Criterion	Method A	Method B	Method C	Method D
Beer-Lambert's range (µg/mL)	5 - 30	5 - 30	5 - 30	5 - 30
max (nm)/ Wavelength range (nm)	276	271.4 - 279.8	279	276.2 - 282.6
Slope	0.023	0.019	0.008	0.025
Intercept	0.021	0.007	0.007	0.015
Correlation coefficient	0.999	0.999	0.998	0.998

Table 2: Validation Parameters.

Parameters		Method A	Method B	Method C	Method D
Accuracy [n=3]	**80%**	99.51	99.12	100	99.33
	100%	99.80	99.88	100.27	99.91
	120%	98.95	99.80	99.76	98.96
Precision	**Intraday [n=3]**	0.68-0.73	0.80-0.85	0.72-1.28	0.70-1.28
	Interday [n=3]	0.73-0.87	0.53-0.80	1.27- 1.44	0.59- 1.06
Repeatability	**[% RSD]**	0.94	0.54	1.12	1.11
Ruggedness [%RSD]	**Analysts I**	0.91	0.87	0.92	0.89
	Analysts II	0.51	0.89	1.02	0.99
LOD (µg/mL)		0.0729	0.0172	0.0972	0.0494
LOQ (µg/mL)		0.221	0.1129	0.294	0.147

n= number of determinations

Table 3: Analysis of Pharmaceutical formulation.

Parameters	Method A	Method B	Method C	Method D
Amount Found (µg/mL)	20.05	19.92	19.87	19.84
% Amount found [n=6]	100.28	99.64	99.37	99.23

CONCLUSION

Overall four methods were established for quantitative analysis of Agomelatine in tablet formulation using zero order, zero order - AUC, first order, and first order -AUC technique of UV Spectrophotometry. The established methods are simple an economical and validated for accuracy, sensitivity and precision. As such, these methods can benefit other researchers, involved in similar studies, to perform routine analysis of Agomelatine in bulk material as well as in Tablet formulation.

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