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ESTABLISHMENT AND VALIDATION OF SPECTROPHOTOMETRIC METHOD FOR THE ANALYSIS AND QUANTIFICATION OF MIRABEGRON AND SOLIFENACIN IN TABLET DOSAGE FORMS BY ABSORPTION RATIO METHOD

Alexlivingston M. Nadar[1]*, Snehalatha Boddu[2], Ashwin S. Nainapatruni[3], Pinky A. Rajbhar[4]

Department of Quality Assurance. Oriental College of Pharmacy, Mumbai University Sanpada- 400705, Maharashtra, India.

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***Corresponding Author**
Alexlivingston M. Nadar
Department of Quality Assurance. Oriental College of Pharmacy, Mumbai University Sanpada- 400705, Maharashtra, India.

ABSTRACT

The current method development was intended for the determination and quantification of **Mirabegron** and **Solifenacin** from a tablet dosage form by using **Absorption Ratio Method** of UV-Visible Spectroscopic method. Methanol was found to be an appropriate solvent as both the drugs were highly soluble in it, after which the recording of the absorbance was carried out at wavelength maxima(λmax) at **248.8nm** and **221.2nm**, respectively. The obtained curve was then analysed using **Shimadzu Software** for determination of Isosbestic pint and we found that Mirabegron and Solifenacin showed same absorbances at **222.6nm** i.e., **Isosbestic point**. Calibration curve was plotted for both the drugs with concentration range of **3-15µg/mL**. The plot exhibited a perfect linear relationship for both the drugs with Regression coefficient **R^2= 0.9996** and **R^2= 0.9999**, respectively. The method was found to fulfil all the validation parameters according to ICH guidelines. The method showed good robustness and reproducibility and can be used for the estimation of these drugs from Tablet forms.

KEYWORDS: Mirabegron, Solifenacin, Absorption Ratio Method, ICH Guidelines.

INTRODUCTION

1) Mirabegron: (MBG), Mirabegron is a beta-3 adrenergic receptor agonist for the management of overactive bladder. It is an alternative to antimuscarinic drugs for this indication. By administrating Mirabegron to healthy volunteers orally, the absorption rate reaches maximum concentration around 3.5 hours by administrating 25mg of drug. The absolute bioavailability raises to 29% simultaneously the absolute bioavailability raises to 35% by administering dose.

2) Solifenacin: It is also used to treat Over reactive Bladder when used in combination with Mirabegron or other drugs. Also used to treat neurogenic Over reactive bladder caused by brain or spinal cord.

Overactive bladder (OAB) is a prevalent and costly condition that can affect any age group. Typical symptoms include urinary urgency, frequency, incontinence and nocturia. OAB occurs because of abnormal contractions of the bladder detrusor muscle caused by the stimulation of certain muscarinic receptors. Therefore, antimuscarinic agents have long been considered the mainstay of pharmacologic treatment for OAB. Currently, there are five such agents approved for the management of OAB in the United States: oxybutynin, tolterodine, trospium, solifenacin and darifenacin.

Literature survey depicted that there are also some HPLC*[12-17], HPTLC*[11-13], UPLC*[7-10] and Electrophoresis*[6] methods present, for the estimation of Mirabegron and Solifenacin.

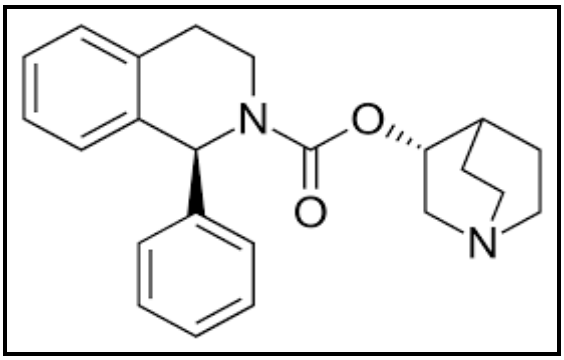

Fig 1: SOLIFENACIN

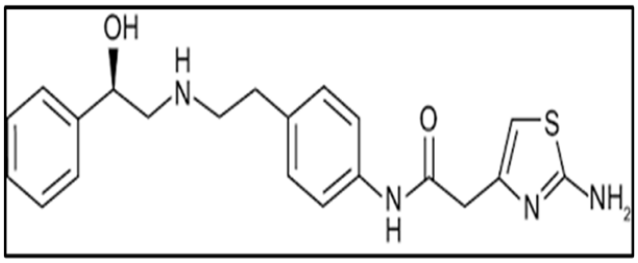

Fig 2: MIRABEGRON

OBJECTIVE

The current method has been developed to make the estimation of Mirabegron and Solifenacin from the tablet dosage form using Absorption Ratio Method more accurate and robust and should possess a good reproducibility.

MATERIALS AND METHODS

Instrumentation: The instrument used to measure the absorbance of the working solutions was a Shimadzu UV-Visible spectrophotometer of model UV 1700 with UV probe software. A Shimadzu AW120 Digital analytical balance and Equitron ultra sonicator were used in the study.

Method Development

Selection of Solvent: According to the literature survey both Mirabegron and Solifenacin were made to be solubilize in HCL and other Organic solvents like DMSO, Methanol, Ethanol. Out of which methanol was selected as it is easily available and has more solubility of both the drugs in it.

Determination of Absorption Maxima

Preparation of Standard Solution of Mirabegron and Solifenacin

30mg of Solifenacin drug was meant to dissolve in 100ml methanol in a 100ml volumetric flask, so the resulting conc was 0.3mg/ml which is **300µg/mL.** After which the resulting conc was diluted to get the conc of **3µg/mL.**

For Mirabegron 150mg of the drug was meant to dissolve in Methanol of 100ml volumetric flask and the volume was made up to 100ml resulting conc was **1500 µg/mL.** From the resulting solution aliquot of 1ml was withdrawn and was diluted with 10ml of Methanol in a 10ml Volumetric flask, resulting Conc was **150 µg/mL**. Again, from the resulting solution aliquot of 1ml was withdrawn and was diluted to 10ml of Methanol in a 10ml Volumetric flask. Resulting Conc was **15 µg/mL**.

Determination: For determination of λmax of both the drugs from a working solution of **3µg/mL Solifenacin** and **15µg/mL Mirabegron**, was scanned in the wavelength range of 200-400nm. Both **Mirabegron** and **Solifenacin** showed maximum absorbance (λmax) at **248.8nm** and **221.2nm,** respectively. Overlay of both the spectra is shown below in FIG 3:

Selection of Isosbestic Point

- Here after the scanning of both the drugs for determination of λmax the obtained overlay spectra was analyzed through the Shimadzu software.

- Were it depicted the Isosbestic Point of **222.6nm** at this wavelength both the drugs had same absorbance and the other wavelength selected was **248.8nm.**

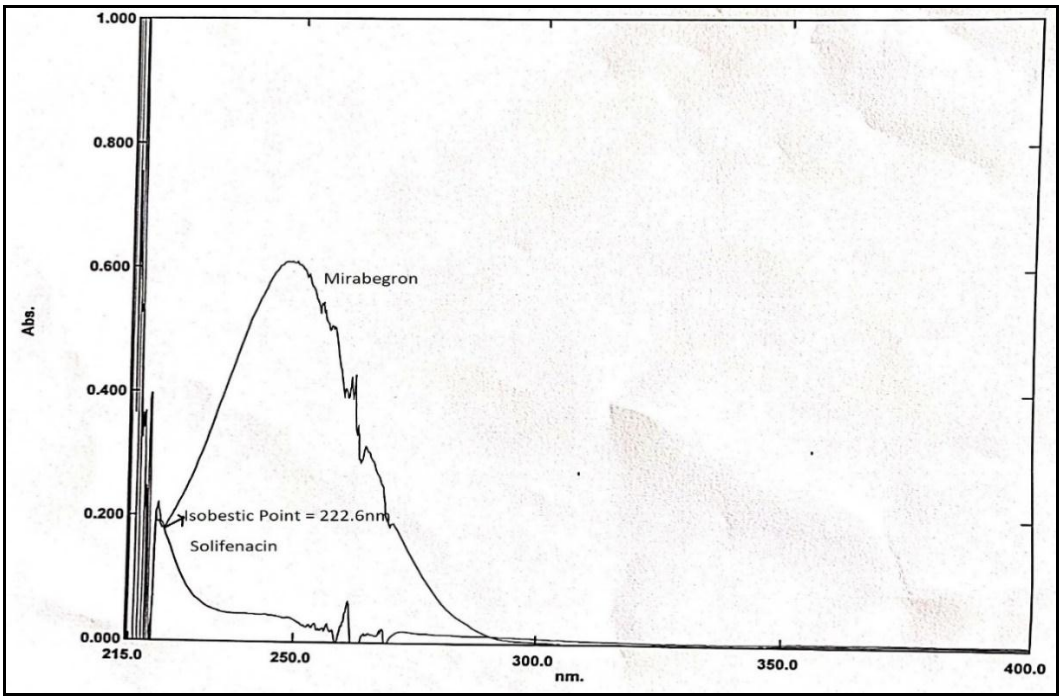

Fig 5: Overlay Spectra of Mirabegron and Solifenacin.

Preparation of Calibration Curve: Working of Standard Solutions

1) Solifenacin: From 30 µg/mL Stock solution, aliquots of 1,2,3,4,5 ml into a 10ml Volumetric flask. After which the solutions are diluted with methanol up to 10ml to get the conc of **3,6,9,12,15 µg/mL.**

2) Mirabegron: From 150 µg/mL Stock solution, aliquots of 0.1, 0.4, 0.6, 0.8, 1 ml into a 10ml Volumetric flask. After which the solutions are diluted with methanol up to 10ml to get the conc of **3,6,9,12,15 µg/mL.**

Calibration curve of Mirabegron and Solifenacin: The wavelength used to measure the absorbance was Isosbestic point and λmax of Mirabegron i.e., **222.6nm** and **248.8nm**. Later calibration curve was plotted against absorbance vs concentration. And regression equation was found out.

Absorbance Ratio Method: It is the modification of Simultaneous equation. In a quantitative assay of the admixture by absorbance ratio method the absorbances are measured

at two different wavelengths one being the λmax of one of the components (λ_2) and other being the wavelength of equal absorptivity of two components (λ_1) i.e., iso-absorptive point.

$Cx = \{(Q_M - Qy)/(Qx - Qy)\} \times (A_1/ax_1)$

$Cy = \{(Q_M - Qx)/(Qy - Qx)\} \times (A_1/ay_1)$

Where, A_1 and A_2 are absorbance's of the mixture at 222.6 nm and 248.8 nm respectively, ax_1 and ax_2 are absorptivities of Solifenacin at 2 wavelengths respectively and ay_1 and ay_2 are absorptivity of Mirabegron at 2 wavelengths, respectively. Cx and Cy are concentrations of Solifenacin and Mirabegron, respectively.

Sample Solution Preparation: Contents of 4 tablets was taken into a mortal pestle and was made fine to a powder form after which the entire powdered was weighed. After which the powder was weighed which would be equivalent to 25mg Mirabegron and 5mg Solifenacin. After which the powder was transferred to a 100mL volumetric flask, and it is dissolved in Methanol. Volume was made up to 100mL after which the sample was sonicated. After a particular time, the sample is then filtered using Whatmann Filter paper. Then the obtained filtrate was diluted appropriately to get the required concentration of **3µg/mL** of Solifenacin and **15µg/mL** of Mirabegron.

Validation of Method: The current method was validated according to the parameters of ICH guidelines like linearity, accuracy, intraday and interday precision, LOD, LOQ and ruggedness.

Range and Linearity: The standard solution of both Mirabegron and Solifenacin at 5 different concentrations ranging from **3-15µg/mL** was prepared to study and plot the calibration curve. The linear regression was later calculated.

PRECISION

Intraday Precision: The absorbance of the sample solutions of Mirabegron and Solifenacin at the concentrations of 6,9 and 12µg/mL was measured three times on the same day and % RSD was found out.

Interday Precision: The absorbance of the sample solutions of Mirabegron and Solifenacin at the concentrations of 6,9 and 12µg/mL was measured on three alternative days and % RSD was found out.

Accuracy: Accuracy studies were carried out to prove the closeness of the value to that of measured value. Here the concentrations of the formulation which was being previously analyzed is altered and spiked by the addition of different concentrations of standard solutions for the determination of percent recovery.

Limit of Detection (LOD): According to ICH guidelines LOD can be calculated by the following equation.

$$LOD = 3.3 \times (N/S)$$

Limit of Quantification (LOQ): According to ICH guidelines LOQ can be calculated by the following equation.

$$LOQ = 10 \times (N/S)$$

Here S- Slope of calibration curve

N- Standard Deviation of peak areas

RESULTS AND DISCUSSION

The standard solutions of both Mirabegron and Solifenacin were diluted appropriately to get the resulting concentration of 15µg/mL and 3µg/mL respectively, after which the solution was scanned at a wavelength range of 200-400nm, and the absorbance maxima and the Isosbestic point was found at 248.8nm and 222.6nm, respectively. Overlay spectra has been obtained which is shown in **FIG: 5.**

Table 1: Linearity Data of Solifenacin: At Isosbestic Point.

Concentration (µg/mL)	Absorbance (222.6nm)
3	0.572
6	0.627
9	0.683
12	0.736
15	0.792

Table 2: Linearity Data of Solifenacin: At 248.8nm.

Concentration (µg/mL)	Absorbance (248.8nm)
3	0.020
6	0.040
9	0.059
12	0.078
15	0.098

Table 3: Linearity Data of Mirabegron: At Isosbestic Point.

Concentration (µg/mL)	Absorbance (222.6nm)
3	0.053
6	0.106
9	0.159
12	0.212
15	0.260

Table 4: Linearity Data of Mirabegron: At Wavelength Max (248.8nm).

Concentration (µg/mL)	Absorbance (248.8nm)
3	0.108
6	0.202
9	0.301
12	0.401
15	0.490

Table 5: Absorbances of Working Solutions.

Sr. No	Drug	Conc (µg/mL)	Absorbance	
			Isosbestic (222.6nm)	λmax (248.8nm)
1	Solifenacin	3	0.281	0.058
2	Mirabegron	15	0.310	0.437
3	Mixture of Mirabegron and Solifenacin	3&15	0.544(x)	0.478(y)

Intraday Precision: The absorbance of the sample solutions of Mirabegron and Solifenacin at the concentrations of 6,9,12µg/mL was measured three times on the same day and % RSD was found out to be (**222.6nm) = 0.709-1.274%, (248.8nm) = 0.496-1.141%** (**222.6nm) = 0.475-0.752%, (248.8nm) = 1.205-1.449%** respectively.

Interday Precision: The absorbance of the sample solutions of Mirabegron and Solifenacin at the concentrations of 6,9,12µg/mL was measured on three alternative days and % RSD was found out to be (**222.6nm) = 1.248-1.933%, (248.8nm) = 0.654-0.756% and (222.6nm) = 0.523-0.804%, (248.8nm) = 1.220-1.563%.**

LOD and LOQ: The LOD and LOQ of Mirabegron at **248.8nm** and **222.6nm (Isosbestic point)** was found to be **0.791, 0.817** and **2.397, 2.475** respectively. The LOD and LOQ of Solifenacin at **248.8nm** and **222.6nm (Isosbestic point)** was found to be **0.435, 1.056** and **1.317, 3.200** respectively.

Accuracy: Recovery studies evaluated the ability of the method to give accurate results after spiking the marketed formulation at 50%, 100%, and 150% with the standard drug solution. The % recovery of Mirabegron and Solifenacin was found to be:

Table 6: Absorbances of Spiked Concentration for Solifenacin at Isosbestic Point.

Sr. No	Solifenacin (Mixture+Standard) Concentration(µg/mL)	Absorbance (a)
1	4.5	0.526 0.523 0.525
2	6	0.563 0.562 0.565
3	7.5	0.581 0.586 0.589

Sr. No	Solifenacin (Only Standard) Concentration(µg/mL)	Absorbance (b)
1	1.5	0.012 0.013 0.012
2	3	0.026 0.027 0.026
3	4.5	0.042 0.045 0.041

Table 7: Recovery Studies of Solifenacin at Isosbestic Point.

Level of Recovery	Amount of Formulation (µg/mL)	Amount of Pure Drug (µg/mL)	Total Amount of Drug (µg/mL)	Absorbance (a)	Difference (a-b) =c	Percent Recovery c/x*100	Mean Percent Recovery
50%		1.5	4.5	0.526 0.523 0.525	0.514 0.511 0.512	94% 93.93% 94.11%	94%
100%	3	3	6	0.563 0.562 0.565	0.537 0.537 0.539	98.71% 98.71% 99.08%	98.83%
150%		4.5	7.5	0.581 0.586 0.589	0.539 0.541 0.548	99.08% 99.44% 100.73%	99.75%

Table 8: Absorbances of Spiked Concentration for Solifenacin at Wavelength Max.

Sr. No	Solifenacin (Mixture+Standard) Concentration(µg/mL)	Absorbance (x)
1	4.5	0.497 0.497 0.495
2	6	0.513 0.516 0.509
3	7.5	0.521 0.519 0.521

Sr. No	Solifenacin (Only Standard) Concentration(µg/mL)	Absorbance (e)
1	1.5	0.006 0.007 0.006
2	3	0.025 0.023 0.024
3	4.5	0.052 0.052 0.051

Table 9: Recovery Studies of Solifenacin at Wavelength Max:

Level of Recovery (%)	Amount of Formulation (µg/mL)	Amount of pure Drug (µg/mL)	Total amount of Drug (µg/mL)	Absorbance (x)	Difference (x-e)= b	Percent Recovery (b/y*100)	Mean Recovery %
50		1.5	4.5	0.497 0.497 0.495	0.491 0.491 0.489	102.71% 102.71% 102.30%	102.57%
100	3	3.0	6	0.513 0.516 0.509	0.476 0.479 0.472	99.58% 100.20% 98.74%	99.51%
150		4.5	7.5	0.521 0.519 0.521	0.463 0.467 0.469	98.11% 97.69% 98.11%	97.97%

Table 10: Absorbances of Spiked Concentration for Mirabegron at Isosbestic Point.

Sr. No	Mirabegron (Mixture+Standard) Concentration(µg/mL)	Absorbance (d)
1	9	0.558 0.555 0.557
2	12	0.654 0.650

		0.655
3	15	0.697 0.699 0.705

Sr. No	Mirabegron (Only Standard) Concentration(µg/mL)	Absorbance (f)
1	3	0.052 0.051 0.053
2	6	0.117 0.117 0.115
3	9	0.157 0.157 0.156

Table 11: Recovery Studies of Mirabegron at Isosbestic Point.

Level of Recovery (%)	Amount of Formulation (µg/mL)	Amount of pure Drug (µg/mL)	Total amount of Drug (µg/mL)	Absorbance (d)	Difference (d-f)= b	Percent Recovery (b/x*100)	Mean Recovery %
50		3	9	0.558 0.555 0.557	0.505 0.504 0.504	92.83% 92.65% 92.65%	92.71%
100	6	6	12	0.654 0.650 0.655	0.537 0.533 0.540	98.71% 98.00% 99.26%	98.66%
150		9	15	0.697 0.699 0.705	0.540 0.542 0.549	99.26% 99.63% 100.92%	99.94%

Table 12: Absorbances of Spiked Concentration for Mirabegron at Wavelength Max.

Sr. No	Mirabegron (Mixture+Standard) Concentration(µg/mL)	Absorbance (m)
1	9	0.521 0.523 0.520
2	12	0.693 0.697 0.691
3	15	0.772 0.776 0.778

Sr. No	Mirabegron (Only Standard) Concentration(µg/mL)	Absorbance (n)
1	3	0.163 0.162 0.163
2	6	0.225 0.222 0.225
3	9	0.315 0.315 0.317

Table 13: Recovery Studies of Mirabegron at Wavelength Max.

Level of Recovery (%)	Amount of Formulation (µg/mL)	Amount of pure Drug (µg/mL)	Total amount of Drug (µg/mL)	Absorbance (m)	Difference (m-n)= b	Percent Recovery (b/y*100)	Mean Recovery %
50		3	9	0.632 0.634 0.630	0.469 0.472 0.467	98.12% 98.74% 97.70%	98.19%
100	6	6	12	0.693 0.697 0.691	0.468 0.475 0.466	97.90% 99.37% 97.48%	98.25%
150		9	15	0.772 0.776 0.778	0.457 0.461 0.461	95.61% 96.44% 96.44%	96.16%

Repeatability: It is the concordance of a series of measurements of the same quantity when the experiments are conducted under same conditions (analyst, apparatus, instrument, and day) in a rapid succession. Here standard Solution of Mirabegron and Solifenacin of Conc 9 µg/mL was being analysed for 6 times.

Table 14: Repeatability of Solifenacin at Isosbestic Point.

	Solifenacin	(222.6nm)			
Sr. no	Conc	Absorbance	Mean	S. D	%RSD
1	9	0.663		0.008	
2	9	0.657		0.009	
3	9	0.672	0.664	0.010	1.273
4	9	0.675		0.011	
5	9	0.653		0.007	
6	9	0.663		0.008	

Table 15: Repeatability of Solifenacin at 248.8nm.

	Solifenacin	(248.8nm)			
Sr. no	Conc	Absorbance	Mean	S. D	%RSD
1	9	0.070		0.001	
2	9	0.070		0.001	
3	9	0.071	0.070	0.001	1.468
4	9	0.072		0.002	
5	9	0.069		0.001	
6	9	0.070		0.001	

Table 16: Repeatability of Mirabegron at Isosbestic Point.

	Mirabegron	(222.6nm)			
Sr. no	Conc	Absorbance	Mean	S. D	%RSD
1	9	0.153		0.002	
2	9	0.156		0.002	
3	9	0.151	0.153	0.001	1.270
4	9	0.152		0.002	
5	9	0.151		0.002	
6	9	0.154		0.002	

Table 17: Repeatability of Mirabegron at Wavelength Max(248.8nm).

	Mirabegron	(248.8nm)			
Sr. no	Conc	Absorbance	Mean	S. D	%RSD
1	9	0.301		0.003	
2	9	0.310		0.003	
3	9	0.308	0.305	0.003	1.143
4	9	0.306		0.002	
5	9	0.302		0.001	
6	9	0.304		0.003	

Table 18: Analysis of Marketed Formulations.

Tablet	Drug	Label Claim(mg)	Amount found(mg)	%Label Claim
Bladmir -S25	Mirabegron Solifenacin	25 5	24.66 4.61	98.66 92.29

Table 19: Regression Analysis Data And Summary Of Validation Parameters For The Current Method.

Parameters	Mirabegron	Solifenacin
Wavelength 1) Isosbestic Point 2) Wavelength Max	 222.6nm 248.8nm	 222.6nm 221.2nm
Beer's Law Limit(µg/ml)	3-15	3-15
Regression equation (Y=mx+c)		

1) Isosbestic Point 2) Wavelength Max	Y = 0.0173x + 0.002 Y = 0.0321x + 0.0115	Y = 0.0183x + 0.5173 Y = 0.0065x + 0.0008
Slope(m) 1) Isosbestic Point 2) Wavelength Max	 0.0173 0.0321	` 0.0183 0.0065
Intercept(c) 1) Isosbestic Point 2) Wavelength Max	 0.002 0.0115	 0.5173 0.0008
Correlation Coefficient (R^2) 1) Isosbestic Point 2) Wavelength Max	 0.9996 0.9997	 0.9999 0.9999
Intraday (n = 6) (% RSD) 1) Isosbestic Point 2) Wavelength Max	0.709-1.274% 0.496-1.141%	0.475-0.752% 1.205-1.449%
Interday (n = 6) (%RSD) 1) Isosbestic Point 2) Wavelength Max	 1.248-1.933% 0.654-0.756%	 0.523-0.804% 1.220-1.563%
LOD(µg/mL) 1) Isosbestic Point 2) Wavelength Max	 0.817 0.791	 1.056 0.435
LOQ(µg/mL) 1) Isosbestic Point 2) Wavelength Max	 2.397 2.475	 3.200 1.317

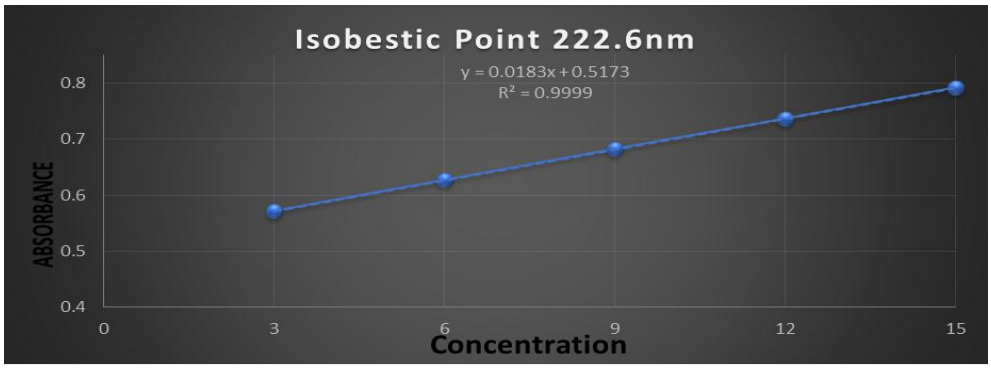

Fig. 7: Calibration curve of Solifenacin at Isosbestic Point.

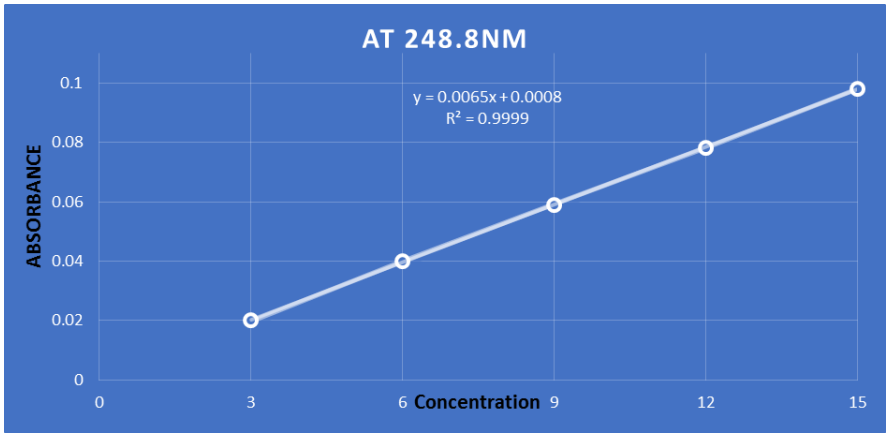

Fig. 8: Calibration curve of Solifenacin at 248.8nm.

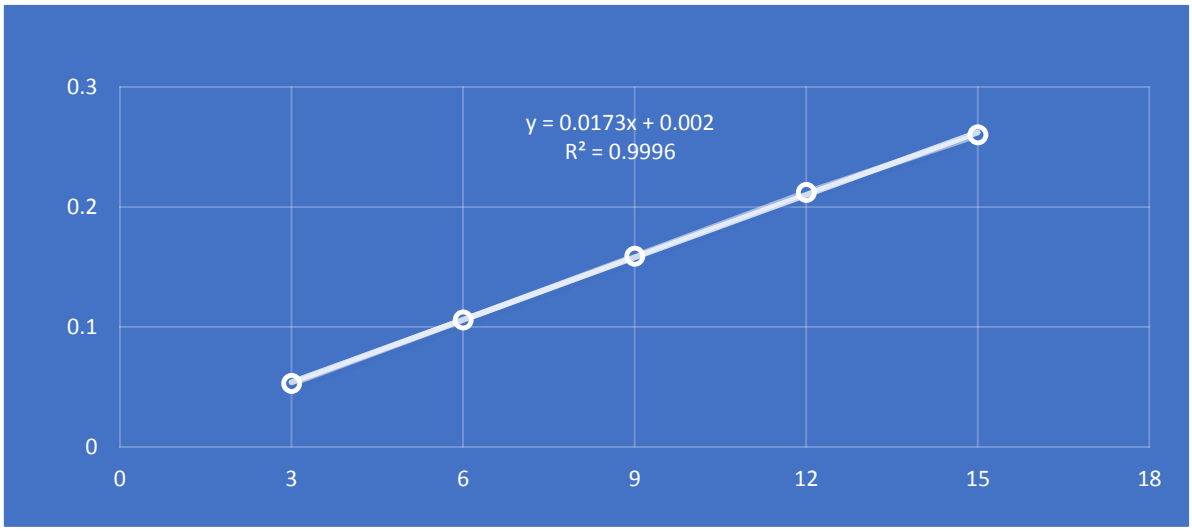

Fig. 9: Calibration curve of Mirabegron at Isosbestic Point.

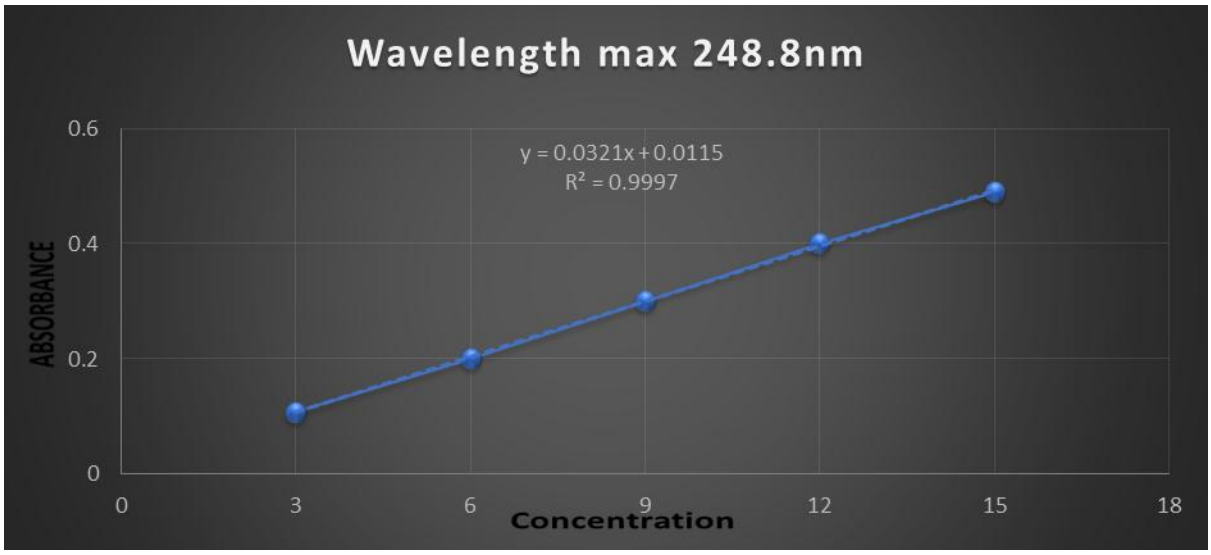

Fig. 10: Calibration curve of Mirabegron at Wavelength Max (248.8nm).

CONCLUSION

A novel and easy method has been developed for the quantification of Mirabegron and Solifenacin by using Absorption Ratio Method of Multicomponent analysis of UV spectroscopy. This method can be employed for the determination of the concentration of both Mirabegron and Solifenacin from any dosage forms specially tablet dosage forms.

DISCUSSION

The results which are being obtained were not been published anywhere and the data obtained from this methodology has proved to be more robust and accurate than that of other methods and this methodology which has being developed can be used for determination and quantification of drugs in tablet dosage forms.

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Data Availability: We authors hereby declare that whatever data is being published to support our developed methodology is being solely available within the article itself.

Conflict of interest: Authors declare no conflict of Interest for this work.

Authorship Contribution

1) Snehalatha B: Responsible for the core of the methodology development as the idea was completely emphasized by them.

2) Alexlivingston M. Nadar: Worked on the developed methodology idea implemented it and executed the core calculations of the entire research and analytical data.

3) Ashwin S. Nainapatruni and Pinky A. Rajbhar: Helped in the analytical development and their core contribution was to fetch the appropriate reagents for the methodology development.

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