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Journal of Drug Delivery and Therapeutics

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Research Article

Development and Validation of Extractive Spectrophotometric Methods for the Estimation of Telmisartan by Using Smartphone Application

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Article Info:

Article History:

Received 23 April 2022
Reviewed 02 June 2022
Accepted 09 June 2022
Published 17 June 2022

Cite this article as:

Saiyed SA, Jadeja P, Mashru R, Development and Validation of Extractive Spectrophotometric Methods for the Estimation of Telmisartan by Using Smartphone Application, Journal of Drug Delivery and Therapeutics. 2022; 12(3-S):178-190

DOI: http://dx.doi.org/10.22270/jddt.v12i3-s.5527

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Abstract

Two simple, sensitive, accurate, precise and reproducible extractive colorimetric methods were developed for estimation of Telmisartan in bulk and pharmaceutical dosage form. These methods are based on the formation of colored ion-pair complex of Telmisartan with Bromocresol green (BCG) and Bromocresol purple (BCP) dyes in acidic medium. The complex was extracted in chloroform and estimated quantitatively at 421 nm and 411 nm for BCG and BCP dyes respectively. For estimation of TMS present in the sample, estimation was also done by using Smartphone Application known as PhotoMetrix Pro. Beer Lambert's law was obeyed over a range of 4-12 µg/ml for TMS with BCG dye by UV (r^2= 0.9997) and PhotoMetrix (r^2= 0.997) and for BCP dye it was obeyed over a range of 2-10 µg/ml by UV (r^2= 0.999) and PhotoMetrix (r^2= 0.998). The developed method was successfully applied for estimation of TMS in three commercial product tablet formulation without interference from common additives. The developed method was validated according to ICH Q2 guideline for linearity, range, accuracy, and precision. Comparison for both method UV and PhotoMetrix was done by performing t-test, and results show that there is no significant difference between both methods and hence Photometrix can be used as an alternative to UV for routine analysis of TMS.

Keywords: Telmisartan, Bromocresol green, Bromocresol purple, Acidic dyes, Colorimetry, UV spectrophotometry, PhotoMetrix.

INTRODUCTION

Telmisartan is an angiotensin II receptor (type AT1) antagonist that is highly selective for type 1 angiotensin II receptors [1]. Chemically it is (4-((2-n-propyl-4- methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl) methyl)-biphenyl-2-carboxylic acid. It acts by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II by selective blocking the binding of angiotensin II to AT1 receptor found in vascular smooth muscles [2] It is effectively used to treat hypertension and renal impairment. It has a lower incidence of cough than ACE inhibitors [3] The molecular formula is C33H30N4O2 and has a molecular mass of 514.617 g/mol. It is a crystalline powder having white to off white color. It is insoluble in water, freely soluble in methanol and acetonitrile.

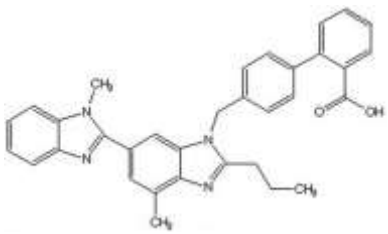


Figure 1: Structure of Telmisartan

Various analytical methods are reported for estimation of TMS in pharmaceutical dosage form. Literature survey reveals UV for telmisartan in bulk [4–6], difference in spectrophotometry [7], spectrophotometry in combination with other drugs [8–15] , colorimetry [16–18], HPLC [19–27], stability indicating RP-HPLC [28–30] Forced degradation [31], are reported for estimation of telmisartan. A colorimetric analysis is a simple spectrophotometric analysis used to figure out the amount of a colored component present in a solution. Colored compounds absorb light in the visible spectrum, according to Beer-Lambert's Law the amount of light absorbed is proportional to the concentration of the component in the solution [32]

In this study a simple, precise, accurate and sensitive Extractive spectrophotometric method for estimation of TMS by using Bromocresol green (BCG) and Bromocresol purple (BCP) dye, followed by extraction of complex in organic solvent was carried out. Also, the developed method was extended to estimation by SmartPhone application. For this purpose, Mobile application called Photometrix, which employs techniques of simple linear correlation for univariate analysis was used. This application is available free in Google Play Store. The method is based on measurement of signal intensities relative to concentration of sample.

MATERIALS AND METHODS

Apparatus and Software

UV spectral studies were done using Shimadzu UV-1700 double beam spectrophotometer connected to a computer having Shimadzu UV probe 2.10 software. The absorbance spectra of drug were carried out in 1 cm quartz cells over the range of 400- 800nm. The samples were weighed on electronic analytical balance (A×120, Shimadzu). Smartphone having Photometric pro application was used to capture images.

Chemicals and reagents

Telmisartan API was received by Zuventus Healthcare as a gift sample. Bromocresol Green dye (Sulab), Bromocresol Purple dye (Allied Chemical Corporation), Sodium hydroxide pellets (Rankem) and Potassium hydrogen Phthalate (Loba Chemicals) of AR grades were used. Double distilled water and Chloroform (Rankem) AR grade were also used in the experiment.

Preparation of BCG dye

Bromocresol green dye was made according to the procedure given in IP. 50 mg dye was added in a 100ml volumetric flask and to that 0.72 ml 0.1M NaOH was added. Then 20 ml methanol is added and made up to mark by double distilled water.

Preparation of BCP dye

Bromocresol purple dye was also made according to the IP procedure. 50 mg dye was added in a 100 ml volumetric flask and to that 0.92 ml of 0.1M NaOH was added. Then 20 ml methanol was added and made up to mark by double distilled water.

Preparation of Phthalate buffer (pH-1.5)

Phthalate buffer was prepared according to the procedure given in IP. 2g Potassium hydrogen Phthalate was added in a 200 ml volumetric flask and to that 50 ml water was added. Then 42 ml of 0.2 M HCl is added and made up to mark with distilled water.

Preparation of standard stock solution

25 mg Telmisartan was weighed accurately and transferred to a 25 ml volumetric flask and dissolved in 1 ml methanol. Then the volumed is made up to mark by distilled water to get 1000 ppm drug solution.

Preparation of working standard

From the standard stock solution 1 ml is pipetted out in a 10 ml volumetric flask to get 100 ppm drug solution. Aliquots of std solution of TMS corresponding to 4-12 ppm are then further made.

Preparation of sample solutions

20 tablets of formulation 1, 2, 3 were accurately weighed and powdered separately. An amount of powder equivalent to label claim of each tablet was weighed and transferred to 100 ml volumetric flask. To that double distilled water added to dissolve powder and sonicated for 10 minutes. Then solution was made up to the mark and filtered. Further dilution was made to get final concentration of 100 ppm of Telmisartan.

Selection of wavelength for Telmisartan

The maximum absorbance of Telmisartan with Bromocresol Green dye was found to be at 421 nm and at 411 nm with Bromocresol Purple.

Method optimization

Optimization of dye volume

To 10 ml of standard working solution, 5 ml of phthalate buffer of pH 1.5 and different volumes of dye (1 to 1.8 ml) were added in separating funnel. 5 ml chloroform was added and shaken for 1 minute. Followed by separation and measurement of organic layer at 421 nm and 411 nm was done against blank. Blank was prepared as same manner instead of TMS drug solution double distilled water was used in procedure. The result showed that highest absorbance was obtained in 1.6 ml of volume of dye for both dyes. Fig 2 and 3

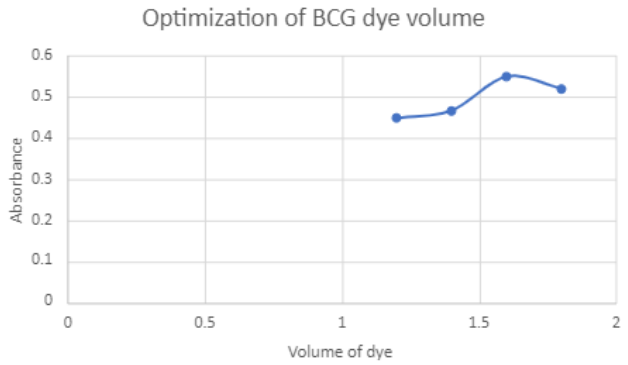


Figure 2: Optimization of BCG dye volume

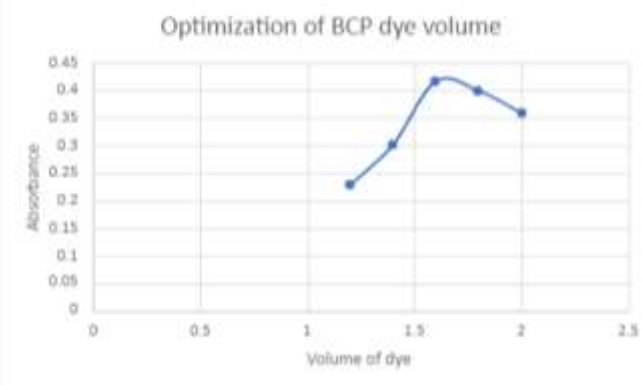


Figure 3: Optimization of BCP dye volume

Optimization of Buffer pH:

To 10 ml of standard working solution, 5 ml of buffer having pH 1 to 2.5 were added, followed by addition of 1.6 ml of BCG dye. To that 5 ml chloroform was added and shaken for one minute and separating chloroform layer was then scanned in the 400 to 800 nm. The results obtained show that the maximum absorbance was found at 1.5 pH of buffer for both dyes. (Figure 4 and 5)

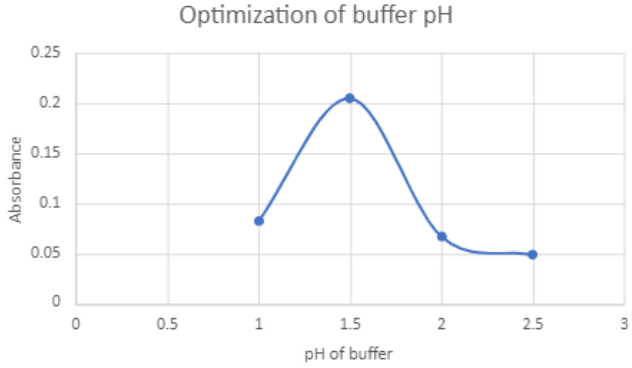


Figure 4: Optimization of Buffer pH

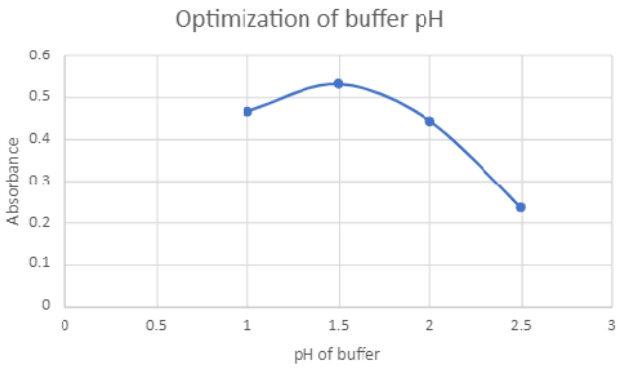


Figure 5: Optimization of buffer pH

Optimization of reaction time:

For optimization of reaction time experiment is performed for 1 to 5 minutes. It was found that reaction time has not much significant effect on the result of experiment. So, 1 minute was taken as an optimum shaking time and it was found that the addition of the dye solutions resulted in an immediate full color development. Color of the complex is stable for more than 24 hours

Table 1: Optimized Conditions for colorimetric method with both the dyes

Parameter	Optimized value
Volume of dye	1.6
pH of buffer	1.5
Reaction time	1 minute

Reaction Mechanism

Bromocresol green and Bromocresol Purple are anionic dye containing sulphonephthalein group. Color of both dyes is due to opening of lactoid ring and formation of subsequent quinoid group. Although tautomers are present at equilibrium state but due to acidic nature of sulphonic group, quinoid group (deprotonated) is predominant. Telmisartan contains tertiary amino group which is protonated in acidic medium So protonated TMS forms ion pair complex with deprotonated BCG and BCP dye which is quantitatively extracted in chloroform layer [33–37] . Probable reaction mechanism is illustrated in Figure 4.

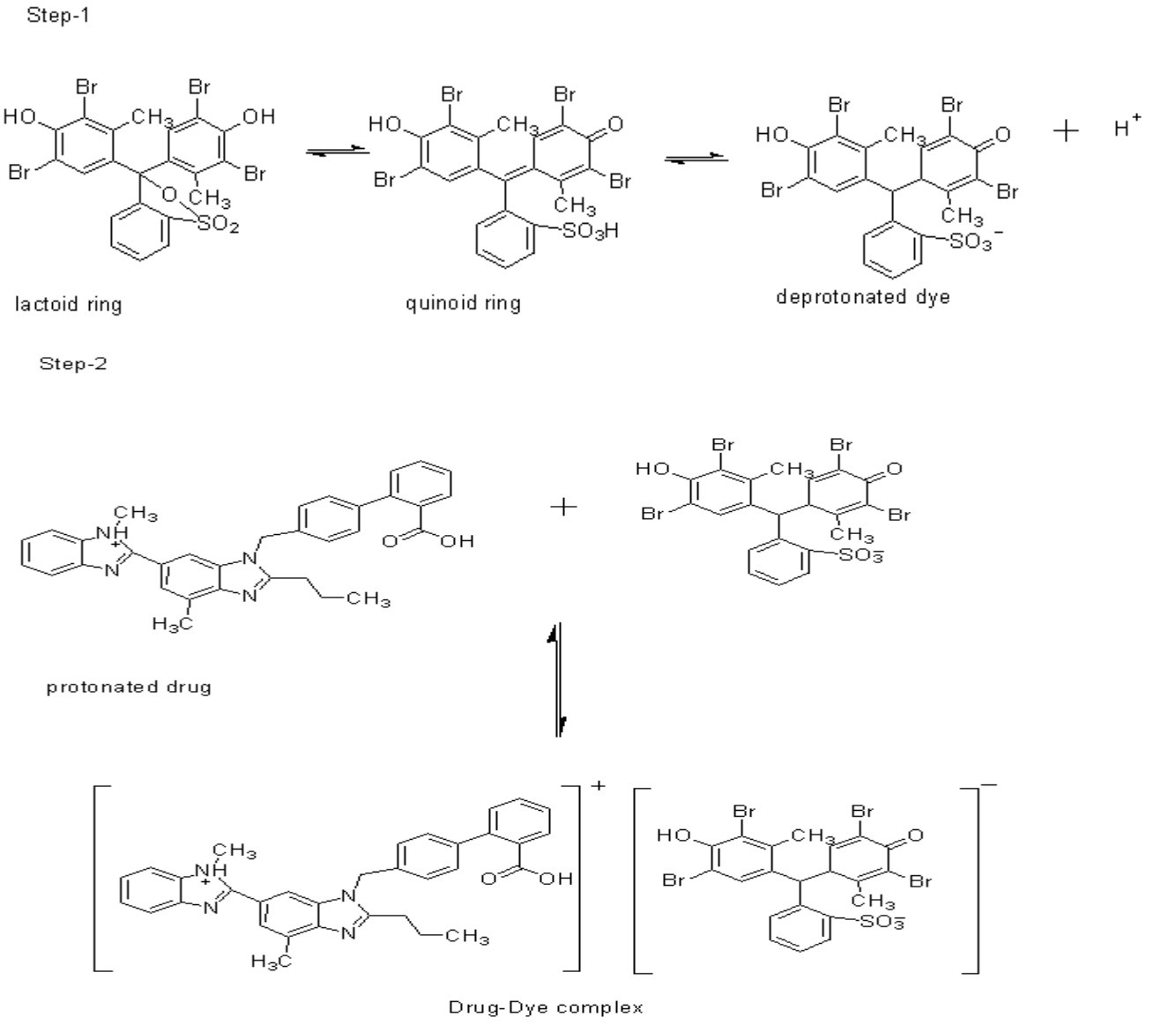


Figure 6: Reaction Mechanism of Telmisartan with BCG dye

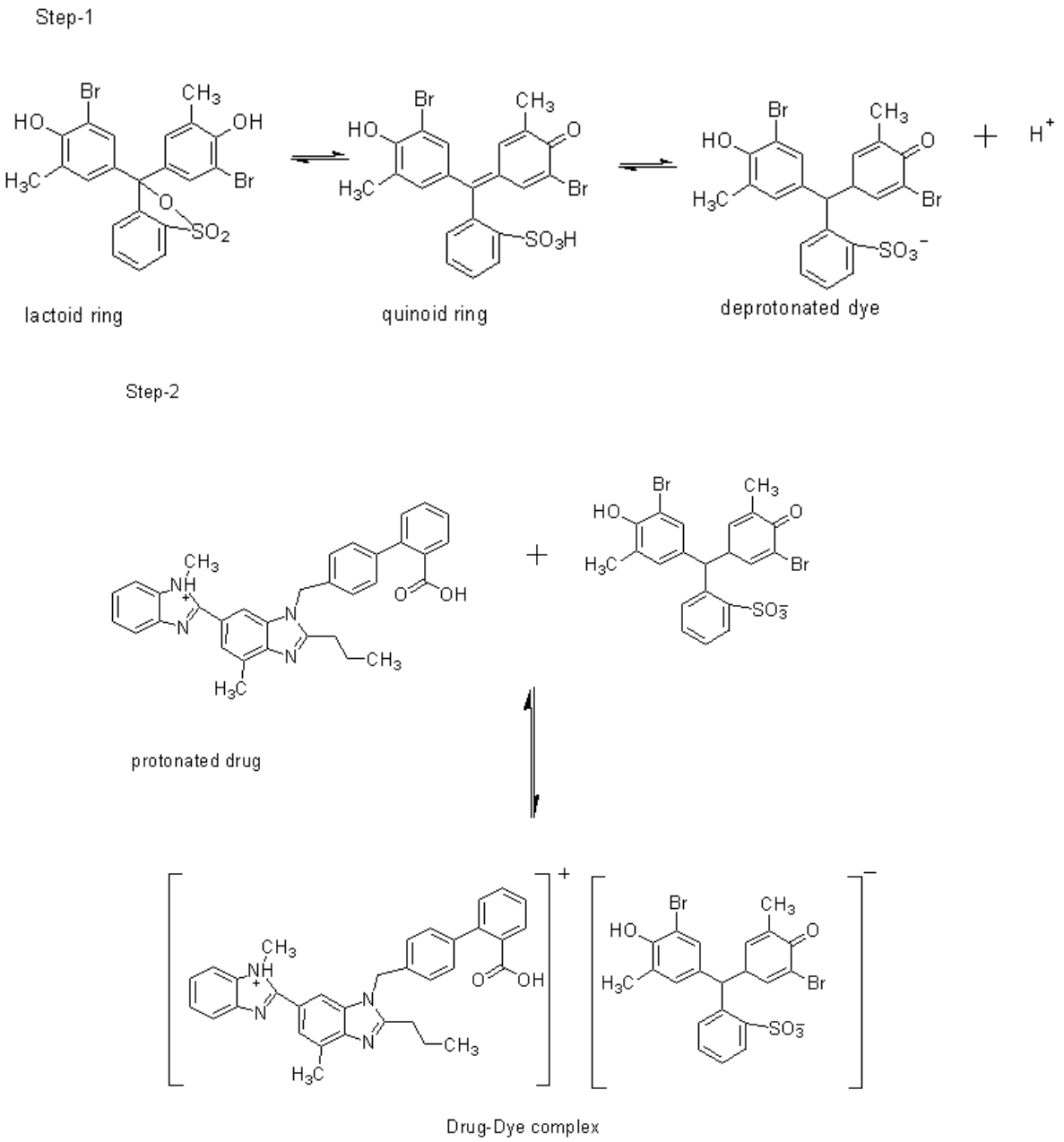


Figure 7: Reaction Mechanism of Telmisartan with BCP dye

Job's plot

A Job plot, also known as the method of continuous variation or Job's method, is a method used in analytical chemistry to determine the stoichiometry of a binding event. The stoichiometry of the complex formed between BCG and BCP with telmisartan was investigated at the optimum experimental conditions, by the continuous variation method. The result indicates the existence of 1:1 charge transfer complex for both dyes at a definite wavelength. Fig 6 and 7.

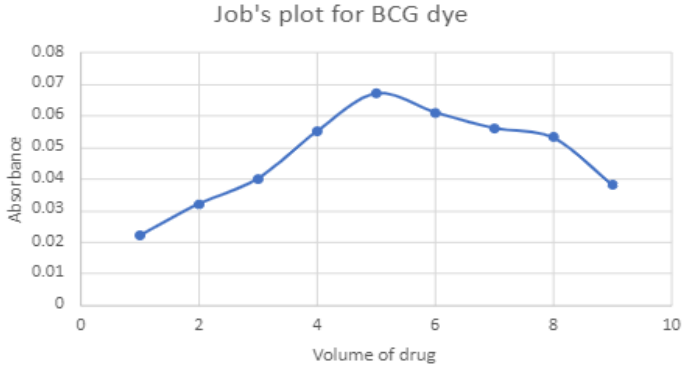


Figure 8: Job's Plot for BCG dye

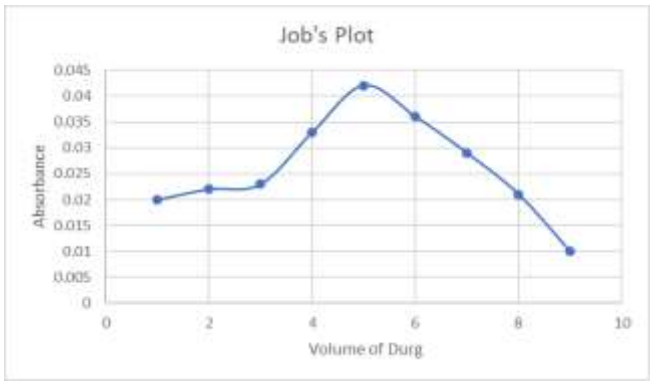


Figure 9: Job's Plot for BCP dye

Preparation of calibration graph

Aliquots were taken from 100 ppm to make 4 to 10 µg/ml for BCG and 2 to 10 µg/ml for BCP solution of TMS. Volume was made up to mark with double distilled water. They were transferred to separating funnel, to that 5 ml of phthalate buffer of pH 1.5 and 1.6 ml of BCG dye was added. To that 5 ml chloroform was added followed by shaking for one minute and separation of chloroform layer. Absorbance of chloroform layer measured at a 421 nm for BCG dye and 411 nm for BCP dye against blank. Calibration graph was plotted for absorbance of organic layer against their respective concentration.

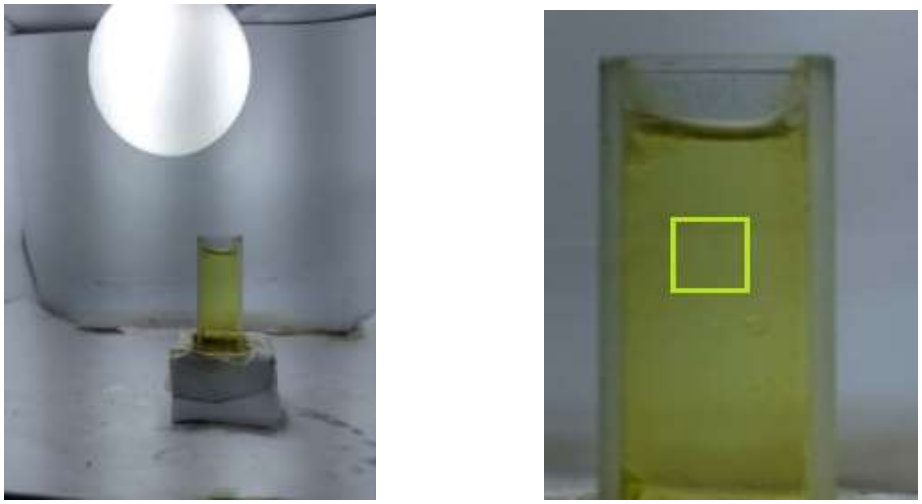
Analysis of marketed formulation

From the prepared sample solution of formulation aliquots were taken to prepare 7 µg /ml for BCG dye and 5 µg /ml solution for BCP dye and treated as same manner given for working standard of TMS and absorbance was measured at 421 nm and 411 nm respectively. The absorbance of sample was calculated by standard curve method.

ESTIMATION OF TELMISARTAN USING SMARTPHONE APPLICATION:

Experimental Setup:

The coloured solution was transfer into a slandered glass cuvette which was placed in 18cm×18cm of white box and 6W LED (Light Emitting Diode) bulb was connected to control the intensity throughout the experiment shown in FIGURE. The image of the colour complex solution was taken with the help of a smart phone and analysed using a photometric application to determine the red-green-blue intensities (RGB scale) of the image. The concentration of the image taken by PhotoMetrix PRO was estimated using a linear regression equation. PhotoMetrix analyses and creates colour histograms on RGB scales, which it then converts into a calibration curve. Using univariate and multivariate analysis, this programme processes and displays the results. For the best results, many smartphone types were used. Figure 5 depicts the steps for utilising the PhotoMetrixPRO application.



(A) **(B)**

Figure 10: Cuvette placed in arranged setup (A), Image captured by mobile phone camera in arranged setup (B)

Preparation of calibration graph by smart phone application

Working standard solution of 4-12 µg/ml of TMS with BCG dye and 2-10 µg/ml with BCP dye was prepared by taking suitable aliquots from standard stock solution and transferred in 10 ml volumetric flask. Volume was made up to 10 ml with double distilled water. These solutions were transferred in previously cleaned and dried separating funnel and treated as same manner described earlier. Once chloroform layer of all solutions was separated, images were captured one by one in PhotoMetrix Pro application. Steps to plot calibration graph in application is illustrated in the figure. In application use univariate analysis in which vector RGB was selected, then calibration option was selected. Once you select calibration, app will ask you for number of samples. Here for calibration, number of samples was taken is 6 (1 was blank and 5 were working standard). Then first blank solution was filled in cuvette and inserted in the box and image was captured for blank. In the same manner one by one images of all standard working solution were captured in an increasing concentration by providing concentration of sample in the application. Calibration graph and regression equation was provided by application is self. Once regression equation was obtained, concentration of sample solution from marketed formulation was estimated. For this purpose, instead of calibration, sampling option in univariate analysis was selected and the image of sample solution prepared from marketed formulation was captured in manner similar to standard solution. After saving the data concentration of sample was given by application from generated calibration graph.

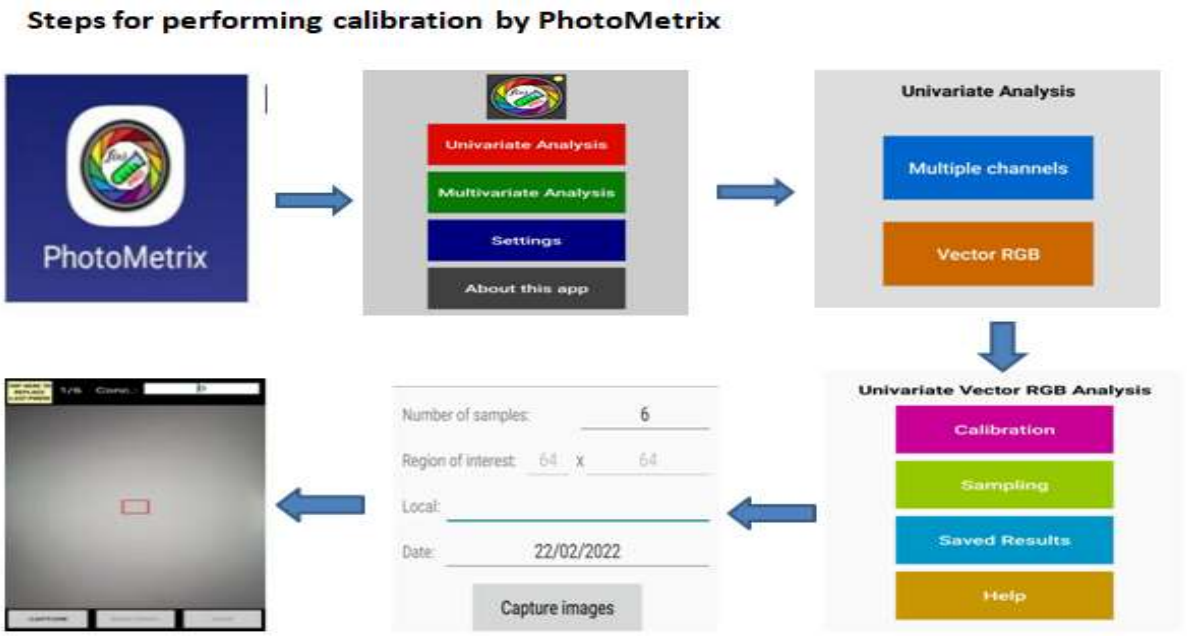


Figure 11: Graphical Presentation of PhotoMetrix PRO Application and Steps to generate calibration graph by application

RESULTS AND DISCUSSION

Method Validation:

1. **Linearity:**

Telmisartan was found to be linear in the concentration range of 4-12 µg/ml at 421 nm for BCG dye and in range of 2-10 µg/ml for BCP dye by obeying Beer's law (Figure 6). A calibration curve was plotted between concentration Vs absorbance (Figure 7). The plot was found to be linear for both dyes

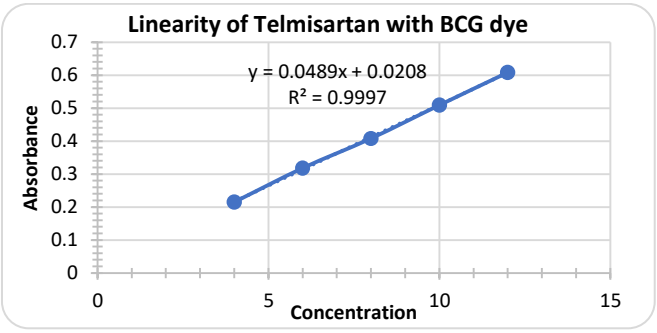


Figure 12: Calibration graph of Telmisartan

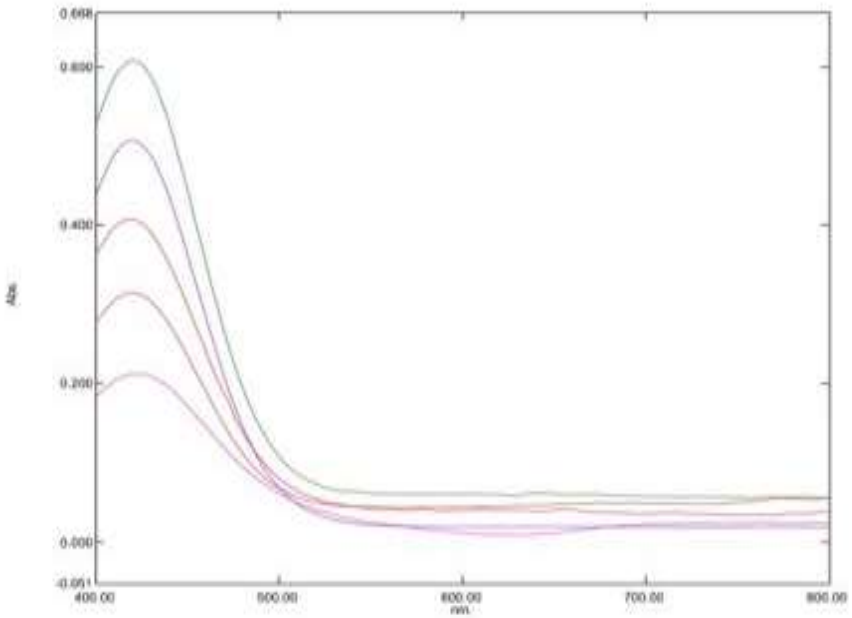


Figure 13: Overlay Spectra of TMS with BCG dye (4 -12 µg/ml)

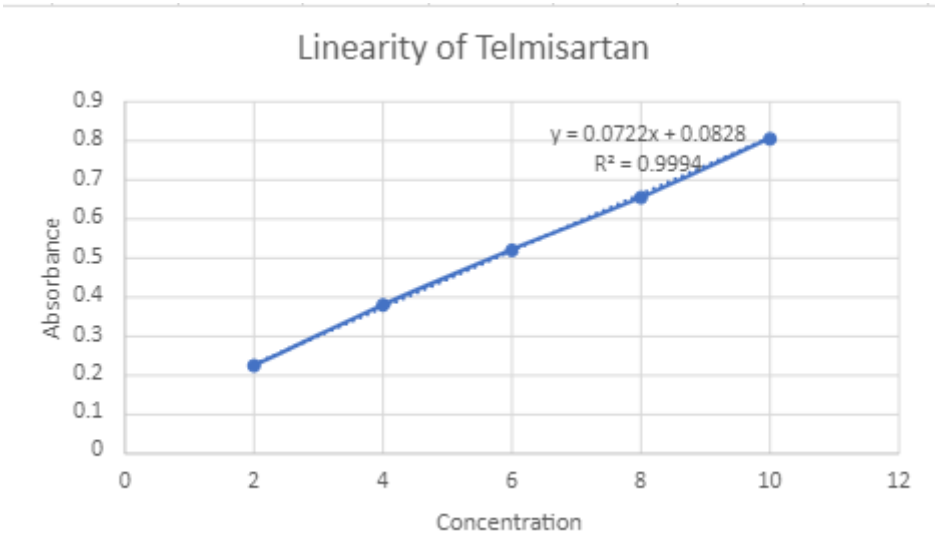


Figure 14: Calibration Graph of TMS with BCP dye

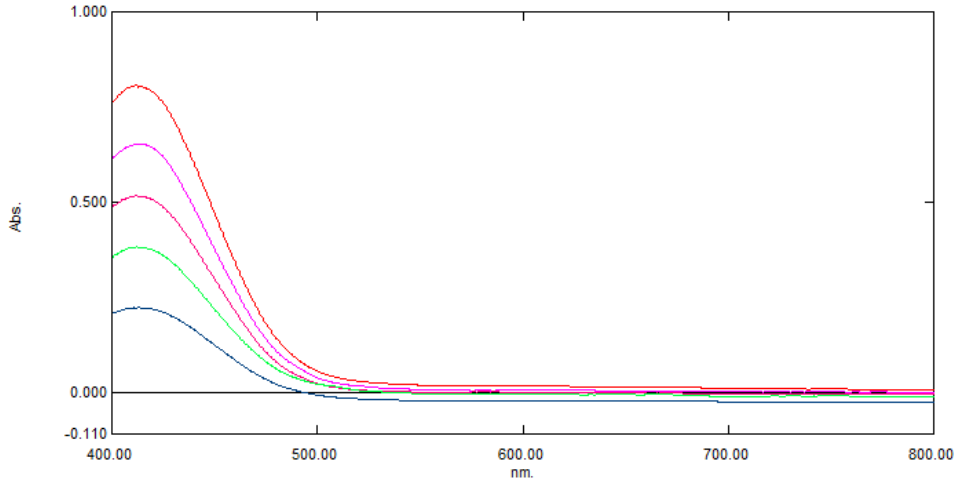


Figure 15: Overlay Spectra of TMS with BCP dye (2 -10 µg/ml)

2. Precision

The precision of an analytical method refers to the degree of agreement between a set of measurements acquired by sampling the same homogeneous sample many times under the method's specified circumstances. The intraday (Repeatability) and interday precision were calculated here. Three-concentration samples with lowest, upper, and middle limits of both medicines were taken and analysed three times at the same concentration level on the same day for intra-day precision and three times on three different days for inter-day precision. The % RSD (Table 2 & Table 3) was calculated and determined to be less than 2.

Table 2: Intraday Precision of Telmisartan with BCG dye

Concentration (µg/ml)	Mean ± SD (n = 3)	% RSD
4	0.199± 0.0015	0.77
6	0.316± 0.003	0.96
8	0.406± 0.0026	0.65
10	0.521± 0.005	0.96
12	0.603± 0.0061	1.01

Table 3: Interday Precision of Telmisartan with BCG dye

Concentration (µg/ml)	Mean ± SD (n = 3)	% RSD
4	0.213 ± 0.0015	0.54
6	0.323 ± 0.0026	0.82
8	0.413 ± 0.0037	0.92
10	0.518 ± 0.0025	0.49
12	0.612 ± 0.0049	0.81

Table 4: Intraday Precision of Telmisartan with BCP dye

Concentration	Mean ± SD (n= 3)	% RSD
2	0.228 ± 0.00435	1.91
4	0.367 ± 0.00378	1.03
6	0.513 ± 0.00459	0.88
8	0.649 ± 0.01069	1.65
10	0.80 ± 0.01126	1.41

Table 5: Interday Precision of Telmisartan with BCP dye

Concentration (µg/ml)	Mean ± SD (n= 3)	% RSD
2	0.224± 0.00208	0.93
4	0.378± 0.006	1.59
6	0.515± 0.00529	1.03
8	0.642± 0.01126	1.76
10	0.776± 0.01361	1.75

3. Accuracy:

Recovery tests were used to determine the method's accuracy at 80%, 100%, and 120%, a known quantity of the pure drug was added to the pre-analysed sample formulation. The percentage recovery and percentage relative standard deviation of the percentage recovery of different formulations were determined and are shown in Table 4, Table 5 & Table 6.

Table 6: Accuracy data for Telmisartan with BCG dye

Drug	% Spiked	Conc. from formulation	Std conc. added	Conc. recovered	% Recovery ± SD (n=3)	% RSD
Telmisartan	80	4	3.2	3.17	98.88 ± 0.41	0.41
	100	4	4	4.075	101.63 ± 0.46	0.46
	120	4	4.8	4.77	99.46 ± 0.2	0.20

Table 7: Accuracy data for Telmisartan with BCP dye

Drug	% Spiked	Conc. From formulation	Std. Conc. added	Conc. Recovered	% Recovery ± SD (n=3)	% RSD
Telmisartan	80	4	3.2	3.232	100 ± 0.601	0.60
	100	4	4	3.95	98.75 ± 0.35	0.36
	120	4	4.8	4.744	98.84 ± 0.75	0.76

4. Specificity

Specificity was performed by using blank and marketed formulation which has excipients. 7 ug/ml solution was prepared for BCG dye and 5 ug/ml for BCP dye from marketed formulation. The specificity of both colorimetric methods is demonstrated in figs. In which specific absorbance at 421 nm and 411 nm for BCG dye and BCP dye respectively.

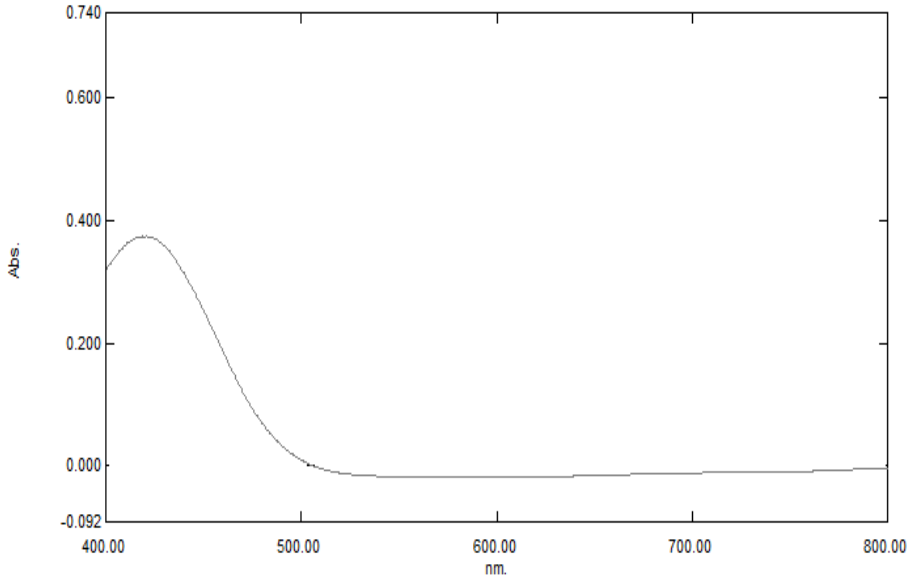


Figure 16: Specificity graph of TMS with BCG dye

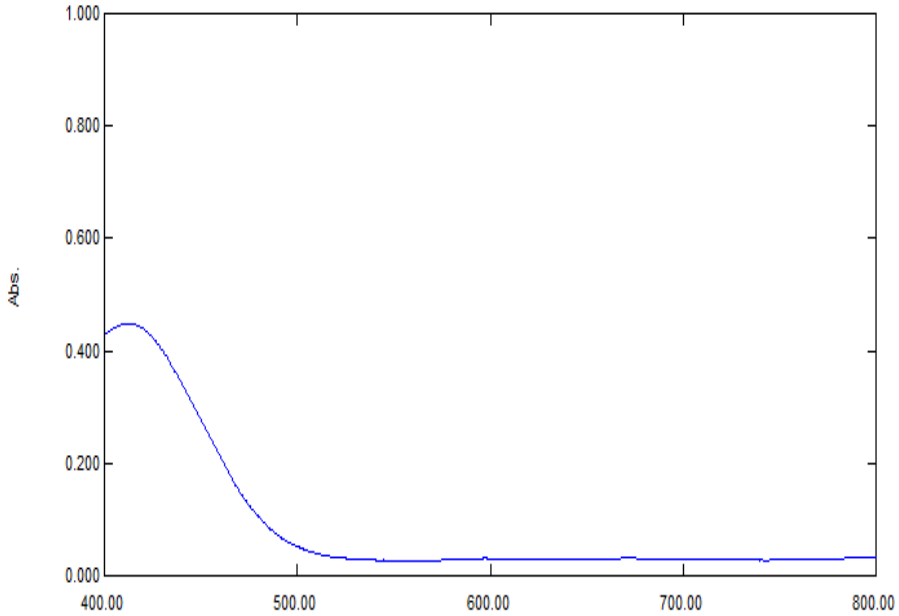


Figure 17: Accuracy data for Telmisartan with BCP dye

5. Sensitivity

The limit of detection (LOD) and limit of quantification (LOQ) were calculated using the given formula

LOD = 3.3×Ω/S
LOQ = 10×Ω/S
Where Ω = standard deviation of the intercept and S = mean of slope.

Values of both LOD and LOQ are shown in table.

6. Ruggedness

The ruggedness of the developed colorimetric methods was studied with two different smartphones. The % RSD of both these parameters was found to be less than 2 as shown in table.

Table 8: Method Ruggedness data for TMS with BCG dye

Parameter	Mean assay	SD	%RSD
Lab 1	99.14	1.07	1.08
Lab 2	100.71		
Smartphone 1	99.57	0.79	0.80
Smartphone 2	100.28		

Table 9: Method Ruggedness data for TMS with BCP dye

Parameter	Mean assay	SD	%RSD
Lab 1	101.98	1.95	1.95
Lab 2	100.25		
Smartphone 1	101.62	1.75	1.76
Smartphone 2	99.18		

Estimation of Telmisartan using Smartphone application:

The linearity for standard TMS was taken in the range of 4-12 µg/ml for BCG dye and 2- 10 µg/ml for BCP dye. The calibration curve and regression equation were generated by an equation as shown in figure. A color gradient was formed according to the intensity of the drug solution as shown in the figure.

Figure 18: Gradient of drug concentration by PhotoMetrix PRO Application

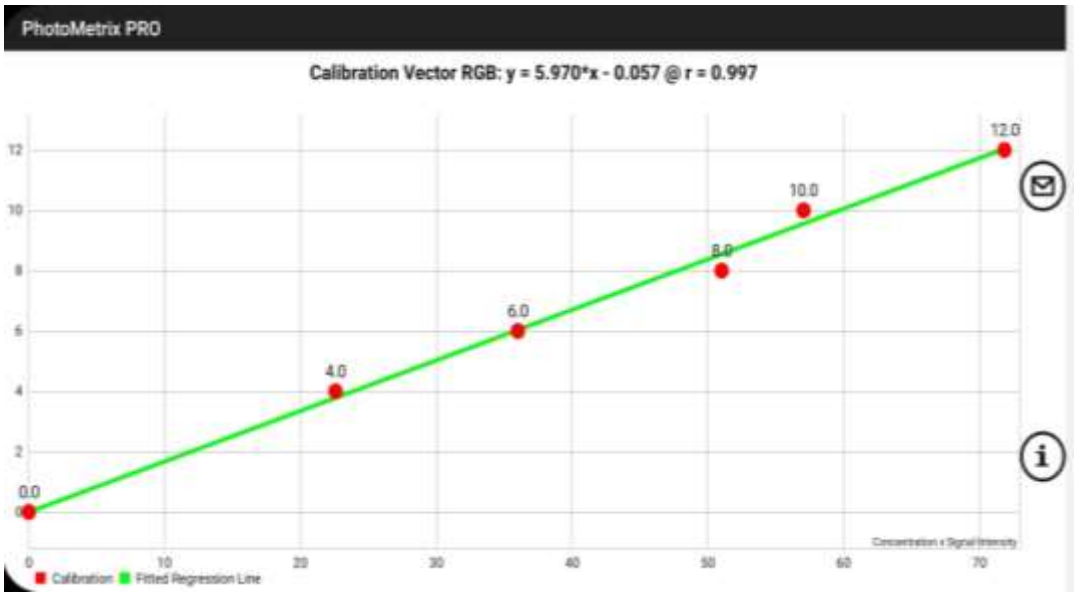


Figure 19: Calibration Graph by PhotoMetrix PRO Application

By using PhotoMetrix PRO application the image was captured and according to concentration, the linear regression equation was observed (Figure 10). Correlation coefficient (r^2) for PhotoMetrix PRO was found to be 0.997 and 0.999 for UV vis spectrophotometry with BCG dye respectively and with BCP dye Photometrix PRO gave 0.998 and 0.9994 for UV-VIS spectrophotometry. Regression equation data for both methods is as given in Table 11.

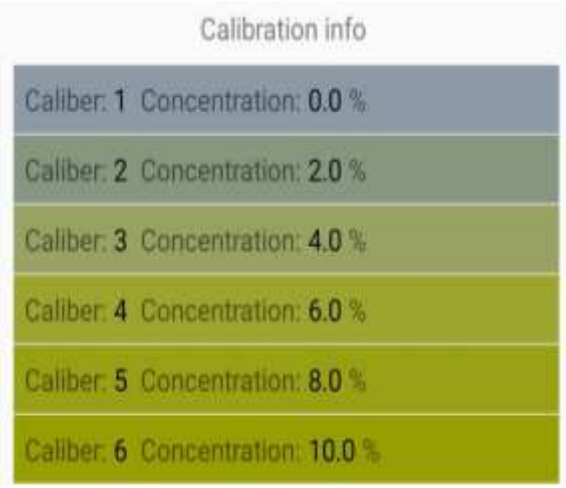


Figure 20: Gradient of Drug Concentration by PhotoMetrix PRO

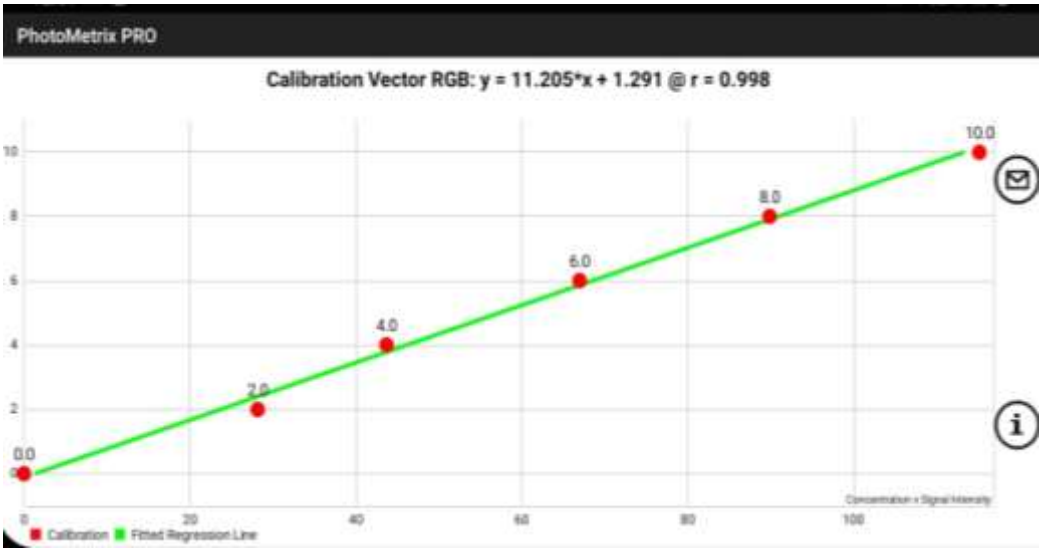


Figure 21: Calibration Graph by PhotoMetrix PRO Application

Table 10: Statistical Data for the regression equation for proposed method using BCG dye

Parameter	UV Method	PhotoMetrix Application
Linearity	4-12	4- 12
Regression equation	0.0489x + 0.0208	5.970x - 0.057
Slope	0.0497	5.970
Intercept	0.0160	0.057
Correlation Coefficient (r^2)	0.9997	0.997
LOD (µg /ml)	0.650	0.386
LOQ (µg /ml)	1.971	1.17

Table 11: Statistical Data for the regression equation for proposed method using BCP dye

Parameter	UV Method	PhotoMetrix Application
Linearity	2-10	2-10
Regression Equation	0.072x + 0.081	11.250x + 1.291
Slope	0.0706	11.25
intercept	0.079	1.29
Correlation Coefficient (r^2)	0.999	0.998
LOD (µg /ml)	0.2009	0.272
LOQ (µg /ml)	0.609	0.825

7. Analysis of marketed formulation

The assay of Formulations was found to be 98.7 %, 100.28%, 99.57% by UV and 99.14 %, 98.65 %, 100.71 % by PhotoMetrix for BCG dye which is within the acceptance criteria (98 – 102%). And for BCP dye it was found to be 100.2%, 98%, 101.9% for UV and 101.6%, 98.2% and 99% for PhotoMetrix for BCP dye which were also within the acceptance criteria. Result for assay is given in table.

Table 12: Comparison Between Uv and Photometrix PRO results for TMS with BCG dye for Assay of Marketed Formulations.

Marketed formulation	Method	Conc.	Conc. found	% recovery ± S.D.	%RSD
Marketed formulation 1	UV	7	6.91	98.7	1.14
	PhotoMetrix	7	6.94	99.14	1.26
Marketed formulation 2	UV	7	7.02	100.28	0.80
	PhotoMetrix	7	6.906	98.65	1.59
Marketed formulation 3	UV	7	6.97	99.57	1.02
	PhotoMetrix	7	7.05	100.71	0.59

Table 13:Comparison Between Uv and Photometrix PRO results for TMS with BCP dye for Assay of Marketed Formulations.

Marketed formulation	Method	Conc.	Conc. found	% recovery ± S.D	% RSD
Marketed formulation 1	UV	5	5.01	100.2	0.70
	PhotoMetrix	5	5.08	101.6	1.84
Marketed formulation 2	UV	5	4.9	98.02	1.79
	PhotoMetrix	5	4.91	98.2	1.68
Marketed formulation 3	UV	5	5.09	101.9	1.47
	PhotoMetrix	5	4.95	99.1	1.54

Comparison between UV spectrophotometric method and Smartphone Image Analysis by T -Test

In order to compare two different methods statistically, the student's t-test was used to compare and analyze the results for the sample. The data are as shown in the table. The calculated t-value was smaller than the critical t-value, therefore showing no statistical difference at a 95% confidence level between UV spectrophotometric and Smartphone Image Analysis.

Table 14: Applied Paired t-test results for TMS with BCG dye

Parameters	Variable 1	Variable 2
Mean (X)	99.67	99.42
Variance (s)	0.69625	1.50345
Observation (n)	5	5
Pearson Correlation	0.215297	
Hypothesized mean difference	0	
Df	8	
t-stat	0.376915	
P(T=t) one tail	0.358701	
tcritical one tail	1.894579	
P(T=t) two tail	0.717403	
tcritical two tail	2.364624	

Table 15: Applied Paired t-test results for TMS with BCP dye

Parameters	Variable 1	Variable 2
Mean	100.38	99.942
Variance	1.82352	1.15162
Observation	5	5
Pearson Correlation	0.262401	
Hypothesized mean difference	0	
Df	8	
t-stat	0.591148	
P(T=t) one tail	0.285371	
Tcritical one tail	1.859548	
P(T=t)	0.570742	
Tcritical two tail	2.306004	

CONCLUSION

Two simple, precise, accurate and sensitive methods were developed for the estimation of TMS in bulk and in its Tablet dosage form. The methods were validated according to the ICH (Q2) guidelines. These methods can be used for the routine analysis of the drugs in their pharmaceutical dosage form. It can be concluded that the application PhotoMetrix Pro can be used as an alternative to sophisticated and high-cost devices in quantitative analysis as it gave satisfactory results.

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