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Visible Spectrophotometric Methods for Determination of Gabapentin in Pharmaceutical Tablet and Capsule Dosage Forms

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Abstract

Two simple, rapid, accurate, precise and economic spectrophotometric methods have been developed for the estimation of gabapentin in pharmaceutical formulation. These methods are based on the formation of chloroform soluble ion-association complexes of gabapentin with bromocresol green in a phosphate buffer of pH 4.0 (Method I) and with bromothymol blue in a phosphate buffer of pH 4.0 (Method II). This property of the drug was followed for the development of colorimetric methods for analysis of drug. The complex of gabapentin with bromocresol green and bromothymol blue showed λ_{max} at 416 nm and 421 nm, respectively. The absorbance was found to increase linearly with increasing concentration of gabapentin, which was corroborated by the calculated correlation coefficient values (0.9966 and 00.9954, respectively for method I and method II). The systems obeyed the beer law in the range of 10-120 and 40-90 µg/ml for bromocresol green and bromothymol blue, respectively. Recovery studies gave satisfactory results indicating that none of common additives and excipients interfere the assay method. Various analytical parameters were evaluated and the results were validated by statistical data. The proposed methods are found to be simple, sensitive, accurate, precise and economic and can be successfully applied for the analysis of gabapentin in pharmaceutical dosage form.

Keywords: *Bromocresol green (BCG), Bromothymol Blue (BTB), Colorimetric analysis, Extractive spectrophotometry.*

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Introduction

Gabapentin (GBP) is chemically, 2-[1-(aminomethyl)cyclohexyl]acetic acid[1] and is used as an antiepileptic drug. GBP is also used in the treatment of neuropathic pain[2]. GBP is official in USP. USP[3] describes liquid chromatography method for its estimation. Literature survey reveals LC/MS/MS[4-7], GC/MS[8-9], HPTLC[10], HPLC[11-19], GLC[20], capillary electrophoresis[21-22], spectrofluorimetry[23-24] and colorimetry[25] methods for determination of GBP in pharmaceutical dosage forms as well as in biological fluids. Literature survey does not reveal any spectrophotometric method for estimation of GBP in pharmaceutical dosage forms. The present communication describes simple, sensitive, rapid, accurate and economical spectrophotometric methods for estimation of GBP in pharmaceutical dosage forms.

Materials and Methods

Gabapentin (99.80 %) was supplied by Torrent Research Centre, Gandhinagar, Gujarat, India as a gift sample. The commercial fixed dose products containing 300 mg GBP were procured from the local pharmacy. A Shimadzu 1700 UV Visible

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Spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 1 cm matched quartz cells was used for all absorbance measurements. Spectra were automatically obtained by UV-Probe system software (UV Probe version 2.10). A calibrated digital pH (ELICO, India) meter was used for pH measurements. Chloroform (AR grade, S.D. Fine Chemical Ltd., Mumbai, India), disodium hydrogen phosphate (AR grade, Finar Chemicals Ltd., India), potassium dihydrogen phosphate (AR grade, Finar Chemicals Ltd., India), bromocresol green (AR grade, Finar Chemicals Ltd., India), bromothymol blue (AR grade, Finar Chemicals Ltd., India), glacial acetic acid (AR grade, S.D. Fine Chemical Ltd., Mumbai, India), absolute alcohol (99%) (Baroda Chemical Industries, Baroda, Gujarat, India), sodium hydroxide (AR grade, S.D. Fine Chemical Ltd., Mumbai, India) and Whatman filter paper no. 41 (Millipore, USA) were used in the study.

Preparation of buffer solution (Phosphate buffer, pH 4.0)

Disodium hydrogen phosphate (504 mg) and potassium dihydrogen phosphate (301 mg) were accurately weighed and dissolved in water (100 ml). pH of solution was adjusted to 4.0±0.02 with glacial acetic acid.

Preparation of bromocresol green dye (0.05%)

Bromocresol green reagent (50 mg) was accurately weighed and transferred to 100 ml volumetric flask. Absolute ethanol (20 ml) and 0.1 N NaOH (0.72 ml) were added and mixed well and volume was made up to 100 ml with water.

Preparation of bromothymol blue dye (0.05%)

Bromothymol blue reagent (50 mg) was accurately weighed and transferred to 100 ml volumetric flask. Ethanol (95 %) (20 ml) and 0.02 M NaOH (4 ml) were added and mixed well and volume was made up to 100 ml with water.

Preparation of GBP standard stock solution and working standard solution

GBP (100 mg) was accurately weighed and transferred into 100 ml volumetric flask, dissolved and diluted with distilled water to obtain the concentration of 1000 µg/ml of GBP. Working standard solution (200 µg/ml) was prepared by diluting standard stock solution (20 ml) to 100 ml with distilled water.

Method

Method I (BCG Method)

Varying quantities of working standard drug solution (0.5, 1.0, 2.0, 3.0, 4.0, 5.0 and 6.0 ml) representing 10-120 µg/ml of gabapentin were transferred to a series of separating funnels. BCG dye solution (2.0 ml) and buffer solution (1.0 ml) were added to each separating funnels. Chloroform (10 ml) was added to each and shaken well and kept for few minutes. Later the extracts were taken into 10 ml volumetric flasks using multiple extractions, treated with anhydrous sodium sulphate and made up the volume with chloroform, and then absorbance of the solution was measured at 416 nm against reagent blank. The standard calibration plot of absorbance versus concentration was prepared to calculate the amount of the analyte drug in unknown samples. From the calibration graph, the regression line equation was generated and is used to calculate the concentration of drug from the sample solution. The sample solutions were prepared and also treated in similar manner and the exact amount of gabapentin present was deduced from the regression line equation.

Method II (BTB Method)

Varying quantities of working standard drug solution (2.0, 2.5, 3.0, 3.5, 4.0 and 4.5 ml) representing 40-90 µg/ml of gabapentin were transferred to a series of separating funnels. BTB dye solution (2.0 ml) and buffer solution (1.0 ml)

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were added to each separating funnels. Chloroform (10 ml) was added to each and shaken well and kept for few minutes. Later the extract were taken into 10 ml volumetric flasks using multiple extractions, treated with anhydrous sodium sulphate and made up the volume with chloroform, and then of the solution was measured at 421 nm against reagent blank. The standard calibration plot of absorbance versus concentration was prepared to calculate the amount of the analyte drug in unknown samples. The sample solutions were prepared and also treated in similar manner and the exact amount of gabapentin present was deduced from the regression line equation.

Optimization of different conditions

Condition under which reaction of gabapentin with dyes fulfill the essential requirements was investigated. Various conditions like pH and volume of buffer, wavelength of maximum absorbance and stability of dye-drug complex were optimized at room temperature.

Selection of suitable pH buffer solution

Ion-pair complex of drug with dye was prepared at different pH in presence of different buffer having different pH (2.0 to 5.5). This ion-pair complex was extracted in chloroform layer with multiple extractions. Maximum absorbance was shown by the complex which was prepared in phosphate buffer having pH 4.0 for BCG and BTB.

Selection of wavelength showing maximum absorbance

The standard solution of gabapentin after extraction with chloroform scanned over the range of 400 nm to 800 nm wavelengths. It showed λmax at 416 nm and at 421 nm for BCG and BTB respectively.

Optimization of volume of buffer solution

Volume of buffer was optimized by changing volume of buffer and other parameters were kept constant. Buffer solution of pH 4.0 for BCG and BTB were used. The working standard solution (5.0 ml) was transferred in seven separating funnels, different volume of buffer solutions (pH 4.0 buffer for BCG and BTB) was added in the different separating funnels and BCG or BTB was added in excess in each. Shaken well and extracted with (5 + 5 ml) of chloroform. Later, the extracts were taken into 10 ml volumetric flasks, treated with anhydrous sodium sulphate and volume was made up with chloroform and then absorbance were measured at 416 nm and 421 nm for BCG and BTB, respectively. It was found that after addition of 2.0 ml of pH 4.0 buffer in BCG and 2.5 ml of pH 4.0 buffer in BTB, absorbance became constant. Hence 2.0 ml of pH 4.0 buffer and 2.5 ml of pH 4.0 buffers were optimized for BCG method and BTB method, respectively.

Stability study of drug dye complexes

The stability of the drug dye complexes was determined individually for both the dyes (BCG and BTB) by following procedure. GBP working standard solution (5.0 ml) was pipette out and added to a separating funnels. Buffer solution (2 ml) and BCG solution (in excess) were added to each. Shaken well and extracted with 10 ml of chloroform. Later the extracts were taken into 10 ml volumetric flasks, treated with anhydrous sodium sulphate and made up the volume with chloroform. The absorbances were measured periodically at an interval of 30, 60, 90, 120, 180, 240, 300 and 360 minutes at 416 nm. Same procedure was applied for the BTB method using buffer solution (2.5 ml) and BTB solution (in excess), and then absorbances were measured at 421 nm. Finally it was found that BCG-GBP complex was stable at least for 6 hrs, whereas BTB-GBP complex was stable at least for 4 hrs.

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Validation of the proposed methods

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines[26].

Linearity

Method I (BCG Method)

Calibration curve was plotted over a concentration range of 10-120 µg/ml for gabapentin. From the working standard solution, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0 and 6.0 ml were transferred to a series of separating funnels. Buffer solution (2.0 ml) was added to each separating funnels, then BCG (in excess) was added and shaken well, 10 ml chloroform was added to each and shaken well and kept for few minutes. Later the extracts were taken into 10 ml volumetric flasks using multiple extractions, treated with anhydrous sodium sulphate and made up the volume with chloroform, and then absorbance of the solution was measured at 416 nm against reagent blank. The standard calibration plot of absorbance versus concentration was prepared to calculate the amount of the analyte drug in tablet and capsule sample solutions.

Method II (BTB Method)

Calibration curve was plotted over a concentration range of 40-90 µg/ml for gabapentin. From the working standard solution, 2.0, 2.5, 3.0, 3.5, 4.0 and 4.5 ml was transferred to a series of separating funnels. Buffer solution (2.5 ml) was added to each separating funnels, then BTB solution (in excess) was added and shaken well, 10 ml of chloroform was added to each and shaken well and kept for few minutes. Later the extracts were taken into 10 ml volumetric flasks using multiple extractions, treated with anhydrous sodium sulphate and made up the volume with chloroform, and then absorbance of the solution was measured at 421 nm. The standard calibration plot of absorbance versus concentration was prepared to calculate the amount of the analyte drug in tablet and capsule sample solutions.

Accuracy (% Recovery)

The accuracy of the methods was performed by calculating recovery of gabapentin by the standard addition method. Known amounts of standard solutions of gabapentin were added at 50, 100 and 125% levels to prequantified sample solutions of 40 µg/ml gabapentin for both BCG and BTB method. Each sample was prepared in triplicate at each level. The amount of gabapentin was estimated by applying obtained values to regression equation.

Method precision (% Repeatability)

The precision of the instrument was checked by repeated scanning and measurement of the absorbance of solutions of 50 µg/ml GBP (n = 6) and 70 µg/ml GBP (n = 6) for BCG and BTB, respectively without changing the parameters for the method. The repeatability was expressed in terms of % relative standard deviation (% RSD) and is reported in Table 5.

Intermediate precision (Reproducibility)

The intraday and interday precision of the proposed methods were performed by analyzing the corresponding responses 3 times on the same day and on 3 different days for 6 different concentrations of standard solutions of GBP (20, 40, 60, 80, 100 and 120 µg/ml) for BCG and GBP (40, 50, 60, 70, 80 and 90 µg/ml) for BTB. The precision were reported in terms of % relative standard deviation (% RSD) and are reported in Table 5.

Limit of detection and Limit of quantification

The limit of detection (LOD) and the limit of quantification (LOQ) of the drug was derived by calculating the signal-to-noise ratio (S/N, i.e., 3.3 for LOD and 10 for LOQ) using the following equations as per International Conference on Harmonization (ICH) guidelines[26].

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$LOD = 3.3 \times \sigma/S$

$LOQ = 10 \times \sigma/S$

Where σ = the standard deviation of the response and S = Slope of calibration curve.

Determination of gabapentin in pharmaceutical formulations (Tablet and Capsule)

Twenty tablets were accurately weighed and average weight was determined. The tablets were powdered in glass mortar. The quantity of the powder equivalent to 100 mg of gabapentin was transferred to a 100 ml volumetric flask. The content was mixed with diluent (50 ml), sonicated for 30 min. to dissolve the drug as completely as possible and the volume was adjusted up to the mark with diluent. The solution was then filtered through whatman filter paper no. 41 (1000 µg/ml). The above solution (20 ml) was diluted to 100 ml with diluent (200 µg/ml). An aliquot of this solution was taken and analyzed as described. The amount of gabapentin present in tablet sample solution was determined by fitting the responses into the respective regression equations for gabapentin in both the methods.

The content of twenty capsules was accurately weighed and the quantity of the powder equivalent to 100 mg of gabapentin was transferred to a 100 ml volumetric flask. The content was mixed with diluent (50 ml), sonicated for 30 min. to dissolve the drug as completely as possible and the volume was adjusted up to the mark with diluent. The solution was then filtered through whatman filter paper no. 41 (1000 µg/ml). The above solution (20 ml) was diluted to 100 ml with diluent (200 µg/ml). An aliquot of this solution was taken and analyzed as described. The amount of gabapentin present in tablet sample solution was determined by fitting the responses into the respective regression equations for gabapentin in both the methods.

Results and Discussion

During the course of study, it was observed that the drug formed colored ion-association complexes with bromocresol green and bromothymol blue which were soluble in chloroform. This property of the drug was followed for the development of sensitive colorimetric methods for analysis of drug. The complex of gabapentin with BCG and BTB showed λ_{max} at 416 nm and 421 nm, respectively. The optimum conditions for color development had been established by varying the different parameters involved. The methods were optimized for different conditions like pH and volume of buffer solution for both dyes to obtain maximum sensitivity. It was found that maximum absorbance was shown by the complex which was prepared in phosphate buffer having pH 4.0±0.02 for BCG and BTB (Figure 1 and 2, respectively). It was also observed that after addition of 2.0 ml of pH 4.0 buffer in BCG and 2.5 ml of pH 4.0 buffer in BTB, absorbance became constant. Hence 2.0 ml of pH 4.0 buffer and 2.5 ml of pH 4.0 buffers were selected for BCG method and BTB method, respectively (Figure 3 and 4, respectively).

Both methods involve formation of ion-associated complex with BCG and BTB at pH 4.0±0.02 phosphate buffer, exhibiting wavelength of maximum absorbances at 416 nm for BCG and 421 nm for BTB (Figure 5 and 6, respectively). The proposed methods were based on addition of drug in its ionized form to an ionized dye, yield a salt (ion-pair) that was extracted into an organic solvent such as chloroform. The indicator dye was added in excess and the pH of the aqueous solution was adjusted to a value where both the drug and dye were in the ionized forms. The ion

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pair was separated from the excess indicator by extraction into the organic solvent. In these methods, beer's law was obeyed with BCG and BTB in the concentration range of 10-120 µg/ml and 40-90 µg/ml, respectively.

The sandell's sensitivity is indicative of the sensitivity of the methods and was found to be 0.1138 and 0.1750 respectively for method I and method II for gabapentin. Molar absorptivity also indicates sensitiveness of the methods and was found to be 1627.70 and 1123.72 for method I and method II for gabapentin. For testing the accuracy and reproducibility of the proposed methods, recovery studies were performed. The data obtained by recovery studies indicate non-interference from the excipients used in the formulations. The percentage recoveries were close to 100% and %RSD were within 2% indicate the accuracy of the methods. This study revealed that the common excipients and other additives are usually present in the tablet dosage forms do not interfere in the analysis. The data of recovery studies for capsule and tablet are given in Table 1 and 2, respectively. These developed methods were used for the estimation of gabapentin from marketed tablet and capsule formulations. The data of results of pharmaceutical capsule and tablet formulations are shown in Table 3 and 4, respectively. Optical characteristics and summary of all the validated parameters for both the methods for gabapentin is reported in Table 5.

Conclusion

The proposed spectrophotometric methods were found to be, simple, sensitive, accurate and precise for determination of gabapentin in tablet dosage form. The method utilizes easily available reagents and solvents for analysis of gabapentin hence the methods were also economic for estimation of gabapentin from tablet and capsule dosage forms. The common excipients and other additives are usually present in the tablet and capsule dosage forms do not interfere in the analysis of GBP in both the methods, hence it can be conveniently adopted for routine quality control analysis of the drug in pharmaceutical formulations.

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TABLE 1: RESULTS OF RECOVERY STUDIES (CAPSULE)

Drug	Level	Amount of sample taken (µg/ml)	Amount of standard spiked (%)	Mean % Recovery ± S.D.* (n = 3)
Gabapentin-BCG	I	40	50 %	99.23 ± 0.77
	II	40	75 %	100.4 ± 0.77
	III	40	125 %	100.5 ± 1.45
Gabapentin-BTB	I	40	50 %	99.62 ± 0.29
	II	40	75 %	99.88 ± 0.25
	III	40	125 %	100.9 ± 0.56

* SD is standard deviation and n is no of replicate.

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TABLE 2: RESULTS OF RECOVERY STUDIES (TABLET)

Drug	Level	Amount of sample taken (µg/ml)	Amount of standard spiked (%)	Mean % Recovery ± S.D.* (n = 3)
Gabapentin-BCG	I	40	50 %	99.23 ± 0.77
	II	40	75 %	99.36 ± 1.18
	III	40	100 %	99.91 ± 1.07
Gabapentin-BTB	I	40	50 %	98.78 ± 0.11
	II	40	75 %	99.12 ± 0.25
	III	40	100 %	101.4 ± 0.05

* SD is standard deviation and n is no of replicate.

TABLE: 3 ANALYSIS OF MARKETED FORMULATION (CAPSULE DOSAGE FORM) OF GBP BY PROPOSED METHODS (n = 6)

Sample No.	Label Claim	Amount Found		% Label Claim	
	GBP (mg/cap)	GBP (mg/cap)		GBP (mg/cap)	
		BCG	BTB	BCG	BTB
1	300	301.1	298.6	100.4	99.52
2	300	304.8	297.7	101.6	99.22
3	300	302.0	297.0	100.7	99.01
4	300	301.1	297.9	100.4	99.32
5	300	297.3	296.7	99.11	98.91
6	300	304.8	298.8	101.6	99.62
Mean				100.6	99.27
S. D.				0.93	0.28

SD is standard deviation and GBP is gabapentin

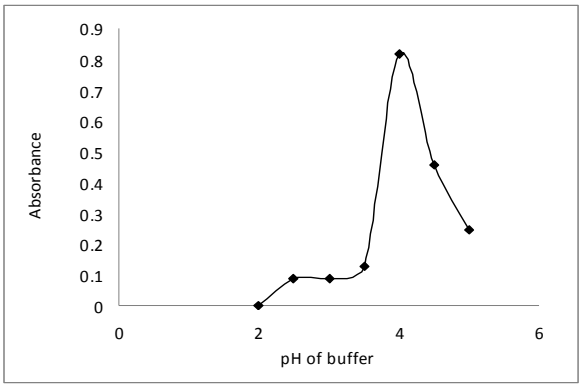

FIG. 1. OPTIMIZATION OF PH OF BUFFER FOR GBP-BCG COMPLEX.

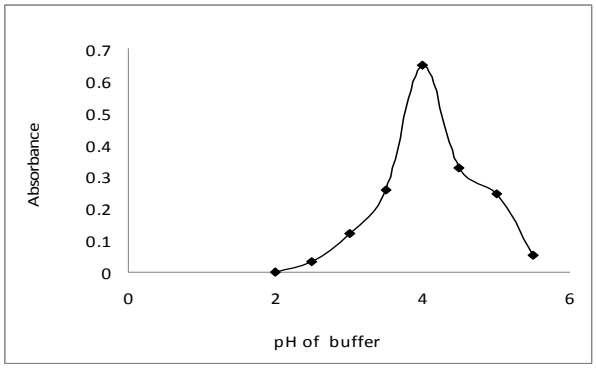

FIG. 2. OPTIMIZATION OF PH OF BUFFER FOR GBP-BTB COMPLEX.

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TABLE 4: ANALYSIS OF MARKETED FORMULATION (TABLET DOSAGE FORM) OF GBP BY PROPOSED METHODS (n = 6)

Sample No.	Label Claim	Amount Found		% Label Claim	
	GBP (mg/tab)	GBP (mg/tab)		GBP (mg/tab)	
		BCG	BTB	BCG	BTB
1	300	300.5	295.1	100.2	98.36
2	300	294.9	294.2	98.31	98.07
3	300	303.2	293.6	101.1	97.87
4	300	296.8	295.4	98.92	98.46
5	300	294.0	295.4	98.00	98.46
6	300	299.5	294.8	99.85	98.27
Mean				99.38	98.25
S. D.				1.18	0.24

SD is standard deviation and GBP is gabapentin

TABLE 5: REGRESSION ANALYSIS DATA AND SUMMARY OF VALIDATION PARAMETERS FOR THE PROPOSED METHODS

Parameters	BCG	BTB
λ_{max}, nm	416	421
Beer Lambert's law limits (µg/ml)	10-120	40-90
Molar absorptivity (l mol^{-1} cm^{-1})	1627.70	1123.72
Sandell's sensitivity (µg/cm^2 /0.001 Absorbance unit)	0.1138	0.1750
Regression equation y = mx + c	y = 0.0065x + 0.0895	y = 0.0145x - 0.4744
Slope (m)	0.0065	0.0145
Intercept (c)	0.0895	-0.4744
Correlation coefficient (r^2)	0.9966	0.9954
Limit of detection (LOD) (µg/ml)	2.90	10.86
Limit of quantification (LOQ) (µg/ml)	8.77	32.91
Repeatability (% RSD, n = 6)	0.357	0.330
Precision (% RSD)		
Interday (n = 3)	0.77 - 1.90	0.87 - 1.77
Intraday (n = 3)	0.14 - 1.08	0.31 - 1.63

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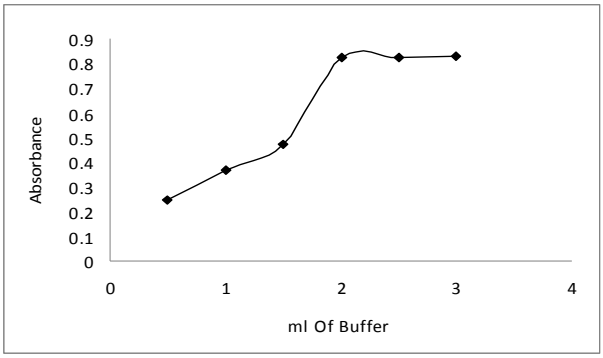

FIG. 3. OPTIMIZATION OF VOLUME OF BUFFER FOR GBP-BCG COMPLEX.

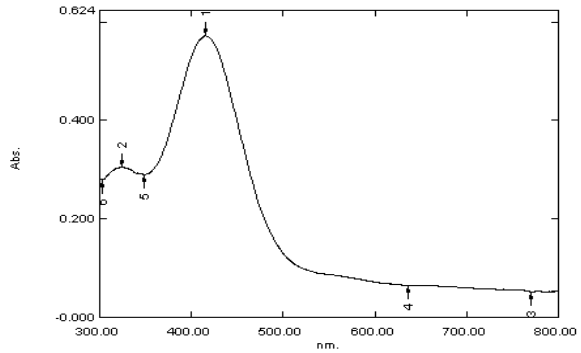

FIG. 4. OPTIMIZATION OF VOLUME OF BUFFER FOR GBP-BTB COMPLEX.

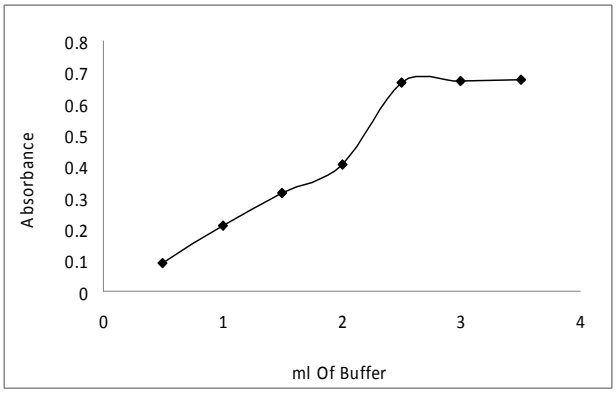

FIG. 5. REPRESENTATIVE ABSORPTION SPECTRA OF GBP-BCG SHOWING ABSORPTION MAXIMA AT 416 NM.

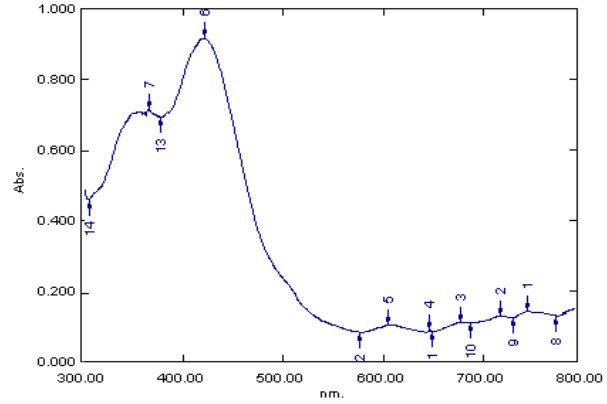

FIG. 6. REPRESENTATIVE ABSORPTION SPECTRA OF GBP-BTB SHOWING ABSORPTION MAXIMA AT 421 NM.

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