International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.2, No.1, pp 624-632, Jan-Mar 2010

Validated spectrophotometric determination of pantoprazole sodium in pharmaceuticals using ferric chloride and two chelating agents

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ABSTRACT: Two simple, sensitive and selective spectrophotometric methods for the determination of pantoprazole sodium sesquihydrate (PSS) have been developed and validated. The methods are based on the reduction of ferric chloride by PSS in neutral medium and subsequent chelation of iron (II) with 1, 10-phenanthroline (phen) (method A) or 2, 2´-bipyridyl (bipy) (method B). The resulting red colored chromogens are measured at 510 and 520 nm, for method A and method B, respectively. Under the optimum conditions, Beer's law is obeyed in the concentration ranges of 0.25-4.0 and 2.5-50 µg ml^{-1} with molar absorptivity values of 5.35 x 10^4 and 0.789 x 10^4 l $mol^{-1}cm^{-1}$ and Sandell sensitivities 0.008 and 0.055 µg cm^{-2} for method A and method B, respectively. The limits of detection (LOD) and quantification (LOQ) are also reported. The proposed methods were applied successfully to the determination of PSS in pure form and in its tablets and no interference was observed from common excipients present in pharmaceutical formulations. Statistical comparison of the results of the proposed procedures with those obtained by the reference method showed excellent agreement and indicated that no significant difference in accuracy and precision. The validity of the methods was established by recovery studies *via* standard-addition technique with satisfactory results.
KEYWORDS*:* pantoprazole sodium sesquihydrate, determination, ferric chloride, complexation reactions, pharmaceuticals.

INTRODUCTION

Pantoprazole sodium sesquihydrate (PSS) is widely used for the treatment of gastric ulcers [1, 2] through inhibition of H^+, K^+,-ATP-ase in gastric parietal cells. PSS reduced the gastric acid secretion regardless the nature of stimulation. It is chemically known as sodium 5- (difluoromethoxy) - 2 – [[(3, 4-dimethoxy-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole sesquihydrate (Fig. 1). Several methods have been reported for the determination of PSS in pharmaceutical formulations and in biological materials including high performance liquid chromatography (HPLC) [3-6], densitometric HPTLC [7], capillary electrophoresis [8, 9], derivative UV-spectrophotometry [10] and difference UV-spectrophotometry [11]. Concerning visible spectrophotometry, few methods have been reported [12-17] for the determination of PSS. Unfortunately, the spectrophotometric methods reported for determination of PSS by Salama et al [12, 13], Moustafa[14] are associated with some drawbacks such as use of heating step, narrow linear ranges, and measurement at shorter wavelengths. The performance of the proposed spectrophotometric methods was compared with other existing spectrophotometric methods (Table 1).

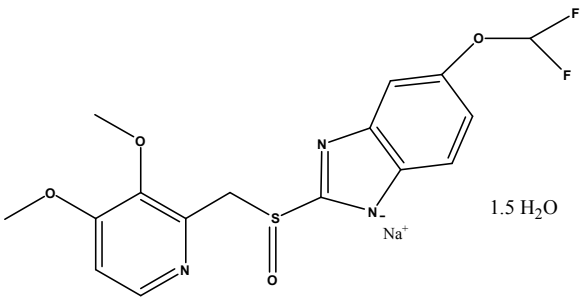

Fig. 1. Structure of pantoprazole sodium sesquihydrate

Table1. Comparison of the performance characteristic of the existing spectrophotometric methods with the proposed methods.

Sl. No.	Reagent/s used	Methodology	Linear range ($\mu g\ ml^{-1}$) and Є in $l\ mol^{-1}cm^{-1}$	Remarks	Ref.
1.	Trivalent iron	1:2 chelated in EtOH medium measured at 455 nm.	30-300	Requires heating (60°C), ethanolic medium used and less sensitive.	13
2.	a) DDBQ	C-T complex measured at 457 nm.	10-60	Narrow linear range, use of organic solvent.	14
	b) Iodine	C-T complex measured at 293 and 359 nm.	18-142	Measured at shorter wavelength, use of organic solvent.	
	c) Cu (II)-eosin	Ternary complex measured at 549 nm.	4-26	Required heating (70°C), narrow linear range, involves liquid-liquid extraction and use of organic solvent medium.	
3.	BrO_3^--Br^-/MO, IC	Unbleached color of MO/IC measured at 510/ 610 nm.	0.12-1.5 (Є=$1.8x10^5$) 0.5-6.0 (Є=$4.1x10^4$)	Less selective, accurate concentration of bromate and dyes to be known.	15
4.	BrO_3^--Br^- / Fe(II)-SCN^- or Fe(II)-tiron	Fe(II)-SCN^- complex or Fe(II)-tiron complex measured at 470 or 670 nm.	0.12-1.25 (Є=$2.2x10^5$) 0.25-2.5 (Є=$1.2x10^5$)	Less selective	16
5.	Potassium ferricyanide and ammonium ferric sulphate	Prussian blue measured at 725 nm	5-90	Required heating (35°C) and the rate of reaction is highly dependent on temperature	17
6.	Iron (III) chloride with I) 1, 10-phenan-throline	Red colored chromogen (ferroin) formed is measured at 510 nm	0.25-4.0 (Є=5.35×10^4)	Sensitive, wide linear dynamic ranges, use of ecofriendly chemicals, use of aqueous system	Present methods
	II) 2,2´Bipyridyl	Red colored chromogen [Fe(II)-Bipy complex]formed is measured at 520 nm	2.5-50.0 (Є=0.78×10^4)		

DDBQ. Dichloro dicyanobenzoquinone; MO. Methyl orange; IC. Indigo carmine; BPD. 2,2'-Bipyridyl: SCN. Thiocyanate.

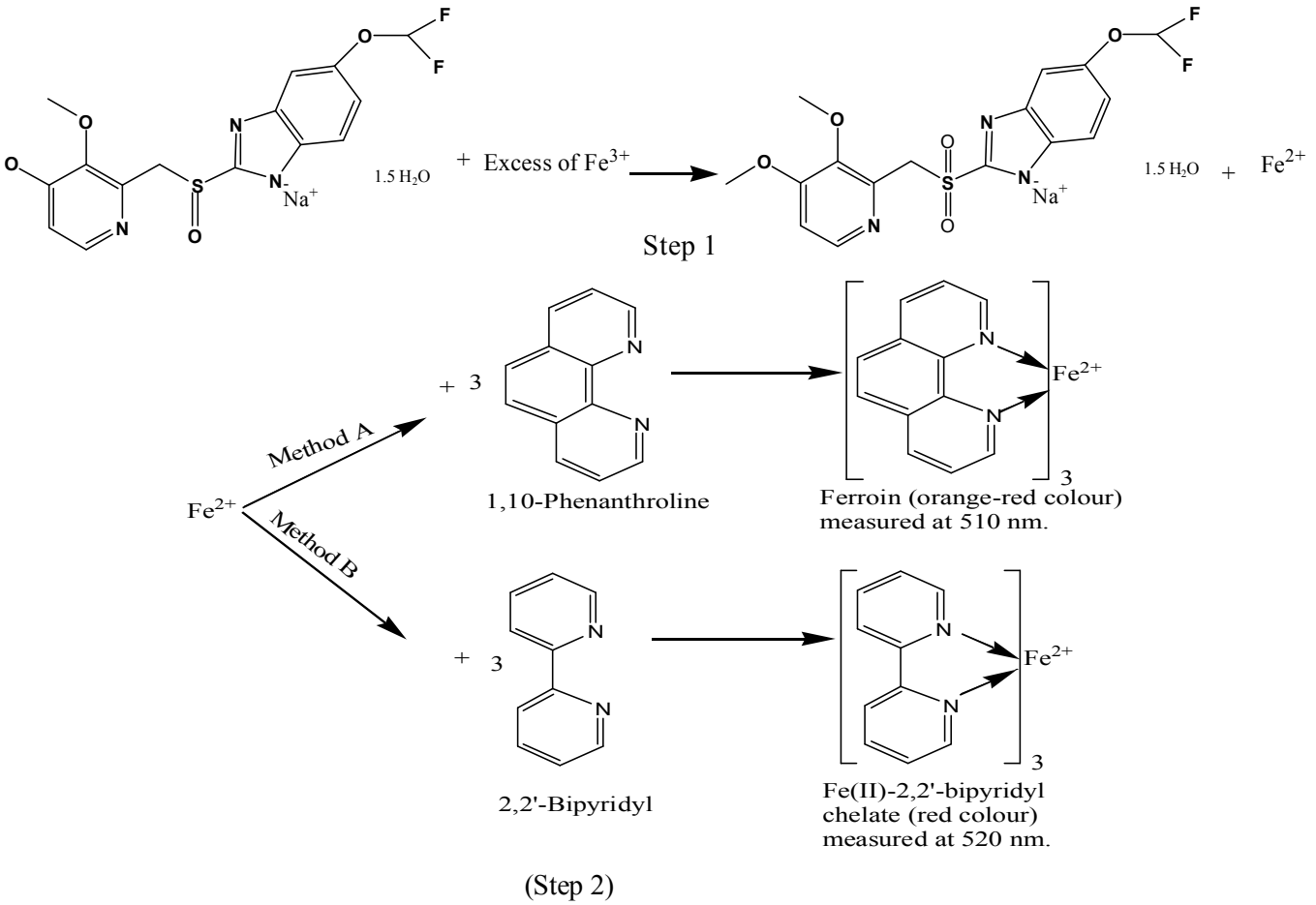

Fig. 2. Possible reaction scheme for the proposed methods

The present work aims to demonstrate two simple, accurate, sensitive and selective visible spectrophotometric methods suitable and convenient for the determination of PSS in pure form and in dosage forms. Scanning for the published methods for the determination of PSS shows that the proposed methods have not been previously applied; consequently the present work describes two new spectrophotometric methods which are less expensive than the published HPLC and capillary electrophoresis. The present analytical procedures involved oxidation of PSS with ferric chloride and determining the iron (II) produced by complexing either with 1, 10-phenanthroline or 2, 2´-bipyridyl. The developed methods were validated according to the current ICH guidelines[18] for linearity, range of determination, selectivity, accuracy and precision.

MATERIALS AND METHODS

Apparatus

All absorbance measurements were made using a Systronics model 106 digital spectrophotometer (Ahmedabad, India) provided with 1-cm matched quartz cells.

Reagents and standards

All chemicals and reagents used were of analytical-reagent grade and distilled water was used throughout the investigation.

Standard PSS Solution

Pharmaceutical grade PSS certified to be 98.98 % pure was received as gift from Cipla India Ltd, Mumbai, India, and used as received. Standard PSS (500 µg ml^{-1}) solution was prepared by dissolving calculated quantity of pure drug in water, and then diluted to 10 and 100 µg ml^{-1} concentrations.

Two brands of tablets containing PSS, pantodac-20 (Aristo Pharmaceuticals Ltd., Mumbai, India) and pantop-40 (Cipla Ltd, Mumbai, India), used in the investigation were purchased from local commercial sources.

Ferric chloride (0.0033 M)

Aqueous solution of 0.05 M ferric chloride hexahydrate (S. D. Fine Chem.,Mumbai, India) was prepared by dissolving 1.35 g of the chemical in 100 ml of water and stored in a dark bottle. The stock solution was then diluted appropriately with water to get a working concentration of 0.0033 M for both methods. The solution was prepared afresh just before using in the experiment.

1, 10-phenanthroline (0.01 M)
Prepared by dissolving 198 mg of the chemical (Qualigens Fine Chemicals, Mumbai, India, assay 100%) in water and diluted to 100 ml with water.

2,2´-bipyridyl (0.01 M)
Prepared by dissolving 156 mg of the chemical (Qualigens Fine Chemicals, Mumbai, India, assay 100%) in water and diluted to volume in a 100 ml calibrated flask.

O-phosphoric acid (0.02 M)
Concentrated acid (Merck, Mumbai, India, sp. gr. 1.75) was appropriately diluted with water to get the required concentration.

Procedures

Method A
Different aliquots (0.25, 0.5, 1.0, 2.0, 3.0 and 4.0 ml) of the standard 10 µg ml^{-1} PSS solution were accurately measured and transferred into a series of 10 ml calibrated flasks by means of a micro burette and the total volume was adjusted to 5 ml by adding water. To each flask, 1.5 ml of ferric chloride (0.0033 M) and 2.5 ml of 1, 10-phenanthroline (0.01 M) were successively added followed by 0.5 ml of O-phosphoric acid (0.02 M), and the volume was brought to 10 ml with distilled water. The flasks were stoppered, the content mixed well and the flasks were allowed to stand for 30 min with occasional shaking. Then, the absorbance of each solution was measured at 510 nm against the reagent blank.

Method B
Varying aliquots (0.25, 0.5, 1.0. 2.0, 3.0, 4.0 and 5.0 ml) of standard PSS solution (100 µg ml^{-1}) were accurately measured into a series of 10 ml calibrated flasks by means of a micro burette and the total volume was brought to 5 ml by adding water. To each flask were added 1 ml of ferric chloride (0.0033 M) and 2 ml of 2, 2´-bipyridyl (0.01 M) followed by 0.5 ml of O- phosphoric acid (0.02 M). The content was mixed well and diluted to the mark with distilled water. The absorbance of each solution was measured at 520 nm against reagent blank after 20 min.
In either spectrophotometric method, a standard graph was prepared by plotting the increasing in absorbance values *versus* concentration of PSS (µg ml^{-1}). The concentration of the unknown was read from the standard graph or computed from the respective regression equation derived using the Beer's law data.

Procedure for tablets
The contents of ten capsules were emptied, weighed and powdered. A portion equivalent to 50 mg of PSS was accurately weighed and transferred into a 100 ml calibrated flask, 40 ml of acetone were added and the content shaken thoroughly for 15-20 min to extract the drug, and filtered on Whatman No. 42 filter paper. The filtrate and washings were evaporated to dryness. The residue was dissolved in water and diluted to the mark with water. First 10 ml of the filtrate was discarded and a suitable aliquot of the filtrate (500 µg ml^{-1} PSS) was diluted stepwise with water to get 10 and 100 µg ml^{-1}concentrations for method A and method B, respectively. The assay of PSS was completed by following the recommended procedures.

Placebo blank analysis
A placebo blank of the composition: talc (10 mg), starch (10 mg), acacia (10 mg), methyl cellulose (10 mg), sodium citrate (10 mg), magnesium stearate (15 mg) and sodium alginate (10 mg) was extracted with acetone and its solution was prepared as described under 'procedure for tablets', and then subjected to analysis.

Procedure for the determination of pantoprazole sodium sesquihydrate in synthetic mixture
To the placebo blank of the composition described above, 50 mg of PSS were added and homogenized, transferred to a 100 ml standard flask and solution was prepared after extraction of PSS with acetone as described under procedure for tablets. The synthetic mixture solution (500 µg ml^{-1} in PSS) was then diluted stepwise with water to obtain working concentrations of 10 and 100 µg ml^{-1} in PSS for method A and method B, respectively. A convenient aliquot was then subjected to analysis by either method described above. This analysis was done to study the interference of excipients such as talc, starch, acacia, methyl cellulose, sodium citrate, magnesium stearate and sodium alginate.

RESULTS AND DISCUSSION

The main purpose of this study was to establish simple spectrophotometric methods for the determination of PSS in pure form and in its pharmaceutical dosage forms. PSS contains a sulfoxide group, which could be oxidized to sulfone group [19, 20] and the drug was found to undergo oxidation with $FeCl_3$ in neutral medium. The complex formation of Fe^{2+} with 1, 10-phenanthroline [21] and 2, 2´-bipyridyl [22-24] has long been recognized. However, these reactions have not been applied yet for the determination of PSS, thus offering a suitable approach for the indirect assay of PSS using $FeCl_3$. The proposed methods involved two steps:

1. Oxidation of PSS with excess $FeCl_3$ in neutral medium
2. Determination of the resulting Fe^{2+} by subsequent chelation with either Phen or Bipy and measuring the absorbance at the respective wavelength (Fig. 2). The probable reaction mechanism is shown in Fig. 3.

Optimization of the reaction conditions

Investigations were carried out to achieve maximum color development in the quantitative determination of PSS. The influence of each of the following variables on the reaction was tested. When the Fe^{3+} concentration was increased, the absorbance value of reagent blank was found to increase. Hence, by considering the sensitivity of the reaction with a minimum blank absorbance, 1.5 ml and 1 ml of 0.0033 M ferric chloride in a total volume of 10 ml were found optimum in method A and method B, respectively and used throughout the experiment.

Even though, oxidation of PSS by Fe^{3+} and subsequent chelation of Fe^{2+} with either Phen or Bipy was found to occur in neutral medium, the presence of O-phosphoric acid was necessary to increase the stability of the developed red color chelate by maintaining the desired pH. A 0.5 ml of 0.02 M O-phosphoric acid in a total volume of 10 ml was found adequate in both the methods. The optimum volume of phen and bipy used for the production of maximum and reproducible color intensity was found to be 2.5 ml of 0.01 M phen for method A (Fig. 4) and 2 ml of 0.01 M bipy for method B (Fig. 4) in a total volume of 10 ml. The standing times for full color development were found to be 30 and 20 min for method A and method B, respectively; and the color was stable for 30 min thereafter in both methods.

Method Validation

The methods were validated according to International Conference on Harmonization (ICH) guidelines [18] for linearity and sensitivity, limits of detection and quantification, precision, accuracy, selectivity and recovery.

Linearity and sensitivity

In both the cases, Beer's law plots were linear with good correlation coefficients (0.9986, 0.9994) in the concentration ranges of 0.25-4.0 and 2.5-50.0 µg ml^{-1} for method A and method B, respectively (Fig. 5 and Fig. 6). The regression analysis of the plot using the method of least squares was made to evaluate the intercept (a), slope (b), regression coefficient (r) and standard deviations of slope and intercept (Table 2).

The moderately high sensitivity of the methods was indicated by the fairly high value of molar absorptivity and low values of sandell sensitivity.

Limits of detection (LOD) and quantification (LOQ)

The limits of detection (LOD) and quantification (LOQ) were calculated according to the same guidelines using the formulae:

LOD=3.3σ/s and LOQ=10σ/s

where σ is the standard deviation of five reagent blank determinations and s is the slope of the calibration curve. The LOD and LOQ values are reported in Table 2.

Precision and accuracy

Intra-day precision and accuracy of the proposed methods were evaluated by replicate analysis (n=5) of calibration standards at three concentration levels (1.0, 2.0 and 3.0 µg ml^{-1} for method A and 20.0, 30.0 and 40.0 µg ml^{-1} for method B). Inter-day precision and accuracy were determined by assaying the calibration standards at the same concentration levels on five consecutive days. Precision and accuracy were based on the calculated relative standard deviation (RSD, %) and relative error (RE, %) of the found concentration compared to the theoretical one, respectively (Table 3).

Selectivity

The proposed methods were tested for selectivity by placebo blank and synthetic mixture analyses. A convenient aliquot of the placebo blank solution prepared was subjected to analysis by the proposed methods according to the recommended procedures. In both the cases, there was interference from the inactive ingredients. But, the interference was successfully overcome by extraction in acetone.

A separate experiment was performed with the synthetic mixture. The analysis of synthetic mixture solution prepared after extraction in acetone yielded percent recoveries of ranged between 95.95 and 98.31 with standard deviation of 1.45-2.72 in all the cases. The results of this study are presented in Table 4 indicating that the inactive ingredients did not interfere in the assay. These results further demonstrate the selectivity as well as the accuracy of the proposed methods under the optimized conditions.

Application to formulations

In order to evaluate the analytical applicability of the proposed methods to the quantification of PSS in commercial tablets, the results obtained by the proposed methods were compared to those of the reference method [6] by applying student's t-test for

accuracy and F-test for precision. The results (Table 5) show that the student's t- and F-values at 95 % confidence level are less than the theoretical values, which confirmed that there is a good agreement between the results obtained by the proposed methods and the reference method with respect to accuracy and precision.

Recovery studies

The accuracy and validity of the proposed methods were further ascertained by performing recovery

studies. Preanalysed tablet powder was spiked with pure PSS at three concentration levels (50, 100 and 150 % of that in tablet powder) and the total was found by the proposed methods. In all cases, the added PSS recovery percentage values ranged between 97.80 and 102.9 % with standard deviation of 0.79 -1.48 (Table 6) indicating that the recovery was good, and that the coformulated substance did not interfere in the determination.

CONCLUSIONS

Two sensitive and accurate visible spectrophotometric methods for the quantitation of pantoprazole sodium sesquihydrate have been developed and validated based on current ICH guidelines. The present methods are advantageous over the previously reported spectrophotometric methods in terms of simplicity. The methods employ mild working conditions without heating or extraction. The procedures are based on well established and characterized redox and complex formation reactions and use cheaper and readily available chemicals. The methods have been demonstrated to be free from rigid experimental conditions. These merits besides, the use of simple and inexpensive chemicals and instruments, recommend the use of the methods in routine quality control laboratories.

Table 2. Sensitivity and regression parameters.

Parameter	Method A	Method B
λ_{max}, nm	510	520
Linear range, µg ml^{-1}	0.25-4.0	2.5-50.0
Molar absorptivity(ε), l mol^{-1} cm^{-1}	5.35 x 10^4	0.799 x 10^4
Sandell sensitivity*, µg cm^{-2}	0.0081	0.0548
Limit of detection (LOD), µg ml^{-1}	0.04	0.32
Limit of quantification (LOQ), µg ml^{-1}	0.12	0.97
Regression equation, Y**		
Intercept (a)	0.0091	0.0018
Slope (b)	0.1168	0.0176
Standard deviation of a (S_a)	0.027	0.012
Standard deviation of b (S_b)	0.007	0.00028
Regression coefficient (r)	0.9986	0.999

*Limit of determination as the weight in µg per ml of solution, which corresponds to an absorbance of A = 0.001 measured in a cuvette of cross-sectional area 1 cm^2 and l = 1 cm. **Y=a+bX, Where Y is the absorbance, X is concentration in µg ml^{-1}, a is intercept, b is slope.

Table 3. Evaluation of intra-day and inter-day accuracy and precision

Method*	PSS taken µg ml^{-1}	Intra-day accuracy and precision			Inter-day accuracy and precision		
		PSS found µg ml^{-1}	%RE	%RSD	PSS found µg ml^{-1}	%RE	%RSD
Method A	1.0	0.98	2.15	1.24	0.97	2.64	1.72
	2.0	1.94	3.04	1.45	1.97	1.72	2.14
	3.0	2.93	2.33	1.62	2.89	3.52	2.52
Method B	20.0	19.58	2.10	1.12	19.51	2.46	1.66
	30.0	29.16	2.80	1.38	29.05	3.18	2.18
	40.0	38.90	2.75	1.29	38.86	2.85	1.85

RE. relative error; RSD. Relative standard deviation.

Table 4. Recovery of the drug from synthetic mixture.

Method	PSS in synthetic mixture taken µg ml^{-1}	PSS recoverd* (Percent ±SD)
Method A	1.0	96.87±2.64
	2.0	97.11±2.72
	3.0	95.95±2.12
Method B	20.0	98.31±1.78
	30.0	98.15±1.56
	40.0	97.47±1.45

*Mean value of five determinations

Table 5. Results of analysis of tablets by the proposed methods.

Tablet Brand name*	Label claim, mg/tablet	Found* (Percent label claim ±SD)		
		Reference method	Method A	Method B
Pantodac[a] 20	20	98.16 ± 1.15	97.65 ± 1.78 **t**= 0.55 **F**= 2.39	99.26 ± 1.81 **t**= 1.17 **F**= 2.48
Pantop[b] 40	40	97.86 ± 1.06	98.55 ± 2.84 **t**= 0.56 **F**= 7.18	97.17 ±1.93 **t**= 0.73 **F**= 3.3

*Mean value of five determinations.
**Marketed by : [a]Zy. Alidac, Mumbai, India. [b]Aristo Pharmaceuticals Ltd., Mumbai, India.
The value of t (tabulated) at 95 % confidence level and for four degrees of freedom is 2.78.
The value of F (tabulated) at 95 % confidence level and for four degrees of freedom is 6.39.

Table 6. Accuracy assessment by recovery experiments.

Method	Tablet studied	PSS in tablet µg ml^{-1}	Pure PSS added µg ml^{-1}	Total found µg ml^{-1}	Pure PSS recovered*, Percent±SD
Method A	Pantodac 20	0.98	0.5	1.47	97.80 ± 1.35
		0.98	1.0	1.96	98.10 ± 1.48
		0.98	1.5	2.46	98.79 ± 1.24
Method B	Pantodac 20	9.93	5.0	15.02	101.7 ± 1.21
		9.93	10.0	20.18	102.5 ± 1.17
		9.93	15.0	25.37	102.9 ± 0.79

*Mean value of three measurments.

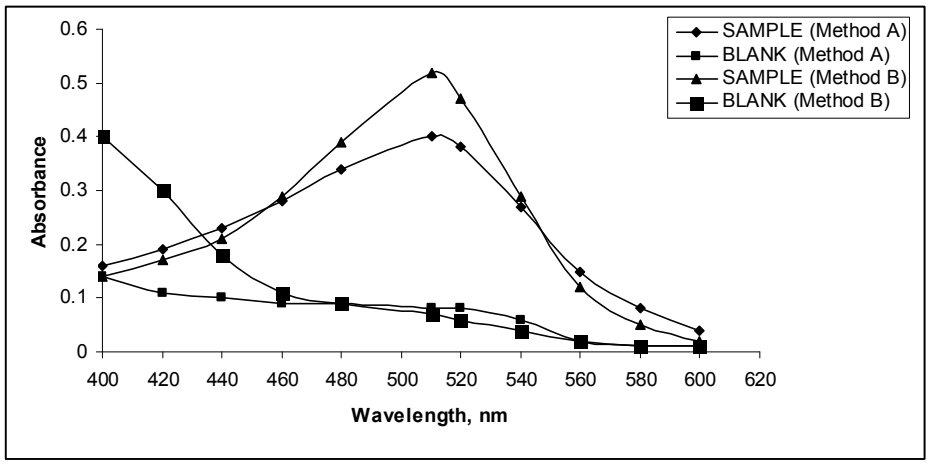

Fig. 3. Absorption spectra for method A (3 µg ml^{-1} PSS) and method B (30 µg ml^{-1} PSS)

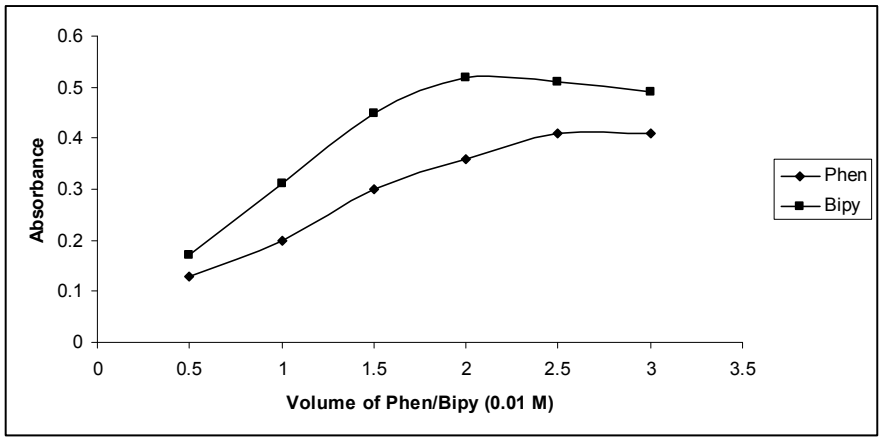

Fig. 4.Effect of 1, 10-phenanthroline (3 µg ml^{-1} PSS) and 2, 2′-bipyridyl (30 µg ml^{-1} PSS)

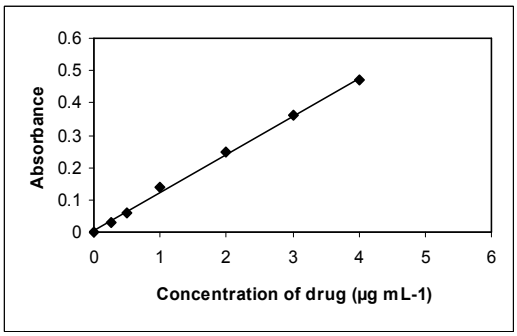

Fig.5. Calibration curve for method A.

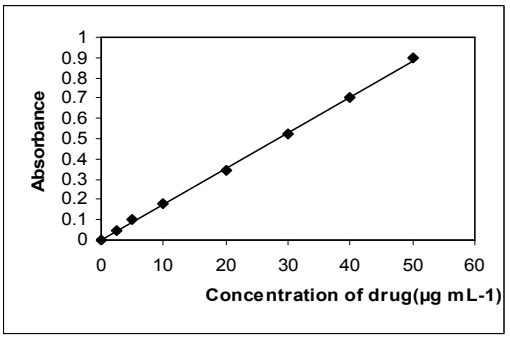

Fig. 6.Calibration curve for method B

ACKNOWLEDGEMENTS

The authors are grateful to Cipla India Ltd, Mumbai, India, for providing the gift sample of pantoprazole sodium sesquihydrate. One of the authors (OZD) is gratefully thanks to the UGC, New Delhi for the award of UGC Meritorious Research Fellowship .

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