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ANALYTICAL METHOD DEVELOPMENT OF ESOMEPRAZOLE IN BULK AND SINGLE COMPONENT FORMULATION

P.M. Rachmale

Modern College of Pharmacy, Yamunanagar, Nigdi, Pune, Maharashtra, India

Keywords:
Esomeprazole, UV Analysis, Method Development of Esomeprazole, Zero Order UV- Analysis, First Order UV-Analysis

Correspondence to Author:

P.M. Rachmale

Modern College of Pharmacy, Yamunanagar, Nigdi, Pune, Maharashtra, India

E-mail: pundlikrachmale@ymail.com

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ABSTRACT

Esomeprazole is a proton pump inhibitor which reduces gastric acid secretion through inhibition of H^+/K^+-ATPase in gastric parietal cells. By inhibiting the functioning of this enzyme, the drug prevents formation of gastric acid. Esomeprazole is combined with the antibiotics, clarithromycin and amoxicillin (or metronidazole in penicillin-hypersensitive patients) in the 7-14 day eradication triple therapy for *Helicobacter pylori*. Infection by *H. pylori* is the causative factor in the majority of peptic and duodenal ulcers. Common side effects of Esomeprazole include headache, diarrhea, nausea, gas, decreased appetite, constipation, dry mouth, and abdominal pain. More severe side effects are severe allergic reactions, chest pain, dark urine, fast heartbeat, fever, paresthesia, persistent sore throat, severe stomach pain, unusual bruising or bleeding, unusual tiredness, and yellowing of the eyes or skin. Proton pump inhibitors may be associated with a greater risk of hip fractures and *Clostridium difficile*- associated diarrhea. Patients are frequently administered the drugs in intensive care as a protective measure against ulcers, but this use is also associated with a 30% increase in occurrence of pneumonia. It is not official in any of the Pharmacopoeias and only listed in The Merck Index and Martindale, The Complete Drug Reference. There is no official method reported for the estimation of Esomeprazole. Literature survey has indicated that there are no analytical methods for estimation of Esomeprazole single component by UV-Visible Spectrophotometry but there are few methods which are reported like RP-HPLC method, validated Kinetic Spectrophotometric in commercial dosage forms, HPLC-UV method for the determination of Esomeprazole in human urine. Hence, the objective of the work is to develop simple, precise, accurate, sensitive, rapid and economical UV-Visible Spectrophotometric methods and a new simple HPLC method of analysis for the estimation of Esomeprazole in bulk and pharmaceutical formulations.

INTRODUCTION: All atoms and molecules are capable of absorbing energy in accordance with certain restrictions i.e. depending on the structure of the substance, energy may be furnished in the form of electromagnetic radiation. The kind and the amount of the radiation absorbed by a molecule depend on the number of molecules interacting with the radiation. The study of these dependencies is called as "absorption spectroscopy". Quantitative spectroscopic analysis is based on the relationship between the amount of light absorbed and the amount of absorbing substance. The basic UV-Visible spectrophotometer is the absorption of the UV-Visible region, which arise s from the electronic transition within the molecules by

the radiant energy of definite and narrow wavelength of monochromatic radiation. Light absorption in the UV- Visible region causes the transition of an electron from a ground state and relaxation of energy takes place very rapidly. The important consequences of rapid relation of the excited states are not appreciably distributed by absorption of light energy from any source. Therefore, the fraction of light absorbed from an incident beam is independent of the intensity of these beams [1].

Advantages of Instrumental Methods: Small amount of sample is needed for analysis, High sensitivity is obtained, Measurements obtained are reliable, The determination is very fast, Complex samples can be handled.

Limitations of Instrumental Methods: Skilled person is required, Cost of equipment is high, Sizable space is required,The sensitivity and accuracy depends on the instruments or wet chemical methods.

Techniques used in Instrumental Methods: There are many techniques available for the analysis of materials; however, they all are based on the materials interaction with energy. This interaction permits the creation of a signal that is subsequently detected and processed for its information content. Chemical instrumentation includes the following principle types [2]:

Spectroscopic techniques: Spectroscopy measures the interaction of the material with electromagnetic radiation. Different types are:

- Ultraviolet and visible spectrophotometry,
- Fluorescence and phosphorescence spectrophotometry,
- Atomic spectrometry (emission and absorption),
- Infrared spectrophotometry,
- Raman spectroscopy,
- X-ray spectroscopy,
- Nuclear magnetic resonance spectroscopy,
- Electron spin resonance spectroscopy .

Literature survey: Reported methods of analysis for Esomeprazole as a single component.

1. **Development and statistical validation of spectroscopic method for estimation of Esomeprazole in tablet dosage form using UV visible spectrometer:** Esomeprazole has the absorbance maxima at 303nm (Method A), and in the first order derivative spectra, showed zero crossing at 303nm, with a sharp peak at 292nm when n=1 (Method B), Method C applied was Area Under Curve (AUC) for analysis of Esomeprazole in the wavelength range of 294-310nm. Drug followed the Beer's Lamberts range of 5-40 µg/ml for the Method A, B C. Results of analysis were validated statistically [3].

2. **Physicochemical characterization U.V. spectrophotometric method development amd validation studies of Esomeprazole magnesium trihydrate:**The method was based on U.V. absrption method. Method

   a. Zero order spectrumMethod B) First order spectrumMethod C) AUC [4].

3. **Estimation of Esomeprazole and Domperidome by absorption ratio method in pharmaceutical dosage forms:** The method involved Q-absorption analysis based on the measurement of absorbance at two wavelengths, i.e λmax of Esomeprazole (303 nm) and Iso-absorptive point of both drugs (290 nm) [5].

4. **Development and validation of HPLC method for the determination of Esomeprazole:**separation was achieved isocratically on a C18 column utilizing mobile phase of acetonitrile/phosphate buffer (60:40, v/v, pH 7) Uvdetection at 205 [6].

5. **Determination of Esomeprazole and its two metabolite in human, rat and dog plasma by liquid chomatography [7].**

Nature of investigation:

UV-Visible Spectrophotometer (Double Beam): Various modes in the mode selection screen of Uv-Visible Spectrophiotometer (Model UV 1700).

Photometric Mode: This is the fixed wavelength measurement mode. This measures the absorbance (ABS) or % transmittance (T %) at a fixed wavelength.

Spectrum Mode: This is the mode in which spectral measurement is performed. There are three types of measurement available i.e. ABS (absorbance), T % (% transmittance) and single beam E (energy) [6].

Quantitation Mode: This is the mode in which unknown concentration of samples are measured by plotting a calibration curve of standard solutions. The following 4 methods in quantitation mode are available, which depend on the number of wavelengths used for the measurement:

1. One – wavelength method
2. Two–wavelength method
3. Three – wavelength method
4. Derivative quantitation [7]

TABLE 1:

Make	Shimadzu Corporation Ltd., Japan
Model	UV 1700
Specification	190 to 1100 nm
Wavelength range Spectral Bandwidth	2nm

Goals of investigation: Esomeprazole is a proton pump inhibitor which reduces gastric acid secretion through inhibition of H^+/K^+-ATPase in gastric parietal cells. By inhibiting the functioning of this enzyme, the drug prevents formation of gastric acid. Esomeprazole is combined with the antibioticsclarithromycin and amoxicillin (or metronidazole in penicillin-hyper-sensitive patients) in the 7-14 day eradication triple therapy for Helicobacter pylori. Infection by H. pylori is the causative factor in the majority of peptic and duodenal ulcers.

Common side effects of Esomeprazole include headache, diarrhea, nausea, gas, decreased appetite, constipation, dry mouth, and abdominal pain. More severe side effects are severe allergic reactions, chest pain, dark urine, fast heartbeat, fever, paresthesia, persistent sore throat, severe stomach pain, unusual bruising or bleeding, unusual tiredness, and yellowing of the eyes or skin.

Proton pump inhibitors may be associated with a greater risk of hip fractures and clostridium difficile-associated diarrhea. Patients are frequently administered the drugs in intensive care as a protective measure against ulcers, but this use is also associated with a 30% increase in occurrence of pneumonia. It is not official in any of the Pharmacopoeias and only listed in The Merck Index, and Martindale, The Complete Drug Reference.

There is no official method reported for the estimation of Esomeprazole. Literature survey has indicated that there are no analytical methods for estimation of Esomeprazole single component by UV-Visible Spectrophotometry but there are few methods which are reported like RP-HPLC method, validated Kinetic Spectrophotometric in commercial dosage forms, HPLC-UV method for the determination of Esomeprazole in human urine.Hence the objective of the work is to develop simple, precise, accurate, sensitive, rapid and economical UV-Visible Spectrophotometric methods and a new simple HPLC method of analysis for the estimation of Esomeprazole in bulk and pharmaceutical formulations.

Drug Profile:

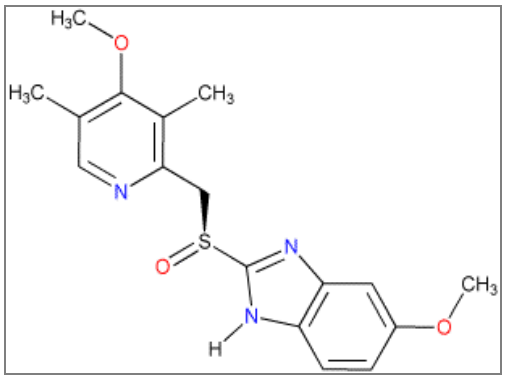


TABLE 2 [12]:

Mol. Formula	$C_{17}H_{19}N_3O_3S$
Mol. Weight	345.417 g/mol
Chemical Name	(*S*)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-3*H*-benzoimidazole
Description	white to slightly colored crystalline powder
Solubility	Very slightly soluble in water
Melting Point	155° C
Category	**1.** Anti-Ulcer Agents 2. Enzyme Inhibitors 3. Proton-pump Inhibitors 4. Antihistamines

MATERIALS AND METHODS:

Plan of work: Selection of single component formulation, Market surveys, Solvent selection, Selection of analytical wavelength, Type of instrument, Preparation of working curve, Sample measurement and calculations, Evaluation of reproducibility and recognitions of variations [13,14].

Method's:

- Zero order spectrum method.
- Derivative spectrum method.

Validation of analytical method's [15]:

1. Analytical Procedure
2. Specificity
3. Sensitivity
4. Accuracy
5. Precision
6. Robustness
7. Limit of detection
8. Linearity
9. Stability
10. Limit of quantitation
11. Range
12. Cost of analysis

Year of experimentation: 2012-13.

Site: Modern college of Pharmacy, Nigdi , Pune.

RESULTS AND DISCUSSION:

Zero Order Spectrum (Calibration Curve Method):

A. **Preparations of drug stock solution:** Accurately about 10 mg of ESOMEPRAZOLE was weighed and transferred to 100 ml volumetric flask. To it 40 ml of ethanol was added to dissolve the drug completely with vigorous shaking then the volume was made up with distilled water up to the mark to give the drug stock solution of concentration 100 µ/ml.

B. **Preparation of Standard Drug Dilutions:** From the stock solution of ESOMEPRAZOLE appropriate volumes were pipetted out and transferred to 10 ml volumetric flasks. The volume was made up to the mark with glass distilled water to give the samples of desired concentrations.

Selection of analytical wavelengths: The standard solutions were then scanned in the spectrum mode of the instrument from 400 nm to 200 nm against glass distilled water as blank. The zero order derivative spectrum obtained with wavelength difference (n=0) showed a sharp peak was obtained at 301 nm as shown in **figure 1**.

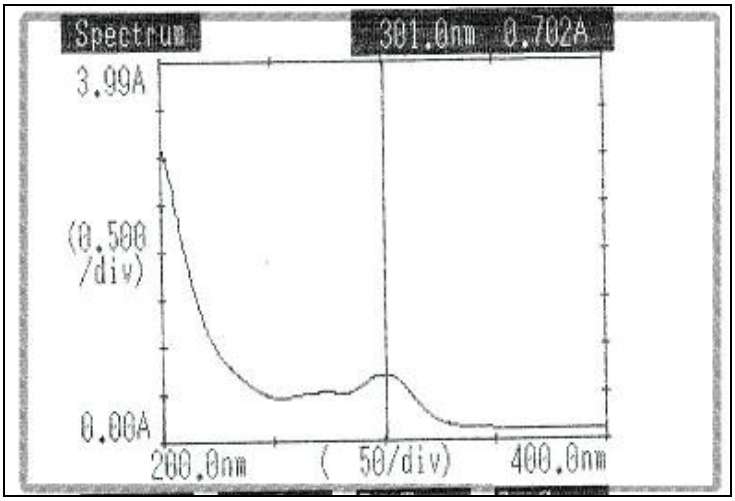


FIG. 1: ZERO ORDER SPECTRUM

TABLE 2: STANDARD CALIBRATION TABLE FOR ESOMEPRAZOLE

Sr. No.	Conc. µg/ml	Absorbance
1	20	0.210
2	30	0.315
3	40	0.420
4	50	0.510
5	60	0.620
6	70	0.700
7	80	0.820
8	20	0.210

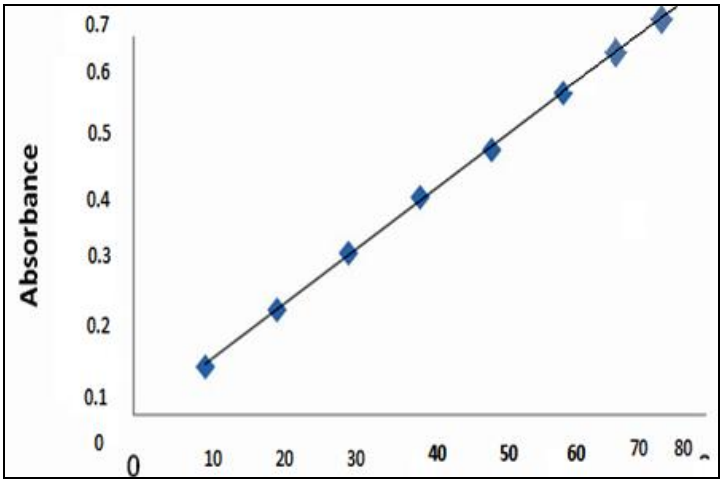


FIG. 2: CALIBRATION CURVE ESOMEPRAZOLE IN ZERO ORDER DERIVATIVE SPECTRUM

TABLE 3: OPTICAL CHARACTERISTICS AND PARAMETERS

Parameters	Method A
λ_{max} (nm)/wavelength range (nm)	301
Beer's-Lamberts range (µg/ml)	20-80
Coefficient of Correlation ($r^{2)}$	0.9990
Regression Equation y = mx+c	
Slope (m)	0.0107
Intercept (c)	0.0000
LOD	0.1296
LOQ	0.3928

TABLE 4: STATISTICAL VALIDATION BY ZERO ORDER SPECTRUM METHOD

Parameter	Mean	S.D*	C.O.V.*	S.E.*
r^2	0.9990	0.0004203	0.042072	0.00017159
Slope	0.0107	0.00088374	0.088370	0.00036078
Intercept	0.0000	0.0000	0.0000	0.0000

TABLE 4[A]: ANALYSIS OF STANDARD ESOMEPRAZOLE

Conc. Taken	ABS. At 301 nm	Conc. Obtained	% of Drug Found *
20	0.210	8.30	83
30	0.315	30.5	95.5
40	0.420	38.7	96.75
50	0.510	46.8	93.6
60	0.620	60.1	100.1
70	0.700	69.3	99
80	0.820	79.2	99

TABLE 4B: ASSAY OF THE TABLE

Tablet	Conc.	Amount present (mg/Tab)	Amount found (mg /Tab)	% of Drug Found
T_1	40	10	39.40	98.5
	70	10	68.10	97.28
	80	10	80.20	100.25

The results of the analysis of tablet formulations by Zero order spectrum method are given below in **Table 5**.

TABLE 5[A]: ANALYSIS OF TABLET FORMULATION

Tablet sample	Amount present (mg/tab)	Amount Found (mg/tab)	% of Label Claim
T_1	40	39.45	98.57
	40	40.01	100.25
	40	38.98	97.45
	40	39.10	97.75
	40	40.10	100.25
	40	39.00	97.5

TABLE 5[B]:STATISTICAL EVALUTION BY ZERO ORDER SPECTRUM METHOD

Tablet sample	% Mean	S.D	C.O.V	S.E
T_1	98.60	1.110	1.125	0.453

Recovery Studies: The result of analysis of recovery studies and its statistical validation are given in **table 6 and 7** respectively.

TABLE 6: RECOVERY STUDIES

Tablet Sample	Level of Recovery (%)	Amount present (mg/tab)	Amount Standard (mg)	Total Amount Recovered (mg)	% Recovery
T_1	80	10	8	18.20	100.41
		10	8	18.32	100.66
		10	8	17.99	99.99
	100	10	10	20.10	100.02
		10	10	21.07	102.14
		10	10	19.08	98.16
	120	10	12	21.09	98.53
		10	12	22.07	100.12
		10	12	21.99	99.99

TABLE 7 : STATISTICAL VALIDATION OF RECOVERY STUDIES

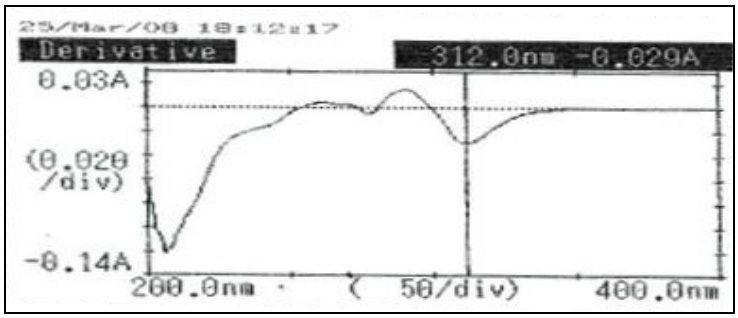
Tablet sample	Level of recovery (%)	% Mean*	S.D.*	C.O.V.*	S.E.*
T_1	80	100.35	0.02764	0.02754	0.01595
	100	100.10	1.625	1.623	0.9370
	120	99.54	0.7208	0.7241	0.4180

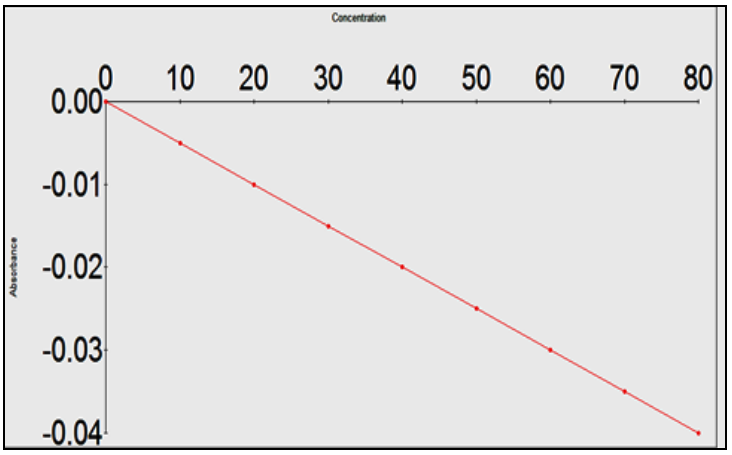
When *n=3 at each level of recovery

TABLE 8: STATISTICAL VALIDATION FOR PRECISION

Component	Mean *	S.D.	C.O.V.	S.E.
Intra-day	99.77	0.0100	0.01002	0.005774
Inter-day	99.50	0.005774	0.005803	0.003333

First Order Derivative Method:





CALIBRATION CURVE OF ESOMEPRAZOLE INFIRST ORDER DERIVATIVE SPECTRUM

TABLE 9: STANDARD CALIBRATION TABLE FOR ESOMEPRAZOLE

Sr. No.	Conc. µg/ml	Absorbance
1	10	-0.005
2	20	-0.010
3	30	-0.015
4	40	-0.020
5	50	-0.025
6	60	-0.030
7	70	-0.035
8	80	-0.040

TABLE 10: OPTICAL CHARACTERISTICS AND OTHER PARAMETERS

Parameters	Method A
λ_{max} (nm)/wavelength range (nm)	312
Beer's-Lamberts range (µg/ml)	10-80
Coefficient of Correlation ($r^{2)}$	0.9991
Regression Equation y = mx+c	
Slope (m)	-0.0119
Intercept (c)	0.0000
LOD	-0.507
LOQ	-1.539

TABLE 11: STATISTICAL VALIDATION BY ZERO ORDER SPECTRUM METHOD

Parameter	Mean	S.D*	C.O.V.*	S.E.*
r^2	0.9991	0.0018316	0.0018330	0.0007477
Slope	-0.0119	0.002328	0.2326	0.0009504
Intercept	0.000	0.0000	0.0000	0.0000

*Average of six readings

TABLE 12: ASSAY OF THE TABLE

Tablet	Conc.	Amount present (mg/Tab)	Amount found (mg /Tab)	% of Drug Found
T_1	40	10	40.12	100.3
	70	10	69.89	99.84
	80	10	80.40	100.5

TABLE 13 : ANALYSIS OF STANDARD ESOMEPRAZOLE

Conc. Taken	ABS. at 312 nm	Conc. Obtained	% of Drug Found *
10	-0.005	9.76	97.6
20	-0.010	19.20	96
30	-0.015	28.90	96.6
40	-0.020	39.78	99.45
50	-0.025	49.45	98.5
60	-0.030	59.90	99.83
70	-0.035	68.20	97.42
80	-0.040	79.10	100.12

*Average of six readings

TABLE 14: ANALYSIS OF TABLET FORMULATIONS

Tablet sample	Amount Present (mg/tab)	Amount Found (mg/tab)	% of Label Claim
T_1	10	9.12	97.8
	10	9.80	99.5
	10	8.99	97.47
	10	10.02	100.05
	10	10.07	100.17
	10	9.99	99.97

T_1 : is the brands of tablet formulations.

TABLE 15: STATISTICAL EVALUATION BY FIRST ORDER DERIVATIVE SPECTRUM METHOD

Table Sample	% Mean*	S.D.*	C.O.V.*	S.E.*
T_1	98.16	0.9622	0.9704	0.3928

*Average of six readings

TABLE 16:RECOVERY STUDIES

Tablet Sample	Level of Recovery (%)	Amount present (mg/tab)	Amount Standard (mg)	Total Amount Recovered (mg)	% Recovery
T_1	80	10	8	18.08	100.44
		10	8	17.99	99.94
		10	8	18.02	100.11
	100	10	10	20.10	100.5
		10	10	20.03	100.15
		01	10	19.99	99.95
	120	10	12	22.04	100.18
		10	12	21.86	99.36
		10	12	21.96	99.81

TABLE 17: STATISTICAL VALIDATION OF RECOVERY STUDIES

Table Sample	Level of Recovery (%)	% Mean*	S.D.*	C.O.V.*	S.E.*
T_1	80	100.16	0.2076	0.2072	0.1198
	100	100.02	0.2273	0.2268	0.1312
	120	99.78	0.3353	0.3360	0.1935

When *n=3 at each level of recovery

TABLE 17A: STATISTICAL VALIDATION DATA FOR ESOMEPRAZOLE

Method	% Mean *	S.D.	C.O.V.	S.E.
Method A	98.7	1.110	98.6	98.7
Method B	99.16	0.9622	99.98	99.16

TABLE 18: STATISTICAL VALIDATION FOR PRECISION

Component	Mean *	S.D.	C.O.V.	S.E.
Intra-day	99.55	0.007528	0.007562	0.003073
Inter-day	99.75	0.004082	0.004092	0.001667

TABLE 19: OPTICAL CALIBRATION CURVE OF ESOMEPRAZOLE

Parameters	Method A	Method B
max (nm)/wavelength range (nm)	301	312
Beer's – Lambert's range (µg/ml)	20-80	10-80
Coefficient of correlation (r^2)	0.9990	0.9996
Regression equation : Y = mx + c		
Slope (m)	0.1296	-0.00198
Intercept (c)	0.0000	0.0000
LOD	0 .0107	-0.507
LOQ	0.1226	-1.539

CONCLUSION: It is not official in any of the Pharmacopoeias and only listed in The Merck Index, and Martindale, The Complete Drug Reference. There is no official method reported for the estimation of Esomeprazole. Literature survey has indicated that there are no analytical methods for estimation of Esomeprazole single component by UV-Visible Spectrophotometry but there are few methods which are reported like RP-HPLC method, validated Kinetic Spectrophotometric in commercial dosage forms, HPLC-UV method for the determination of Esomeprazole in human urine.

Hence, the objective of the work is to develop simple, precise, accurate, sensitive, rapid and economical UV-Visible Spectrophotometric methods and a new simple HPLC method of analysis for the estimation of Esomeprazole in bulk and pharmaceutical formulations.

The methods were based on the development of calibration curve for the standard drug and the analysis of the formulation aws done using the calibration curve in the quantitation mode of the Spectro-photometer (Method A). The standard drug solution were scanned in the spectrum mode and the first order derivative spectra with (n=1) processed showed zero crossing at the absorbance maxima of the normal spectra, the derivative dA/dƛ is plotted against the concentration of the standard solution (Method B).

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