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Determination of Esomeprazole by Complexation Method

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ABSTRACT

Esomeprazole magnesium trihydrate is an effective proton pump inhibitor used for dyspepsia and peptic ulcer. In the present study and a simple, accurate and precise spectroscopic method has been developed for the estimation of esomeprazole in raw material and tablet dosage forms. The method involves complexation of esomeprazole in H_2SO_4 with iron(II) and 1,10-Phenanthroline and the colour developed was stabilized by using o-phosphoric acid. The coloured solution showed an absorption maximum of 507 nm. A calibration curve was plotted (0.5-4 µg/ml) and found a regression co efficient r^2=0.9723. The limit of detection was found to be 0.522318 and limit of quantification was found to be 0.15833. A result of analysis obtained from the studies was validated statistically and by recovery studies. The methods showed good reproducibility and recovery with %RSD less than 1.

Keywords: Spectroscopic method, Esomeprazole, Optical characters, Recovery studies

INTRODUCTION

Esomeprazole is available as (S)-Esomeprazole Magnesium (ESO) (Figure 1). It is chemically bis (5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-H-enzimidazole-1-yl), 1,2 (S)-Esomeprazole trihydrate. Esomeprazole is the (*S*)-(−)-enantiomer of omeprazole. It decreases secretion of acid through inhibition of the H^+/K^+-ATPase in the parietal cells of the stomach [1]. By inhibiting the functioning of this transporter, the drug prevents formation of stomach acid. It is used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease and Zollinger-Ellison syndrome [2-4] (Figure 1).

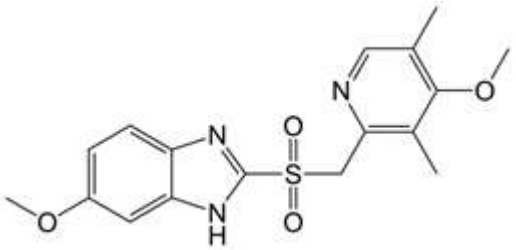
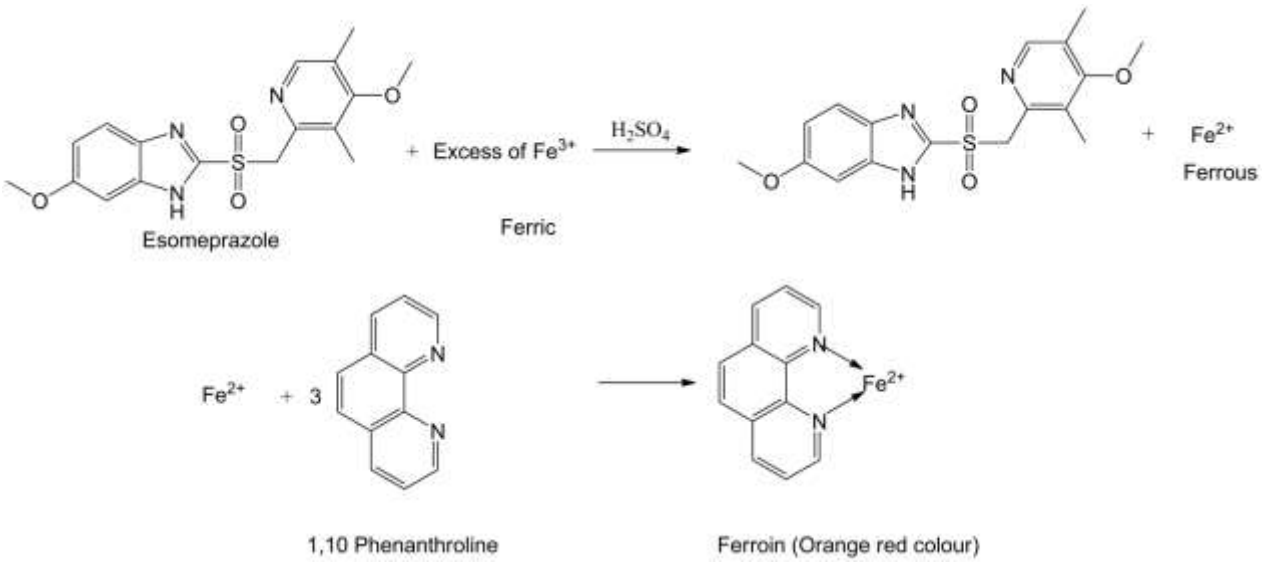


Figure 1: Esomeprazole

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 difficil*e 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. Esomeprazole magnesium occurs as white or slightly coloured powder which is slightly hygroscopic. Soluble in methanol, slightly soluble in water and practically insoluble in heptane [2,4,5]. Available as nexium (Esomeprazole magnesium) in market. It is not official in any of the Pharmacopoeias.

A number of UV spectroscopic and gas chromatographic method 4, Thin Layer Chromatography (TLC) and several High Performance Liquid Chromatography (HPLC) [5] methods for the estimation of omeprazole are revealed by survey of literature. Here an attempt has been made to develop and validate a simple accurate colorimetric method by using complexation of the drug with iron (II) and 1,10-Phenanthroline in acid

medium (Scheme 1) [6-11].



Scheme 1: Complexation of the drug with iron (II) and 1,10-Phenanthroline in acid medium

MATERIALS AND METHODS

Esomeprazole was generously gifted by Cipla India, Ltd, Mumbai. The sample was authentified by checking the Melting point, (155°C). Formulations were procured from local Market and the selected formulations include Sompraz 20 (Sun Pharma, Sikkim) and Nexpro (torrent pharmaceuticals, Sikkim). All reagents and chemicals used were procured from Nice chemicals Pvt. Ltd. Spectral and absorbance measurements were made on Shimadzu-1700 Pharm spec double beam UV-Visible spectrophotometer with a pair of 10 mm matched quartz cell.

Preparation of standard solution and calibration curve

Solvent was selected as 0.1 N H_2SO_4 standard esomeprazole was dissolved in the solvent and proper dilutions are made to produce solutions of 10-100 µg/ml concentrations. The color development was done by adding 1.5 ml of $FeCl_3$ (0.0033 M) and 2.5 ml of 1, 10-phenanthroline (0.01 M) and the color were stabilized by 0.5 ml of ortho phosphoric acid (0.02 M). The λ_{max} of the solution was found as 507 nm. The color was stable up to 2.5 h. A calibration curve was plotted using working concentration 0.5-4 µg/ml by plotting absorbance at 507 nm against reagent blank against concentration.

Assay

Two marketed formulations were selected. Twenty tablets of each formulation were weighed and powdered. An amount equivalent to 50 mg esomeprazole was dissolved in 0.1 N H_2SO_4 to produce 500 µg/ml. Ultrasonicated and filtered through Whatman filter paper no 42. Then Esomeprazole solution was prepared by diluting stock solution to produce 10 µg/ml, The color development was done by adding the reagents and absorbance was measured at 507 nm. The amount of Esomeprazole in each formulation was calculated using corresponding calibration curve.

Accuracy and precision

The reliability of proposed method was established by preparing esomeprazole formulations containing 10 µg/ml for each formulations (which is preanalyzed) added pure desloratadine solution to obtain a final concentrations 12-20 µg/ml. The solutions were analyzed at 507 nm using 0.1 N H_2SO_4 as blank. Amount present and % recovery was calculated. Precision of the procedure was calculated by inter day and intra-day variations. Accuracy of the method was measured as percentage of deviation between added and measured concentrations (recovery study) [6-8].

RESULTS AND DISSCUSSION

Optimization of the reaction conditions

Investigations were carried out to achieve maximum color development in the quantitative determination of Esomeprazole. 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. 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 and used throughout the experiment. 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. The optimum volume of phenanthroline used for the production of maximum and reproducible color intensity was found to be 2.5 ml of 0.01 M phenanthroline (Figure 2) in a total volume of 10 ml. The standing times for full color development were found to be 30 min and the color was stable for 30 min thereafter [11-16].

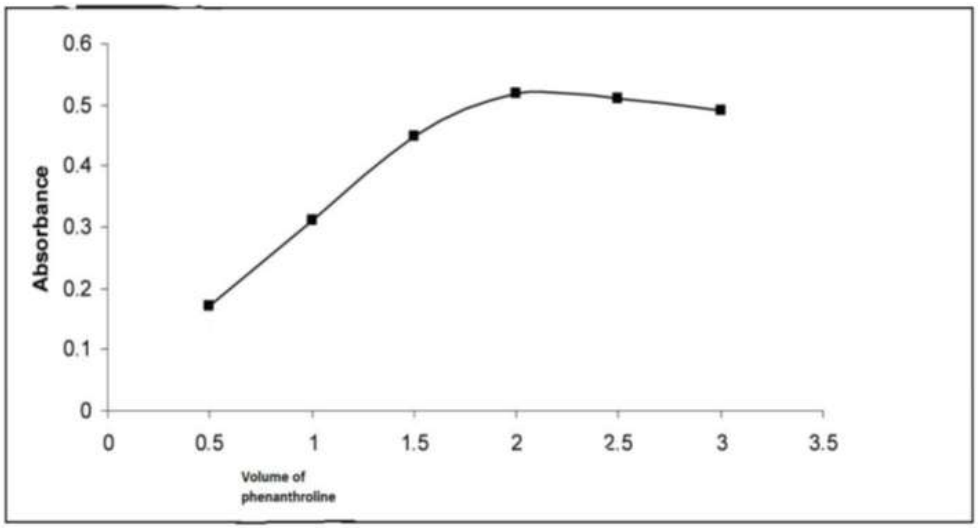


Figure 2: Optimization curve of 1,10-phenanthroline

Esomeprazole solution was prepared and the linearity of the drug and calibration curve was constructed (Figure 3). The optical characteristics, like Beer's law limits (0.5-4 µg/ml), molar extinction co-efficient (14633.40561 mol/cm), Sandell′s sensitivity 0.02150536 µg/cm^2), correlation coefficient (r) (0.96223), slope (m) (0.0730) and intercept (c) (0.0670) were calculated for esomeprazole after color development and are produced in Table 1. Correlation coefficient (r) values is found to be close to 1 indicating that the concentrations used for plotting calibration curve is obeying Beer's law strictly. The value of molar absorptivity and Sandall's sensitivity, indicate the sensitivity of the method. The limit of detection and limit of quantification were determined from the linearity studies and have done six times and then calculated by using slope and standard deviation. The limit of detection is found to be 0.522518 and limit of quantification is found to be 0.158339. The percentage recoveries are found to be 100.15%, 98.063% for the formulations Somprax and Nexpro respectively Tables 2 and 3.

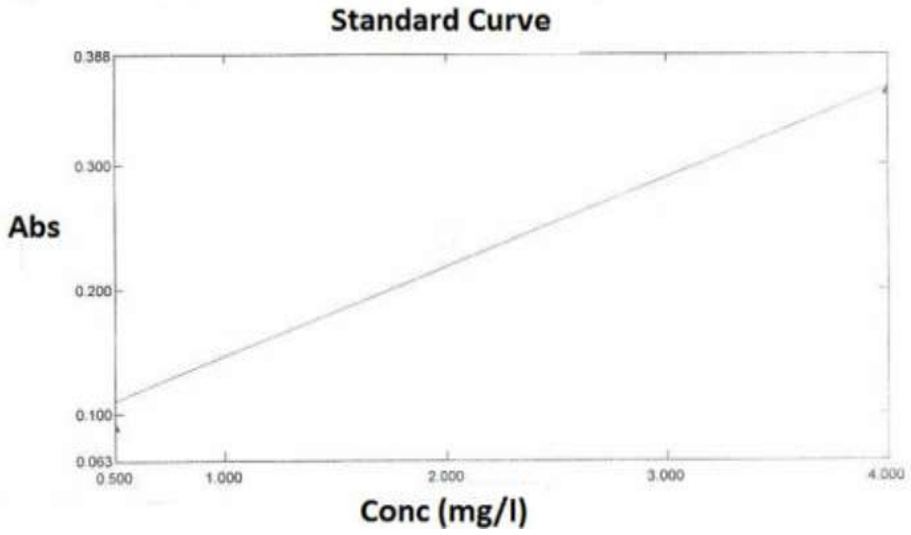


Figure 3: Calibration curve for the coloured complex

Table 1: Calculated for esomeprazole after color development

S. No.	Labelled amount (mg/tab)	Amount found (mg)	Percentage obtained	S.D	% RSD	SE
1	20	19.89	99.48	0.2513	1.252	0.1026
2	20	20.36	101.79			
3	20	20.46	102.3			
4	20	20.39	101.96			
5	20	20.06	100.3			
6	20	19.93	99.64			
S. No.	**Labelled Amount (mg/tab)**	**Amount found (mg)**	**Percentage obtained**	**S.D**	**% RSD**	**SE**
1	40	40.089	101.78	0.074	1.07	0.0302
2	40	40.106	102.12			
3	40	40.272	104.5			
4	40	40.106	102.12			
5	40	40.1	102			
6	40	40.2	103.4			
Mean		40.146	102.65			

Table 2: Repeatability for formulation 1

S. No.	Inter day (Percentage recovery)	Intra day (Percentage recovery)
1	100.5	99.93
2	99.43	99.63
3	100.15	100.1
S.D	0.5456	0.238
%RSD	0.61685	0.18864

Table 3: Repeatability for formulation 2

S. No.	Inter day (Percentage recovery)	Intra day (Percentage recovery)
1	98.33	98
2	100.54	99.64
3	98.58	98.5
S.D	0.96599	0.5789
%RSD	0.977002	0.5873

Precision and accuracy

Intra-day precision and accuracy of the proposed methods were evaluated by replicate analysis (n=3) of calibration standards at three concentration levels (1.0, 2.0 and 3.0 $\mu g/ml^{-1}$. Inter-day precision and accuracy were determined by assaying the calibration standards at the same concentration levels on three 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 (Tables 4 and 5).

Table 4: Repeatability for formulation 1

S. No.	Inter day (Percentage recovery)	Intra day (Percentage recovery)
1	100.5	99.93
2	99.43	99.63
3	100.15	100.1
S.D	0.5456	0.238
%RSD	0.61685	0.18864

Table 5: Repeatability for formulation 2

S. No.	Inter day (Percentage recovery)	Intra day (Percentage recovery)
1	98.33	98
2	100.54	99.64
3	98.58	98.5
S.D	0.96599	0.5789
%RSD	0.977002	0.5873

Selectivity

The proposed methods were tested for selectivity by synthetic mixture analysis. The interference from the inactive ingredients. But, the interference was successfully overcome by extraction with sulphuric acid. A separate experiment was performed with the synthetic mixture. The analysis of synthetic mixture solution prepared after extraction in sulphuric acid yielded percent recoveries of ranged between 98.063 and 100.15 with standard deviation of 0.904 in all the cases. The results of this study are presented in Tables 6 and 7 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.

Table 6: Recovery studies for formulation 1

S. No.	Previous amount present (mcg/ml)	Amount added (mcg/ml)	Total amount present	Amount recovered (mcg/ml)	%recovery
1	10.1622	2	12.1457	1.9834	100.1529
2	10.2947	4	14.3973	4.1026	
3	10.245	6	16.3178	6.0729	
4	10.0463	8	17.8411	7.7951	
5	10.1622	10	20.1589	9.9969	

Table 7: Recovery studies for formulation 2

S. No.	Previous amount present (mcg/ml)	Amount added (mcg/ml)	Total amount present	Amount recovered (mcg/ml)	%recovery
1	10.2119	2	12.1126	1.9006	98.063
2	10.543	4	14.59603	4.056	
3	10.2119	6	16.4503	6.23	
4	10.29	8	18.076	7.79	
5	10.33	10	19.92	9.59	

Application to formulations

In order to evaluate the analytical applicability of the proposed methods to the quantification of Esomeprazole 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 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.

CONCLUSION

A sensitive and accurate visible spectrophotometric method for the quantitation of Esomeprazole magnesium 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 redox reactions and complex formation reactions and use cheaper and readily available chemicals. The use of simple and inexpensive chemicals and instruments, recommend the use of the methods in routine quality control laboratories.

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