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Development and Validation of Complexometric Titrimetric Method for Estimation of Esomeprazole Magnesium in Bulk and Tablet Dosage Form

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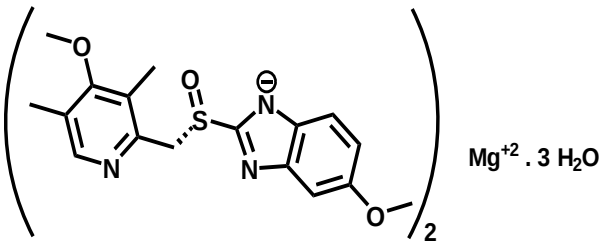
ABSTRACT

A simple, accurate and precise titrimetric method was developed for the estimation of Esomeprazole magnesium trihydrate in bulk and tablet dosage form by using complexometric titration. In this method, EDTA solution (0.01M) was employed as a titrant, Eriochrome black T as an indicator and methanol as a solvent to solubilize the poorly water soluble drug. The validation of the proposed method was carried out for linearity and range, accuracy, precision, ruggedness and recovery. The method was found linear with correlation coefficients of 0.9996. Concerning accuracy and precision, the RSD% values were found to be less than 2. There is no interference from the excipients present in the formulation as confirmed by standard addition method with recovery % 100.4 and RSD% 2.1. The developed method was compared with a reported UV spectroscopic method and there is no statistically significant difference.

1. Introduction

Esomeprazole is a cost effective gastric proton-pump inhibitor (PPI) used in treatment of gastric-acid related diseases [1]. Chemically, it is bis (5-methoxy-2-[(S)-[(4-methoxy-3, 5-dimethyl-2 pyridinyl) methyl] sulfinyl]-1H-benzimidazole-1-yl). Its molecular formula is $(C_{17}H_{18}N_3O_3S)_2$ Mg . 3 H_2O with a molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis [1]. It was developed as the S-isomer of omeprazole in an attempt to improve its pharmacokinetic properties [2]. It is the first PPI available for clinical use as a single isomer. It demonstrates pharmacological and clinical benefits beyond those seen with the racemic omeprazole.



Esomeprazole Magnesium Trihydrate

Different methods have been reported for its determination such as spectrophotometry [3-11], chromatography [12-21] and electrochemistry [22]. However, all the reported methods are either not sufficiently sensitive or tedious, require highly sophisticated instrumentation and pre-analysis treatment before dosage forms assays. Visual titrimetric methods may serve as useful alternatives to many of these techniques because of their cost-effectiveness, ease of operation, good sensitivity, fair accuracy and precision.

The present work describes a simple, precise and inexpensive titrimetric method for the quantitative determination of EMT in both raw material and dosage forms.

2. Material and Methods

2.1. Apparatus

A standard burrets, pipettes, standard volumetric flasks, measuring cylinders, conical flasks and digital spectrophotometer provided with 1 cm matched quartz cells was used for absorbance measurements.

2.2. Materials

Esomeprazole magnesium trihydrate (EMT) standard powder obtained from Azal-Sudan as a gift. Disodium EDTA was AR Grade (SDFCL, India); Magnesium chloride hexahydrate (Lab-tech chemicals, India), Ammonia (Lab-tech chemicals, India), Ammonium chloride (Lab-tech chemicals, India), Calcium carbonate, Hydrochloric acid and Purified (distilled) water.

2.3. Preparations of reagents

2.3.1. Preparation of EDTA

EDTA solution (0.01 M) was prepared by transferring 1.86 gm of EDTA salt dihydrate to 500 ml volumetric flask. 1ml of ammonia solution was added then the volume was adjusted to 500 ml with distilled water.

2.3.2. Preparation of Ammonia / Ammonium chloride buffer (PH: 10)

The buffer solution was prepared by dissolving 6 gm of accurately weighed ammonium chloride in 44 ml of ammonia solution, then 66 ml of distilled water was added to complete the volume to 100 ml

2.4. Chemical Analysis

2.4.1. Standardization of 0.01 M EDTA

25 mg of dry calcium carbonate was weighted then dissolved in 10 ml 0.1 M HCL solution, diluted with water and transferred into Erlenmeyer flask then 5 ml of

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Ammonia/Ammonium chloride buffer and 2 ml of 1% magnesium chloride were added. A pinch of Eriochrome black T was added, the resulting solution was titrated against EDTA solution till the color changed to blue.

2.4.2. Titration

In order to determine the content of esomeprazole magnesium, the drug was accurately weighed and transferred to a conical flask and dissolved in sufficient amount of methanol then 10 ml of Ammonia/Ammonium chloride buffer was added. Traces of Eriochrome black T powder was added to the drug solution. The solution was titrated against EDTA solution (0.01 M) until the drug solution color changes from violet to blue. An indicator blank titration was performed and necessary volume correction was made.

2.4.3. Tablet assay by the proposed method

Ten tablets of Protas® (40 mg) were weighed accurately and ground into a fine powder. Powder equivalent to 20 mg of Esomeprazole was weighed accurately and transferred into a 100 mL Erlenmeyer flask and dissolved in sufficient amount of methanol then 10 ml of Ammonia/Ammonium chloride buffer was added. Traces of Eriochrome black T powder was added to the solution. The solution was titrated against EDTA solution (0.01 M) until the color changes from violet to blue. An indicator blank titration was performed and necessary volume correction was made.

3. Results and Discussion

The present study was carried out to develop a simple, precise accurate, cost-effective, economical and environmentally friendly method for the analysis of Esomeprazole magnesium trihydrate in bulk and tablet dosage form. The developed method was simply based on the complex formation between the magnesium cation in EMT and the standard EDTA in 1:1 mole ratio and all calculations were based on a simple titre value formula: 1 ml of 0.01 M of EDTA reacts with 7.675 mg of the drug.

During the method development, the conditions of the proposed method were optimized. The concentration of EDTA solution 0.01 M was found to be more appropriate than 0.005 and 0.1 M. The drug was found to be insoluble in distilled water, sparingly soluble in ethanol and freely soluble in methanol hence methanol was selected as a solvent. A trial for solubility enhancement for the drug was carried out, by addition of hydrochloric acid (0.1 M), to enhance the magnesium ion liberation from EMT in a form of magnesium chloride, to ensure that all magnesium ions will be involved in the reaction, especially, in the case of the tablet and capsule dosage form assay. But the recovery % values were similar to those with methanol alone. Furthermore, a yellow disturbing color was appeared upon the addition of HCl that made the detection of the end point much more harder. Eriochrome black T was a good option as an indicator because it is sensitive, economic and forms fairly stable complex with magnesium ion. The addition of magnesium chloride to the solution of EDTA is not necessary since the complex formed between the indicator and magnesium ion is highly stable. 1 ml of ammonia solution was added in order to enhance the solubility of EDTA in water. Ammonia / ammonium chloride buffer PH (10.5) was suitable media for the reaction to take place and for the EDTA-metal complex to be stable.

The proposed method was validated according to ICH guidelines. The linearity of the proposed method was established by least-square regression analysis of the calibration curve. The constructed curve was linear over the concentration range of 20-50 mg (R^2 = 0.9996). However, 50 mg is not the maximum capacity for the method, since titrimetric methods usually have high concentration capacities (table 1 and figure 1). Intra-day precision was estimated by assaying samples of the pure drug at three levels 24, 30 and 36 mg. Each sample was replicated five times and the results were averaged for statistical evaluation (table 2). Inter-day precision was evaluated by analyzing standard drug at three different levels, on three consecutive days (table 2).

Both intra-day and inter-day variation showed RSD % with values less than two, indicating a high degree of precision of the method.

Table 1. Linearity study of EMT.

Amount taken, mg	Average titrant volume (RSD), ml (n=3)
20	2.68 (2.37)
30	3.96 (0.00)
40	5.24 (1.21)
50	6.56 (0.97)

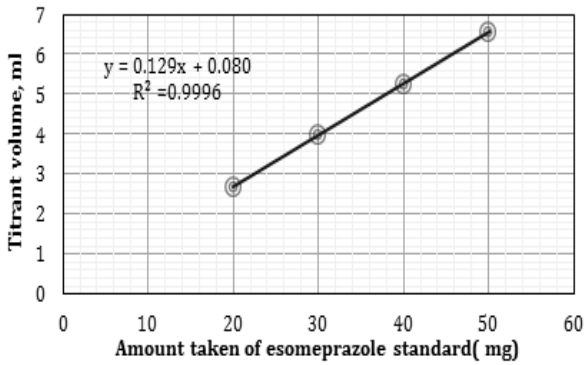

Figure 1 . Standard calibration curve of Esomeprazole magnesium.

The ruggedness was evaluated by analyzing the samples by varying few parameters like analysts and instruments. The obtained results (table 3) (RSD % < 2) confirm the independence of this method on the analysts and the types of instruments as long as the analysts are well qualified and the instruments are good. Thus, the results confirm the suitability of the proposed method for analysis of EMT.

Table 3. Ruggedness study.

Amount of EMT taken, mg	Inter-analysts		Inter-instruments	
	Titrant volume, ml	RSD, %	Titrant volume, ml	RSD, %
30	3.70 3.80 3.80	1.53	3.90 3.90 3.80	1.49

The recovery of the added amounts of standard drug was studied at 3 different levels 80, 100 and 120 %. Each level was repeated five times. From the amount of the drug found, the mean recovery % and RSD % were calculated.

Table 2. Intraday and inter-day precision and accuracy.

Amount of EMT taken, mg	Intra-day precision and accuracy			Inter-day precision and accuracy		
	Average weight of EMT found, mg	RSD, %	RE, %	Average weight of EMT found, mg	RSD, %	RE, %
24	23.75	1.51	1.06	23.82	2.15	0.74
30	29.94	1.22	0.21	29.99	1.74	0.04
36	36.30	1.29	0.84	36.05	1.46	0.13

Values of each level were determined and summarized in Table 4. The values of RSD % was satisfactory and mean recovery % were close to 100 %, demonstrating a good recovery of the proposed method. Accuracy studies were performed at three levels 24, 30 and 36 mg each concentration was determined in five analytical runs, and the RE % values were found to be less than 5 % indicating an acceptable accuracy.

Table 4. Recovery study

% of nominal value	Amount taken, mg	Amount found, mg	Average recovery	RSD, %
80	24	23.81	99.19	1.28
100	30	30.02	100.06	0.40
120	36	36.12	100.34	0.83
Mean			99.86	0.84

The accuracy of this method was further ascertained by comparing its results with the results obtained by a reported U.V method. The student's t-test was applied to determine whether there is a significant difference, at 95 % confidence level, between the results of these methods or not (table 5). The value of t-calculated (1.976) was less than t-tabulated (2.306), demonstrating that there is no a significant difference between the results of the proposed method and those of the reported method. The F-calculated also was less than F-tabulated (3.44). The results showed that the proposed method is as accurate and precise as that of the reported UV method. The similarity of the results is an obvious evidence that during the application of this method, the excipients present in the formulation do not interfere in the assay carried out by the proposed method. As an additional check of accuracy of the proposed method, recovery studies by using standard addition method were applied and the recovery % values were close to 100 % with satisfactory RSD % values, assuring that the method is suitable for application without interference of excipients and can be applied directly to the commercial tablets preparation without any previous treatment (table 6).

release of the drug from the capsule leading to misjudgement of the recovery percent.

4. Conclusion

The developed method is simple, cost-effective, accurate, rugged and precise. It does not involve any critical reaction conditions and overcomes a lot of drawbacks associated with the other methods such as high cost, multiple steps, several clean-up steps, pre-analysis treatments of the samples and organic solvents toxicity. This method can serve as an alternative method for the routine analysis of Esomeprazole magnesium in pure forms and in pharmaceutical tablet formulations.

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References

1.G. J. P. J, "Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis," Dig. Liver Dis., vol. 36, no. 4, pp. 253–259, 2004.

2.V. Gupta, D. Mishra, K. Raj, R. Dwiwedi, D. Rishika, and S. Narwal, "A Review:Development & Validation of HPLC Method for the Determination of Esomeprazole in Pharmaceuticals," Indo Glob. J. Pharm. Sci., vol. 2, no. 2, pp. 191–196, 2012.

3.P. R. Kumar, S. Shyale, S. M. S. Kumar, and P. Chemistry, "Physico-chemical characterization, UV spectrophotometric method development and validation studies of Esomeprazole Magnesium Trihydrate," J. Chem. Pharm. Res., vol. 2, no. 3, pp. 484–490, 2010.

4.P. V Kasture, "Analytical Method Development of Esomeprazole in Bulk and Tablet Dosage Form," Int. J. Pharm. Formul. Anal., vol. 2, no. 2, pp. 51–53, 2011.

5.N. Rahman, Z. Bano, S. Najmul, and H. Azmi, "Spectrophotometric Determination of Esomeprazole Magnesium in Commercial Tablets Using 5- Sulfosalicylic

Table 5. comparison study

Amount of EMT taken, mg	Tablet assay					
	Reported UV method			Proposed method		
	Amount found, mg	Percent%	Mean (RSD %)	Amount found, mg	Percent%	Mean (RSD %)
20	20.32 19.89 19.89 20.00 20.44	101.60 99.47 99.47 100.00 102.20	100.18 (1.26)	19.88 19.88 19.88 19.56 19.93	99.42 99.42 99.42 97.80 99.65	98.88 (0.76)
t-value	1.976					
F-value	2.75					

Table 6. Standard addition method

Pure EMT Added, mg	Titrant volume for pure EMT, ml	Average titrant volume for pure EMT, ml (RSD %)	Titrant volume for the mixture, ml	Recovery %	Mean % (RSD %)
30	3.80 3.80 3.80	3.80 (1.50)	7.70 7.70 7.60	102.56 102.56 100.00	101.71 (1.45)
39	5.10 5.10 5.10	5.10 (0.00)	8.90 8.80 8.70	100.00 98.03 96.07	98.03 (2.00)
45	5.80 5.80 5.90	5.85 (0.99)	9.60 9.60 9.60	101.70 101.70 101.70	101.70 (0.00)

(Amount taken of EMT from tablets = 30mg)

Spectrophotometric Method for Estimation of Esomeprazole in Tablet Dosage Form," indian J., vol. 2, no. 2, pp. 154–156, 2009.
7. M. C. Sharma and S. Sharma, "Spectrophotometric Methods for the Estimation of Esomeprazole magnesium trihydrate in Pharmaceutical Formulations Using Indigo Carmine Reagent," pharmatech, vol. 3, no. 2, pp. 1186–1190, 2011.
8. P. Mohan Raj, R. Veereswara Rao, P. B. Mukherjee, V. S. Sarvanan, N. Gopal, T. M. Kalyankar, and T. Shivakumar, "UV-spectrophotometric determination of esomeprazole in tablet dosage forms," Asian J. Chem., vol. 19, no. 4, pp. 3250–3252, 2007.
9. K. S. and G. V. K. Damodhar Reddy, "Determination of drugs based on oxidation by alkaline KMNO4 : A kinetic spectrophotometric study," Int. J. Pharm. Sci. Res., vol. 5, no. 7, p. 8232, 2014.
10. G. S. And M. D. Ar.Magesh, R.Vijayalakshmi, D.Satyavati, "Validated Spectrophotometric Estimation Of Esomeprazole Using Hydrotrophic Solubilisation Technique," Orient. J. Chem., vol. 26, no. 3, pp. 1191–1193, 2010.
11. V. V. G. and D. A. V .Chandewar, "Spectrophotometric Estimation Of Esomeprazole Magnesium in Solid Dosage form," Int. J. Pharm. Technol., vol. 2, no. 3, pp. 617–622, 2010.
12. A. Ğa and A. Öztunç, "Development and Validation of High Performance Liquid Chromatographic Method for The Determination of Esomeprazole in Tablets," J. food drug Anal., vol. 14, no. 1, p. 4000, 2006.
13. J. R. P. B. H. Patel , B. N. Suhagia, M. M. Patel, "Determination of Pantoprazole, Rabeprazole, Esomeprazole, Domperidone and Itopride in Pharmaceutical Products by Reversed Phase Liquid Chromatography Using Single Mobile Phase," Chromatographia, vol. 65, no. 11, pp. 743–748, 2007.
14. M. L. Ia Hultman, Helene Stenhoff, "Determination of esomeprazole and its two main metabolites in human, rat and dog plasma by liquid chromatography with tandem mass spectrometry," J. Chromatogr. B, vol. 848, no. 2, pp. 317–322, 2007.
15. T. S. Kumar, B. K. Kumar, A. S. Kumar, M. M. Mohan, S. S. Nanda, and P. Venkateshwarrao, "Development and Validation of RP-HPLC Method for Simultaneous Estimation of Esomeprazole and Domperidone in Pharmaceutical Dosage Form," J. Pharm. Res., vol. 4, no. 11, pp. 4097–4099, 2011.
16.[16] D. K. Jain and N. J. Nitesh Jain 1, Rita Charde 1, "The RP-HPLC method for simultaneous estimation of esomeprazole and naproxen in binary combination," Pharm. Methods, vol. 2, no. 3, pp. 167–172, 2011.
17. D. Vasudha Bakshi V. Tejasvi reddy , S.Hari hara kumar , M Akiful haque, "Method Development and Its Validation for Simultaneous Estimation of Domperidone and Esomeprazole by RP-HPLC in Combination Tablet Dosage Form," Int. J. Appl. Pharm. Sci. Res., vol. 1, no. 1, pp. 46–55, 2016.
18. A. N. Poornima, S. S. A, M. Ahmed, V. K. C. Aradhya, M. C. Ravi, and A. K. S. M, "RP-HPLC method development and validation for simultaneous estimation of esomeprazole and ondansetrone combined tablet dosage form'' World J. Pharm. Pharm. Science, vol. 4, no. 1, pp. 1041-1051, 2014.
19. M. N. Rao, K. B. M. Krishna, and B. H. Babu, "Development and Validation of a Stability Indicating HPLC Method for the Simultaneous Analysis of Esomeprazole and Itopride in Bulk and In Capsules," J. Appl. Pharm. science, vol. 6, no. 02, pp. 72–80, 2016.
20. D. G. Maheshwari and P. D. Trivedi, "Simultaneous Estimation of Esomeprazole and Domperidone in Combined Dosage form by HPLC," Int. J. Appl. Sci. Eng., vol. 9, no. 3, pp. 187–194, 2011.
21. D. . E. M. Ahmed R . AL- Sharqawi , Dr . Wael Abu Dayyih, "Method Development and Validation by High Performance Liquid Chromatography for simultaneous Determination of Esomeprazole and Tadalafil in Pharmaceutical Formulation," 2013.
22. A. Radi and A. Abd-elkader, "Voltammetric Behaviour of Esomeprazole at Screen Printed Carbon Electrode and its Determination in Capsule Dosage Form," Eurasian J. Anal. Chem., vol. 9, no. 2, pp. 92–101, 2015.