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DETERMINATION OF LAFUTIDINE THROUGH OXIDATIVE COUPLING REACTION IN BULK SAMPLE AND DOSAGE FORMS- A NEW APPROACH

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ABSTRACT: A simple, sensitive, highly accurate method has been developed for the determination of Lafutidine in bulk sample and dosage forms. This method is based on the oxidative coupling reaction of drug with 3-methyl-2-benzothialinone hydrazine hydrochloride (MBTH) reagent in the presence of ferric chloride to form green colored chromogen exhibiting maximum absorption at 630 nm. Beer's law was obeyed and quantitative results were obtained in the range of 1-18 μ g/mL. The results of the analysis for the methods have been validated statistically.

INTRODUCTION: Lafutidine, a newly developed histamine H₂-receptor antagonist, inhibits gastric acid secretion. It is currently marketed in Japan, China and India. It is not only suppresses gastric acid secretion, but also possesses cytoprotective properties. After oral administration, Lafutidine is quickly absorbed in the GIT. The plasma protein binding ability of Lafutidine is 88%. The drug is predominantly metabolized via CYP2D6 and CYP3A4 enzymes.

It decreases inflammation by modulating calcitonin gene-related peptide and vanilloid receptors. It is also found to stimulate mucin biosynthesis and promote the restitution of damaged mucosa. Lafutidine is mostly excreted in urine as drug metabolites and as unchanged drug, to some extent.

IUPAC name of Lafutidine is 2-[(2-furylmethyl)sulfinyl] - N- ((2Z)-4-[[4-(piperidin-1-ylmethyl) pyridine - 2 - yl] oxy]but - 2 - en - 1 - yl) acetamide **Fig. 1**.

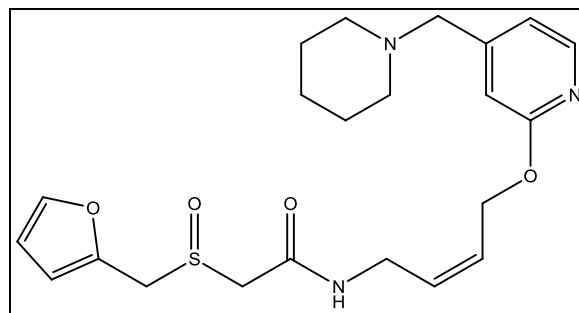


FIG. 1: STRUCTURE OF LAFUTIDINE

Lafutidine is a white to pale yellow crystalline powder. It is freely soluble in methanol, whereas it is practically insoluble in water. But Lafutidine is soluble and stable¹ in acidic medium. A survey on literature revealed that few UV-Spectrophotometric²⁻⁷, Spectrofluorimetric⁸, High performance liquid chromatographic⁹⁻¹⁸ and other¹⁹ methods were available for the estimation of the titled drug. However, according to the knowledge of the author no visible spectrophotometric method was reported

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so far. So, in the present investigation it was aimed to develop a novel visible spectrophotometric method with good accuracy, simplicity, precision and economically viable for the determination of Lafutidine in bulk and tablet dosage forms.

MATERIALS AND METHOD:

Instrumentation:

A UV-Visible spectrophotometer (Make-Analytical Technologies, model- Spectro-2080) with 10mm matched quartz cells was used. All weighing were done on electronic balance.

Reagents and Chemicals:

All the chemicals and reagents used were of analytical grade and only freshly prepared solutions were used in the present work.

MBTH Solution:

Prepared by dissolving 0.2 g of MBTH in 100 mL distilled water.

FeCl₃ Solution:

Prepared by dissolving 0.7g of ferric chloride in 100 mL 0.5N Hydrochloric acid solution.

Standard Stock Solution of Lafutidine:

100 mg of Lafutidine was accurately weighed and transferred into a standard 100mL volumetric flask and dissolved in 25mL of 0.1N Hydrochloric acid by shaking manually for 2 min. The volume was made up to the mark with the same solution. The concentration of the solution is 1000 µg.mL⁻¹.

Working Standard Solution of Lafutidine:

10 mL of standard stock solution was transferred into another 100 mL volumetric flask and made it up to the mark with 0.1N Hydrochloric acid to get 100 µg.mL⁻¹ solution.

Recommended Procedure:

Aliquots of working standard of Lafutidine solution (0.3,0.6,0.9,1.2,1.5 and 1.8mL) were added to a series of 10mL volumetric flasks. After that 2.0 mL of 0.2% MBTH solution followed by 1.0ml of 0.7% FeCl₃ were added to each flask and kept aside for 30 min. The volume was made upto the mark with distilled water. The absorbance was measured at 630nm against similar reagent blank. The amount of Lafutidine was determined from the

calibration curve (**Fig.3**).

Procedure for the Assay of Lafutidine in Pharmaceutical Dosage Forms:

Twenty tablets were weighed accurately and reduced to fine powder, Out of which drug equivalent to 100 mg of Lafutidine taken in a 100ml volumetric flask and dissolved in 25mL of 0.1N Hydrochloric acid by shaking manually for 2 min. The volume was made up with the same solution up to the mark, filtered by using Whattmann-42 filter paper. The filtrate was quantitatively diluted with 0.1N Hydrochloric acid to produce concentrations in the linear range of the assay of Lafutidine.

2. RESULTS AND DISCUSSIONS:

The proposed method for the determination of Lafutidine through Oxidative Coupling Reaction in Bulk Sample and Dosage Forms was found to be accurate, simple and rapid. Lafutidine possesses different functional groups such as secondary amine, ketone and ether of varied reactivity. The method is based on the oxidative coupling reaction with MBTH in the presence of FeCl₃. Under the reaction conditions, MBTH loses two electrons and one proton on oxidation, forming the electrophilic intermediate which can be substituted on Lafutidine to form a green coloured product. Probable mechanism of the reaction was given in the scheme (**Fig 2**).

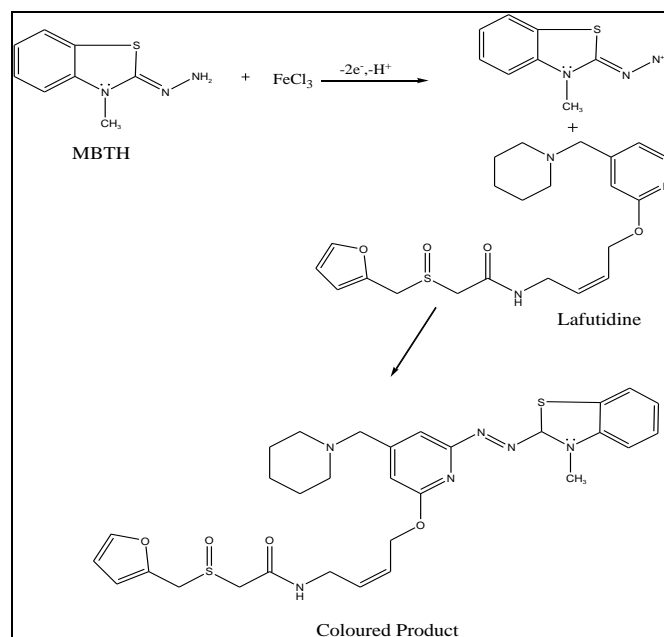


FIG.2: MECHANISM OF THE REACTION

The optimization of reaction conditions like time required for maximum colour development, effect of buffer, effect of concentration of ferric chloride and MBTH and effect of temperature were studied. Time scan was carried out to find the time required for maximum colour development.

It was noticed that a minimum of 25 minutes required for maximum colour development (Fig.3). It was also observed that the colour is stable for more than 5 hours.

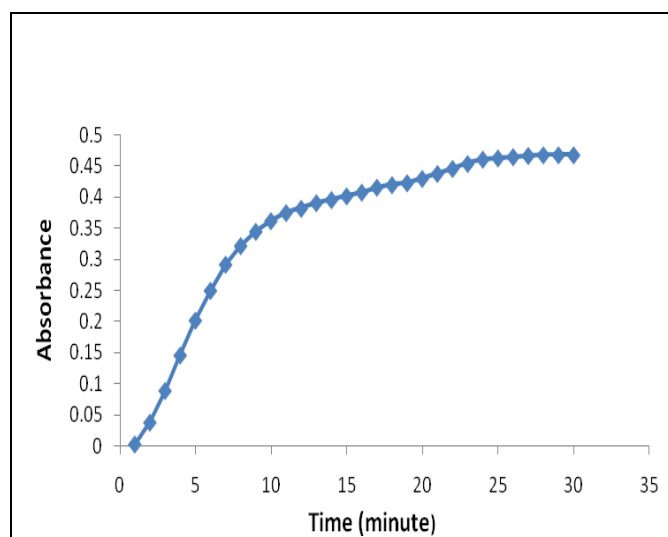


FIG.3: TIME SCAN: PROGRESS OF REACTION OF LAFUTIDINE WITH MBTH-FeCl₃

Colour development of drug with reagents (MBTH & FeCl₃) was carried out in acidic, basic and neutral media. But it was found that neutral medium has more absorbance compared to the other two shown in Table 1.

TABLE 1: EFFECT OF BUFFER ON COLOUR DEVELOPMENT

S.No	Medium	Absorbance
1	Acidic	0.434
2	Basic	0.464
3	Neutral	0.536

Different orders of additions were carried with Drug, MBTH and FeCl₃. But, not much variation in absorbance was observed. It was found that the order of addition of Drug, MBTH and FeCl₃ gave good results. Colour development experiment was carried out by changing the concentration of FeCl₃ from 0.5mL to 2.5mL. It was found that 1.0mL of FeCl₃ is optimum concentration shown in Table 2.

TABLE 2: VARIATION OF ABSORBANCE w.r.t FeCl₃

Volume of NaIO ₄ (0.2%)	Absorbance
0.5 ml	0.387
1.0 ml	0.628
1.5 ml	0.594
2.0 ml	0.603
2.5 ml	0.573

Colour development experiment was carried out by changing the concentration of MBTH from 0.5mL to 2.5mL. It was found that 2.0mL of MBTH is optimum concentration shown in Table 3.

TABLE 3: VARIATION OF ABSORBANCE w.r.t MBTH

Volume of MBTH (0.2%)	Absorbance
0.5 ml	0.419
1.0 ml	0.563
1.5 ml	0.601
2.0 ml	0.635
2.5 ml	0.559

Absorption spectra:

The absorption spectra of Lafutidine drug with 3-methyl-2-benzothialinonehydrazone hydrochloride (MBTH) in the presence of Ferric Chloride to form colored chromogen exhibiting maximum absorption at 630 nm. The reagent blank exhibited negligible absorbance despite having the same wavelength in the same region. The maximum absorption, progress of reaction of lafutidine and Beer's law validity were shown in Fig. 4-6.

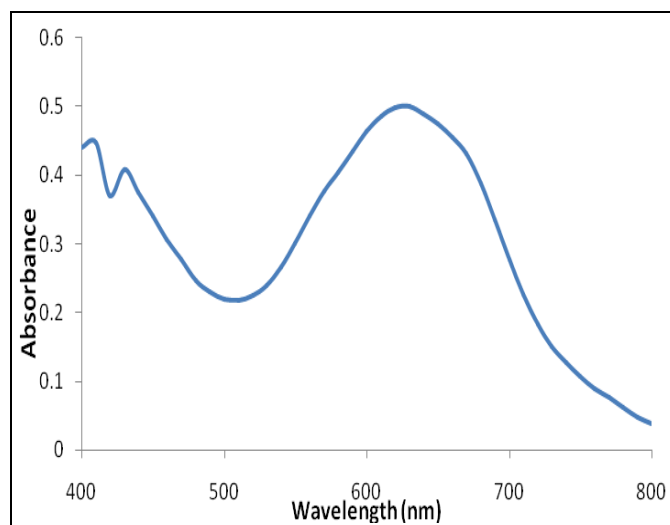


FIG.4: ABSORPTION SPECTRUM OF LAFUTIDINE WITH MBTH-FeCl₃

The analytical parameters obtained with the optimization experiments were given in Table 4.

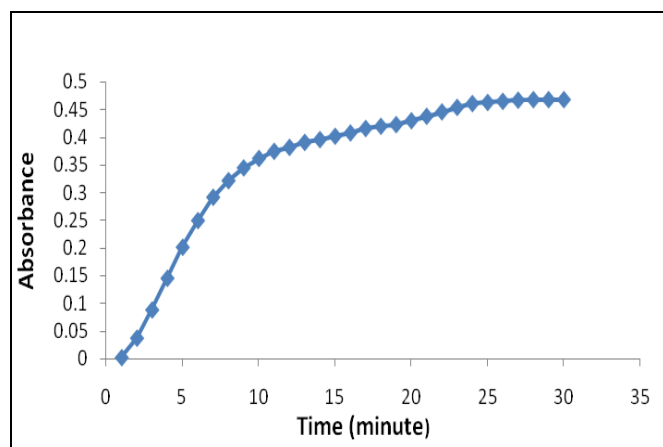


FIG.5: TIME SCAN: PROGRESS OF REACTION OF LAFUTIDINE WITH MBTH-FeCl₃

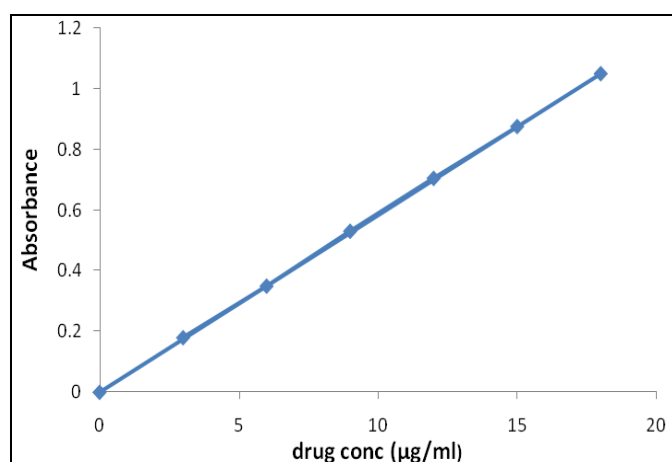


FIG.6: BEER'S LAW PLOT OF LAFUTIDINE WITH MBTH-FeCl₃

TABLE 4: ANALYTICAL PARAMETERS OBTAINED WITH OPTIMIZATION

Parameter	Value
Maximum absorption	630 nm
Colour of the product	Green
Molar absorptivity(L.mol ⁻¹ cm ⁻¹)	2.51x10 ⁴
Sandell's sensitivity (µg/cm ²)	0.01719
Beer's law limit(µg/ml)	1-18
Regression equation(Y=a+bX) slope(b)	0.05666
Intercept(a)	0.025
Y-absorbance and X-concentration in µg/ml	
Standard Deviation	0.37782
Limit of Detection (µg.mL ⁻¹)	0.22
Limit of Quantitation (µg.mL ⁻¹)	0.66

CONCLUSION: The proposed method was found to be simple, selective and sensitive. The statistical parameters clearly indicate the reproducibility and accuracy of the methods. Analysis of the authentic samples containing Lafutidine showed no interference from the common excipients. Hence, the method could be considered for the

determination of Lafutidine in the quality control laboratories.

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