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Analytical Method Development and Validation for Simultaneous Determination of Amoxicillin, Omeprazole and Rifabutin in Bulk and in a Synthetic Mixture by UV Spectroscopy

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ABSTRACT

Today Helicobacter pylori (H. pylori) infection is one of the very common bacterial infections worldwide. Upper gastro intestinal tract is primarily affected with this bacterial infection. H. pylori are primarily responsible for dyspepsia, gastric and duodenal ulcers and gastric carcinogenesis and obliteration of the infection has become an important treatment goal in clinical practice. Analysis of multi component formulations by any single analytical method is a very challenging task. A new, simple, precise, accurate, reproducible, and efficient UV spectrophotometric method is developed and validated for the simultaneous estimation of ternary mixture of amoxicillin (AMX), omeprazole (OMP) and rifabutin (RFB) in bulk and in a synthetic mixture which is recently approved by FDA in 2019 to be used for treatment of H. pylori by Vierordt's method or simultaneous equation method. The solutions of standard and sample were prepared in 0.1 N HCl. The λmax for AMX, OMP, and RFB were 230.0nm, 316.0nm, and 248.0nm, respectively. Calibration curves are linear in the concentration ranges 5-25μg/ml for AMX, 1-5μg/ml for OMP, and 1-5μg/ml for RFB, respectively. Results of study of simultaneous equation method were analyzed and validated for various parameters consistent with ICH guidelines.

Keywords: Helicobacter pylori, Amoxicillin, Omeprazole, Rifabutin, Vierordt's method, Method validation.

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INTRODUCTION

Helicobacter pylori (H. pylori) infection is extremely common worldwide. Around 40-50% of the world population affecting by this infection. H. pylori have been known as a group 1 carcinogen by the World health organization. According to World health organization H. pylori is associated with development of gastric cancer. Experimentally H. pylori obliteration has been demonstrated to have a prophylactic result against gastric cancer [1-4]. In human beings positive effect of H. pylori obliteration in reducing gastric cancer incidence has been reported [5-7]. The indications for H. pylori obliteration as proposed by an international agreement of experts (Maastricht III Consensus Report) [8, 9]. The revised Maastricht guidelines endorsed all the previous indications for H. pylori treatment. Triple therapies used PPI, primarily omeprazole (OMP), combined with amoxicillin (AMX) and rifabutin (RFB), which are given four capsules every 8 hours with food for 14 days regimen [9].

Omeprazole (OMP, Fig.1A) (RS)-6-methoxy-2-((4-methoxy-3, 5-dimethylpyridin-2-yl) methyl sulfinyl)-1H-benzo (d) imidazole is a proton pump inhibitor (PPI) and an anti-secretory compound. It works by suppressing gastric acid secretion by inhibiting the gastric H+ /K+ATPase (hydrogen-potassium adenosine triphosphatase) at the secretory surface of the gastric parietal cell [10-12]. OMP has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. After rapid disappearance from plasma, OMP can be found within the gastric mucosa for a day or more.

It is freely soluble in ethanol and methanol, slightly soluble in acetone and isopropanol and very slightly soluble in water. In triple therapy for H. pylori, OMP is useful in combination with the antibiotics clarithromycin and amoxicillin (or metronidazole in penicillin-hypersensitive patients) in the 7-14 day eradication. Literature survey suggested that there are some methods based on UV [13], HPTLC [14], capillary electrophoresis [15], HPLC [16-22] for the determination of OMP independently and in mixture with other drugs in dosage forms and biological fluids. Amoxicillin (AMX Fig. 1B) is a β-lactam antibiotic drug which belongs to the group of

penicillin group drugs [23]. It is a moderate-spectrum β-lactam antibiotic used to treat infections caused by penicillin-sensitive Gram-positive bacteria as well as some Gram-negative bacteria [24]. AMX chemically as (2S, 5R, 6R) [[(2R)-2-amino-2 (4 hydoxyphenyl) acetyl] amino]-3,3-dimethyl-7-oxo-4-thia1-azabicyclo [3.2.0] heptanes-2-carboxyic acid [25,26]. Various spectrophotometric, [27-30] HPLC, [31-36] HPTLC [37] and spectrofluorimetric [38] methods are reported in the literature for the estimation of AMX independently and in mixture with other drugs. Rifabutin (RFB Fig. 1C) is a synthetic derivative of rifamycin S isolated from Amycolatopsis rifamycinica that acts by inhibiting the DNA dependent RNA-polymerase of bacteria; it has been shown to have significant mycobactericidal (hence anti-tuberculosis) activity. RFB is a less potent microsomal enzyme inducer than rifampin, therefore it is the preferred rifamycin class antibiotic for treatment of TB in HIV-infected patients. RFB is readily absorbed from the gastrointestinal tract with a Cmax of about 375ng/ml reached 3.3h after a single 300-mg oral dose, under fasting conditions. RFB is actively degraded to its 25-O-desacetyl derivative in vitro with an activity almost equivalent to that of its parent compound [39, 40]. Few HPLC, [40-44] and capillary electrophoresis [45] methods are reported in the literature for the estimation of RFB individually and in combination with other drugs. However, no spectrophotometric method has yet been reported for simultaneous estimation of AMX, OMP, and RFB in pharmaceutical dosage forms. These methods mentioned in the literature, especially the chromatographic techniques, are time-consuming, costly, and require expertise. A simple and accurate UV spectrophotometric method developed can be highly useful for the routine analysis of capsule formulations. Hence, an attempt has been made to develop and validate in accordance with ICH guidelines [46].

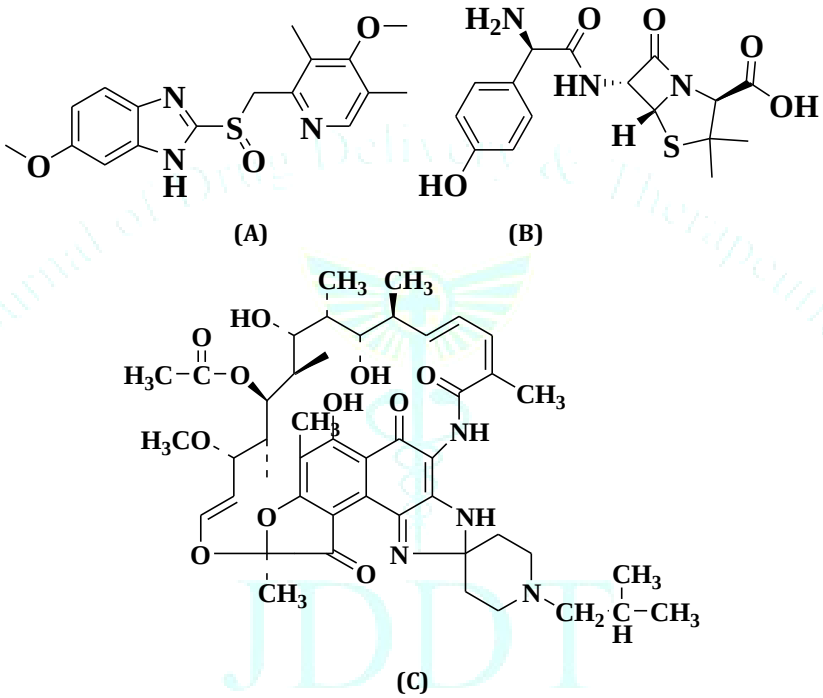

Figure 1 Chemical structure of (A) Omeprazole(B) Amoxicillin (C)Rifabutin

EXPERIMENTAL

Reagents and chemicals

Reference standard of AMX, OMP and RFB was a generous gift from Bioplus life science, Bangalore. Methanol, acetonitrile, HCl was procured from Rankem, RFCL Limited, New Delhi, India. All solvents and reagents were of analytical grade. All the solutions were protected for light and were analyzed on the day of preparations. Triple distilled water was generated in house. Talicia capsule (AMX 250mg/OMP10mg/RFB 12.5mg) was purchased from local market of Bhopal, India. Distilled water was obtained by Mili Q apparatus by Millipore (Milliford, USA) for whole experimental work.

Instrument

In UV-spectrophotometric method, Labindia model-3000+ series were used, which is a wavelength accuracy ±1 nm, with 1cm quartz cells.

Method development

Standard stock solution (Stock-A)

For preparation of standard stock solutions, weigh and dissolve 100 mg of each drug in 100 ml volumetric flask separately. Add some amount of 0.1 N HCl as a solvent for solubilizing the drugs. The flask was sonicated for about 10 minutes to solubilize the drug and the final volume was made up to the mark 100 ml with 0.1 N HCl to get a concentration of 1000 µg/ml (Stock-A) for each drugs.

Sub stock solution (Stock-B)

Aliquots of 2.5 ml withdrawn with help of pipette from standard stock solution Aof AMX, OMP and RFB and transferred into 25 ml volumetric flask separately and diluted up to 25 ml with 0.1 N HCl that gave concentration of 100 µg/ml (Stock-B).

Preparation of working standard solution

0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml and 2.5 ml from sub stock solution (Stock-B) were taken individually in 10 ml volumetric flask and volume was made up to 10 ml with 0.1

N HCl. This gave the working solutions of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml and 25µg/ml respectively for AMX. 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, 5 µg/ml of OMP and RFB also prepared in similar way.

Selection of wavelength for linearity

10µg/ml standard solutions of allAMX, OMP and RFBwere prepared from respective sub-stock solutions. The solutions were scanned in the wavelength region of 200-400 nm.The maximum absorbance of AMX, OMP and RFBwas observed at 230.0 nm, 316.0nm and 248.0 nm, respectively.AMX showed linearity in the concentration range of 5-25 µg/ml and OMP and RFB showed linearity 1-5µg/ml at their respective maxima. Calibration curve was plotted, absorbance versus concentration (Figure2-4).

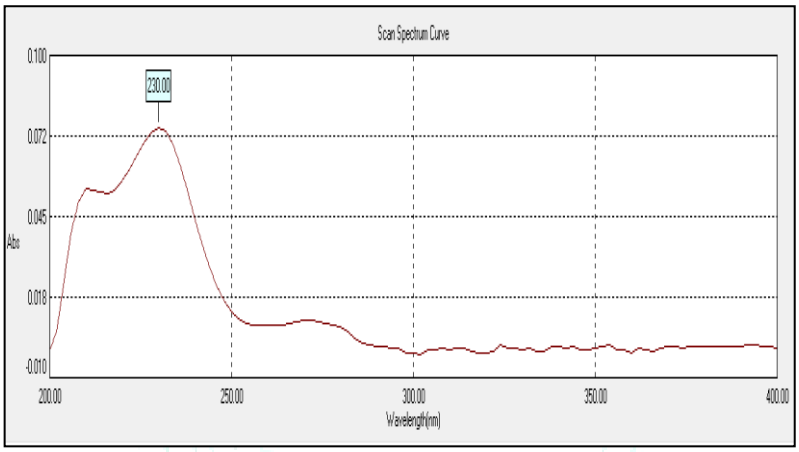

Figure 2: Determination of $\lambda_{max}$of AMX

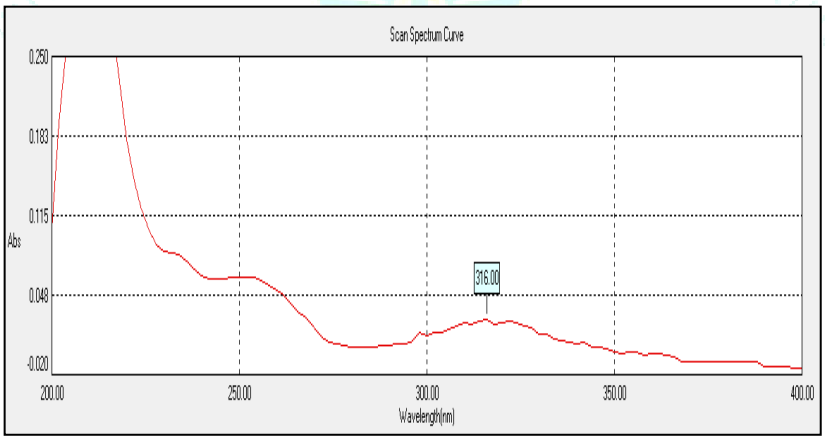

Figure 3: Determination of $\lambda_{max}$of OMP

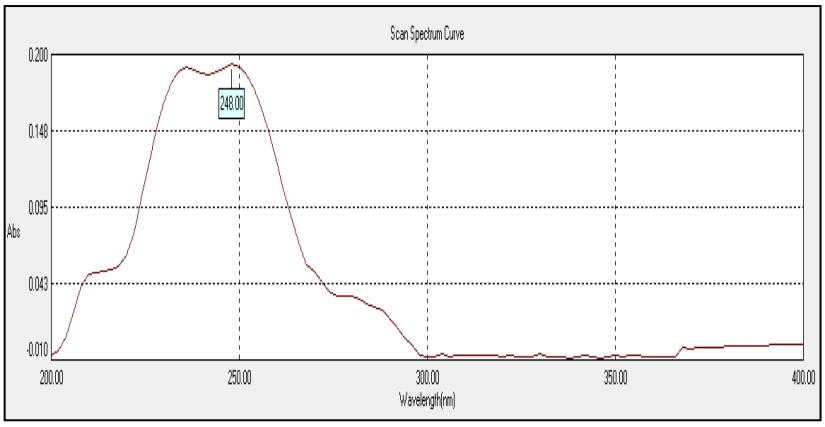

Figure 4: Determination of $\lambda_{max}$of RFB

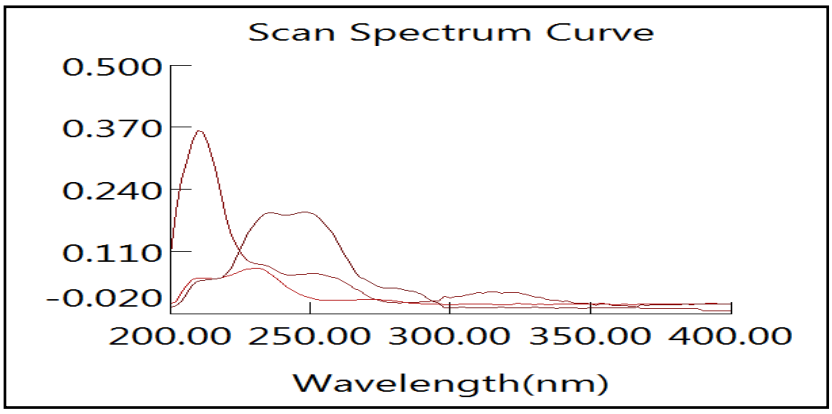

Figure 5: Overlay spectra of AMX, OMP and RFB

Preparation of calibration curve

Different aliquots were prepared from standard stock solution by dilution method. Pipette out the drug solution into a series of 10 ml volumetric flasks. Final volume was made up to the mark with the diluent to get a set of solutions having a concentration range of 5-25µg/ml for AMX and 1-5µg/ml for OMP and RFB. Triplicate dilutions of each drug solutions were prepared separately. The prepared working solutions of AMX, OMP and RFBwere scanned 230.0 nm, 316.0nm and 248.0 nm, respectively. The absorbance's were recorded and were plotted against the concentrations to obtain their respective calibration curves.

Simultaneous equation method

Simultaneous equation method is also known as vierodt's method. Absorption of drugs (d_1, d_2, and d_3) at the wavelength maximum of the other is a fundamental principle of this method. The wavelength maximum (λ_{max}) of AMOX, OMPR and RIFB were determined with the help of UV-spectroscopy which are 230.0 nm, 316.0nm and 248.0nm respectively.

The absorbance's were measured at the selected wavelengths and absorptivities ($A^{1\%,\ 1cm}$) for all the drugs at appropriate wavelengths were determined as mean of five independent determinations. Concentrations of the drugs in the samplewere calculated by using following equations.

$$CX = \frac{(A1(ay2az3 - az2ay3) - ay1(A2az3 - az2A3) + az1(A2ay3 - ay2A3))}{ax1(ay2az3 - az2ay3) - ay1(ax2az3 - az2ax3) + az1(ax2ay3 - ay2ax3)}$$

$$CY = \frac{(ax1(A2az3 - az2A3) - A1(ax2az3 - az2ax3) + az1(ax2A3 - A2ax3))}{ax1(ay2az3 - az2ay3) - ay1(ax2az3 - az2ax3) + az1(ax2ay3 - ay2ax3)}$$

$$CZ = \frac{(ax1(ay2A3 - A2ay3) - ay1(ax2A3 - A2ax3) + A1(ax2ay3 - ay2ax3))}{ax1(ay2az3 - az2ay3) - ay1(ax2az3 - az2ax3) + az1(ax2ay3 - ay2ax3)}$$

Where, A_1, A_2 and A_3 are absorbances of AMOX, OMPR and RIFB at λ_1, λ_2 and λ_3
ax1, ax2 and ax3 are the absorptivity of AMOX at λ_1, λ_2 and λ_3 respectively
ay1, ay2 and ay3 are the absorptivity of OMPR at λ_1, λ_2 and λ_3 respectively
az1, az2 and az3 are the absorptivity of RIFB at λ_1, λ_2 and λ_3 respectively

Mixed standard study

Capsules of AMX, OMP and RFB combination are available in 250:10:12.5mg. Mixed standard are prepared in the ratio of 1:2 from standard sub stock solution of 10µg/ml in 3 replicate of 5 concentrations. Solutions containing known concentration of three drugs are considered as laboratory samples (mix standards) to check the results of developed method.

Methods validation

Validation of the method was carried out in accordance with the International Conference on Harmonization Q2B guidelines 2005 [46].

Linearity

The linearity of analytical method was performed to confirm its capability to obtain test results that are directly proportional to the concentration of drug in sample within a specify range. Different levels of standard solutions were prepared and estimate into the UV and the results was recorded. The results of linearity are reported in table 1.

Accuracy

The accuracy of proposed method was evaluated by percent recovery studies. The recovery of the developed method was studied at 80%, 100% and 120% at three replicate and three concentrations level by standard addition method. The value of % means just close to 100, SD and % RSD are less than 2 indicate the accuracy of method. Result of recovery study shown in table 2.

Precision

Precision is closeness between series of measurements. Repeatability and Intermediate precision were studied under this parameter. Repeatability result indicates the precision under the same operating condition over short

interval time. The intermediate precision study is expressed within laboratory variation on different days and analyst to analyst variation by different analyst. The value of SD and %RSD are less than 2 indicate the precision of method. Result of precision shown in table 3.

Sample stock solution for assay

The results of the analysis of synthetic mixture were reported. Ten tablets powdered equivalent were mixed in a ratio of 250: 10:12.5 mg. A quantity of this Synthetic mixture powder equivalent to 25mg of AMX (1.0mg OMP and 1.25 mg RFB) was taken in 10 ml volumetric flask. Then 5ml of 0.1 N HCl was added and the flask was sonicated for about 10 min to solubilize the drug present in synthetic mixture and the volume was made up to the mark with 0.1 N HCl. Filter the solution using Whatman filter paper No. 41. Collect the filterate and further diluted with 0.1 N HCl to get the final concentrations of all drugs in the working range. The absorbances of final dilutions were observed at selected wavelengths and the concentrations were obtained from simultaneous equation method. The procedure was repeated for five times. The assay value of drugs was close to 100, SD and % RSD are less than 2 indicate the no interference of excipients in the estimation of drugs.

Table 1 Results of Linearity of AMX, OMP and RFB

Parameter	AMX	OMP	RFB
Concentration (µg/ml)	5-25	1-5	1-5
Correlation Coefficient (r^2)*	0.999	0.999	0.999
Slope (m)*	0.021	0.089	0.101
Intercept (c)*	0.002	0.004	0.002

*value of three replicate

Table 2 Results of recovery study

% Level	% MEAN±SD*		
	AMX	OMP	RFB
80%	98.02±1.749	98.17±1.025	98.75±0.693
100%	99.04±0.610	97.32±1.188	96.60±1.132
120%	99.17±0.449	98.63±1.610	98.26±1.278

* Value of three replicate and five concentrations

Table 3 Results of precision

Parameter	% MEAN±SD*		
	AMX	OMP	RFB
Repeatability	98.865±0.126	95.589±0.110	96.195±0.098
Intermediate precision			
Day to day precision	99.139±0.093	96.141±0.096	97.362±0.096
Analyst-to-Analyst	98.640±0.109	98.287±0.024	96.677±0.093
Reproducibility	99.016± 0.101	96.007±0.117	97.237±0.076

* Value of five replicate and five concentrations

Table 4 Assay of capsule formulation

Conc. Present (µg/ml)			Mean % Conc. Found		
AMX	OMP	RFB	AMX	OMP	RFB
5	1	1	99.30	98.50	95.50
10	2	2	99.15	98.50	97.75
15	3	3	98.77	99.50	99.50
20	4	4	99.35	96.75	97.13
25	5	5	98.86	98.00	98.70
		Mean	99.09	98.25	97.72
		S.D	0.260	1.000	1.534

*Average of three replicate and five concentrations

DISCUSSION

The developed method was validated in accordance with the International Conference on Harmonization [46] guidelines. Parameters like precision, accuracy, specificity, linearity and range, robustness and ruggedness was studied for the proposed method. The high value of the correlation coefficients (r 2 = 0.999 for AMX, 0.998 for OMP, and 0.999 for RFB) confirmed the linearity of the calibration plots. Recovery was in the range of 98.26-99.17%; the values of standard deviation and % RSD were found to be less than 2 showing the high accuracy of the method. Robustness and ruggedness were also carried out and percentage RSD was found to be less than 2.0%. The assay of AMX, OMP, and RFB was found to be 99.09%, 98.25%, and 97.72 %. Thus, the method provides a simple, convenient, rapid and accurate way to determine AMX, OMP, and RFBsimultaneously.

CONCLUSION

The vierodt's method has been successfully applied for simultaneous determination of AMX, OMP, and RFB in combined sample solution, and they were found to be accurate, simple, rapid, and precise. Once the equations were constructed, analysis required only measuring the absorbance values of the sample solution at the selected wavelengths followed by few simple calculations. The proposed method was completely validated showing satisfactory data for all the method validation parameters tested. Simultaneous equation method comparably noted to be very efficient in every aspect. Unlike HPLC, by using simultaneous equation method (UV) the data's can be generated applying simple calculations. So these methods can be easily and conveniently adopted for routine quality control analysis of these cited drugs.

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