

ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF CEFIXIME:
REVIEW

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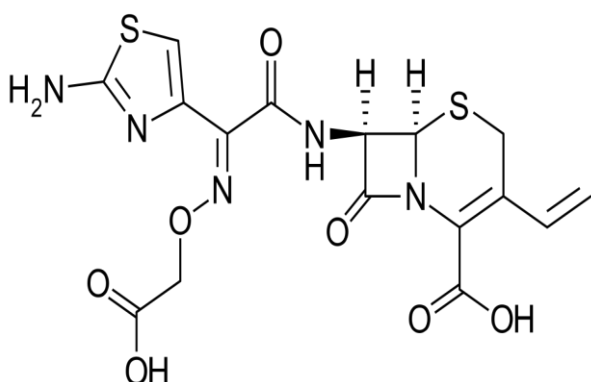
ABSTRACT

Analytical method development and validation are the continuous and interdependent task associated with the research and development, quality control and quality assurance departments. Analytical procedures play a critical role in equivalence and risk assessment, management. It helps in establishment of product specific acceptance criteria and stability of results. Validations demonstrate that the analytical procedure is suitable for its intended purpose. Literature survey reveals that the analytical methods based on UV spectrometry, RP-HPLC & HPTLC for the determination of Cefixime individually and in combination with other drugs. The methods were validated according to ICH guideline in terms of accuracy, precision, robustness, and other aspects of analytical validation. The developed methods are simple, sensitive and reproducible and can be used for the routine analysis of Cefixime in bulk and Tablet dosage form.

KEYWORDS: Cefixime, Literature Survey, Method Development, Validation, ICH Guidelines.

INTRODUCTION

Cefixime is an antibiotic useful for the treatment of bacterial infections. This includes otitis media, strep throat, pneumonia, urinary tract infections, gonorrhea, and Lyme disease. For gonorrhea typically only one dose is required. In the United States it is a second line treatment to ceftriaxone for gonorrhea.^[1]



Cefixime is chemically (6-aminothiazolo[5,4-d]thiazine-2-ylideneamino)-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, is a third generation cephalosporin antibiotic which is effective against a variety of gram-negative bacteria, including *K. pneumoniae*, *Escherichia coli* (*E. coli*), and *H. influenzae*. Cefixime binds

penicillin-binding proteins and is stable to many penicillinases and β -lactamases. It has a molecular formula of $C_{16}H_{15}N_5O_7S_2$ and molecular weight of 453.452 g/mol. Cefixime is sparingly soluble in water, slightly soluble in methanol R and ethanol. Brand name of Cefixime is Ceftas.^[2]

REVIEW OF LITERATURE

1. Amit Kumar^[3] *et al.*, To develop simple, sensitive, rapid, accurate and precise spectrophotometric method for estimation of cefixime and ofloxacin in tablet dosage forms. Pure drug samples of cefixime and ofloxacin were dissolved in a mixture of methanol and 0.1N HCl (1:1). Two wavelengths selected for formation and solving the simultaneous equations were 285.8nm for cefixime and 296.6nm for ofloxacin.
2. Avanija Dube^[4] *et al.*, To simple, rapid, accurate and precise spectrophotometric methods have been developed for simultaneous estimation of Cefixime and Ofloxacin from tablet dosage form. Method I involves formation of 'simultaneous equations' at 234 nm (λ max of Cefixime) and 296 nm (λ max of Ofloxacin); while Method II involves, formation of 'Absorbance ratio equation' at 275 (isoabsorptive point) and 296 nm using methanol as a solvent. The linearity was observed in the concentration range of 4 - 20 μ g/ml for Cefixime and 2 - 10 μ g/ml for Ofloxacin.

3. **Narendra Nyola^[5] *et al.***, A rapid, sensitive and specific uv-visible method was developed and validated for the estimation of Azithromycin and Cefixime in a tablet dosage form. The method was validated in terms of linearity, accuracy, precision, specificity, limit of detection and limit of quantitation. The optimum conditions for the analysis of the drug were established. The maximum wavelength of Azithromycin and Cefixime were found to be 235 nm and 288 nm respectively. The percentage recovery of Azithromycin and Cefixime were 100.28-100.33 and 99.68-100.29 respectively. Beer's law were obeyed in the concentration range of 10-50µg/ml for Azithromycin and 2-10 µg/ml for Cefixime.
4. **P.G. Bhang^[6] *et al.***, The simple, precise and economic UV methods have been developed for estimation of Cefixime in single component. Cefixime has the absorbance maxima in zero order spectra in 230 nm (method A). Method B applied was first order derivative for the analysis of Cefixime at 238.5nm. Method C applied was area under curve in the wavelength range of 234-228 nm. Drug followed Beer-Lamberts law in the concentration range of 503.5 µg/ml for zero order, 10-60 µg for area under curve methods and first order derivative spectrum. The percentage recovery of Cefixime ranged from 98.05 to 101.075 in pharmaceutical dosage form result of analysis was validated statistically and by recovered study.
5. **S S Pekamwar^[7] *et al.***, A simple, accurate, sensitive, economical and reliable first order derivative spectrophotometric method was developed and validated for the estimation of cefixime and moxifloxacin in pharmaceutical dosage form. The optimum conditions for the analysis of the drugs were established. First order derivative method was developed for quantification of cefixime and moxifloxacin. Spectrum was obtained by dissolving cefixime and moxifloxacin in methanol and water (60:40 v/v); wavelength selected was 260 nm for cefixime and 316 nm for moxifloxacin. The Beer's law was obeyed in the concentration range of 2-12 µg/ml. Results of tablet analysis showed percent relative standard deviation (% RSD) in the range of 0.1576 to 0.2183 for cefixime and moxifloxacin which indicate repeatability of the method respectively.
6. **S. N. H. Azmi^[8] *et al.***, A simple, accurate and precise direct spectrophotometric method has been developed for the determination of cefixime in tablets and capsules. The method is based on the reaction of cefixime with a mixture of potassium iodide and potassium iodate to form yellow coloured product in ethanol-distilled water medium at room temperature which absorbed maximum at 352 nm. The factors affecting the reaction product were carefully studied and optimized. The validation parameters based on International Conference on Harmonisation (ICH, USA) guidelines were followed. The effect of common excipients used as additives has been tested and the tolerance limit was calculated for the determination of cefixime. Beer's law is obeyed in the concentration range of 4 – 24µg mL⁻¹ with apparent molar absorptivity of 1.52×10^4 L mol⁻¹cm⁻¹ and Sandell's sensitivity of 0.033 µg/cm²/ 0.001 absorbance unit. The limits of detection and quantitation for the proposed method are 0.32 and 1.06 µg mL⁻¹, respectively.
7. **K Kavitha rani^[9] *et al.***, To develop and validate a simple, accurate, precise HPLC method for the estimation of cefixime and ofloxacin. The chromatographic separation was achieved on a Hypersil BDSC18 column (4.6x250 mm, 5µm particle size). Different mobile phase systems in different proportions were tried. For HPLC method a mobile phase consisting of Methanol and Water (70:30) produced symmetric peak shape with good resolution for both the drugs. The retention times of cefixime and ofloxacin were found to be 2.96 min and 4.15 min, respectively. The proposed method was found to have excellent linearity in the concentration range of 20- 80mg/ml with correlation coefficient r²=0.999 and 0.999 for cefixime and ofloxacin respectively.
8. **Arpit Patwari^[10] *et al.***, High performance liquid chromatography and absorbance correction methods were developed and applied for the simultaneous determination of ofloxacin and cefixime. Chromatographic separation was achieved on reversed-phase C18 column(25 cm × 4.6 mm id, 5 µm) in the isocratic mode using methanol-water-triethylamine (25:75:1.5, v/v/v), pH adjusted to 3.50 ± 0.05 with orthophosphoric acid as the mobile phase at a flow rate 0.9 ml/min. Quantitation was achieved with UV detection at 254 nm. In the proposed HPLC method, quantification was achieved over the concentration range of 5-30 and 5-30 µg/ml, with mean recoveries of 99.95±1.31 and 100.36±1.24% for ofloxacin and cefixime respectively. In the absorbance correction method, quantification was achieved over the concentration range of 5-25 µg/ml for both drugs, with mean recoveries of 101.23±0.85 and 100.53±1.40% for ofloxacin and cefixime respectively. Determination was performed at 262.5 and 345.5 nm for ofloxacin and cefixime.
9. **K. Kathiresan^[11] *et al.***, A rapid and sensitive RP-HPLC 1,2 method with UV-150 detection (220nm) for routine analysis of Cefixime and Dicloxacillin tablet formulation was developed, chromatography was performed with mobile phase containing a mixture of potassium hydroxide buffer and acetonitrile (60:40 v/v) using column C18 – inertstil

with flow rate 1.0ml/min in the range of 20ml. In the linearity range of 60-140 µg/ml, cefixime and Dicloxacillin shows a correlation coefficient of 0.9959 and 0.9949 respectively.

10. **M. Prasad Rao^[12] *et al.***, To develop a new, simple, sensitive, accurate, and economical analytical methods for the estimation of related compounds in Cefixime formulations. Validate the proposed methods in accordance with USP, EUROPE and ICH guidelines for the intended analytical application. Identify whether the given sample is Cefixime by IR spectroscopy and solubility test. To determine the wavenumber in cm⁻¹ (reciprocal to wave length region) of given sample by Infrared Spectroscopy. To determine the moisture content present in the given sample of Cefixime by Karl Fischer method. Find out the assay and related substances (impurities) of given Cefixime by using the validated method with help of High performance Liquid Chromatography.
11. **Nidhi S Patel^[13] *et al.***, A stability-indicating reverse phase high performance liquid chromatography method was developed and validated for cefixime and linezolid. The wavelength selected for quantitation was 276 nm. The method has been validated for linearity, accuracy, precision, robustness, limit of detection and limit of quantitation. Linearity was observed in the concentration range of 2-12 µg/ml for cefixime and 6-36 µg/ml for linezolid. For RP-HPLC, the separation was achieved by Phenomenex Luna C18 (250×4.6 mm) 5 µm column using phosphate buffer (pH 7): methanol (60:40 v/v) as mobile phase with flow rate 1 ml/min. The retention time of cefixime and linezolid were found to be 3.127 min and 11.986 min, respectively.
12. **Pranay kumar Deekonda^[14] *et al.***, A simple, rapid, selective, precise and economical RP-HPLC method has been developed and validated for the quantitative estimation of Cefixime and Ofloxacin in pharmaceutical preparation. Chromatographic separation was achieved on using Kromasil C18 column (250 mm x 4.6 mm, 5µm i.d) analytical column with mobile phase consisting of 40:60 v/v mixture of Ammonium Acetate buffer: Acetonitrile. flow rate was 1.0 ml/min and the detection of wavelength was 294nm. In the developed method Cefixime and Ofloxacin elute at typical retention times of 2.26 min and 3.24 min respectively. The proposed method has permitted the quantification of Cefixime in the linearity range of 60 -140 µg/mL and for Ofloxacin in the range of 60 - 140 µg/ mL. The intraday and interday precision was found less than 2% and the LOD and LOQ for Cefixime were found to be 0.146 - 0.44 µg/ml and for Ofloxacin were found to be 0.16 - 0.49 µg/mL respectively.

13. **Hossein Danafar^[15] *et al.***, A simple and available reversed-phase HPLC method with UV detection has been urbanized and validate for cefixime evaluate in human plasma using a C18 analytical column and a mobile phase of tetrabutylammonium hydroxide (pH 6.5)-acetonitrile (3:1v/v). The detection wavelength was 280 nm. To method observed major linear response concentration association all through the cefixime concentration range of 15- 100 ng/ml, with the average accuracy within-run and between-run values of 97.29% and 99.27%. The average drug recovery from plasma was 98.2% throughout the linear concentration range. The limits of detection (LOD) and quantitation (LOQ) of the method were 5 and 15 ng/ml, respectively.

CONCLUSION

Literature survey suggested that various HPLC, UV, and few HPTLC methods were developed and reported. The published methods were validated for various parameters as per ICH guidelines. Statistical analysis proved that the published methods were reproducible and selective. Thus it can be concluded that the reported and published methods can be successfully applied for the estimation of the Cefixime in bulk and pharmaceutical dosage form.

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