

ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF CEFADROXIL:
REVIEW

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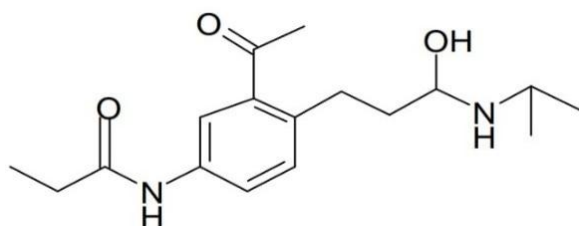
ABSTRACT

Analytical method development and validation are the uninterrupted and free task associated with the research and development, quality control and quality assurance departments. Analytical procedures play a important role in the equivalence and risk assessment, management. Validations demonstrate that the analytical procedure is suitable for its intended applications. Literature survey reveals that the analytical methods based on UV spectrophotometry, RP-HPLC & HPTLC for the determination of Cefadroxil individually and in combination with other drugs. The methods were validated according to ICH guideline in terms of accuracy, precision, robustness, and other parameters. The reported methods are simple, sensitive and reproducible hence this can be used for the routine analysis of Cefadroxil in bulk and pharmaceutical dosage form.

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

INTRODUCTION

Cefadroxil is a semi-synthetic first generation oral cephalosporin, similar to cephalexin and cephadrine in structure and spectrum of antibacterial activity. It is used in the treatment of mild to moderate infections of the respiratory and urinary tracts, skin and soft tissue infections. It has been used in the prophylaxis of recurrent urinary tract infections in children. Although the microbiological activities of cephalosporins are similar when measured by traditional susceptibility testing^[1]



CEFADROXIL

Cefadroxil is chemically (6R, 7R)-7-[(2R)-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrate, is a cephalosporin first generation drug effective against gram-positive and gram-negative bacterial infections. It has a molecular formula of C₁₆H₁₇N₃O₅S and molecular weight of 363.38g/mol. CFD is freely soluble in water and methanol. Brand name of Cefadroxil is Duricef.

REVIEW OF LITERATURE

1. Patel C.^[3] *et al.*, Have established a simple and sensitive spectroscopic method for the estimation of CEFAD in pharmaceutical dosage forms. This method is based on CEFAD, showing absorbance at 257 nm in methanol. This method obeys Beers law in the concentration range of 10 to 100 µg mL⁻¹ respectively. The proposed method is precise, accurate and reproducible and can be extended to the analysis of CEFAD in bulk and tablet formulations.

2. S Sethuraman^[4] *et al.*, Have reported a simple accurate, precise and cost effective UV-spectrophotometric method for the estimation of Cefadroxil. A first generation cephalosporin an antibiotic drug in bulk and pharmaceutical dosage form. The solvent used in the combination of water and methanol in the ratio of 75:25 and the λ max of the absorption maxima of the drug was found to be 224nm. The method obeys Beers law in the concentration range of 10-50 µg/ml respectively. The developed method was subjected to stress degradation under different conditions as per ICH guidelines.

3. Pradip D.^[5] *et al.*, Have developed a simple, precise, accurate, and economical UV visible spectrophotometric method has been developed for estimation of Cefadroxil drug by AUC method. The standard and sample solutions were prepared by using double distilled water as a solvent. Quantitative determination of the drug was performed at wavelength range 260-266 nm. The

linearity was established over the concentration range of 05-25 µg/ml for Cefadroxil with correlation coefficient value of 0.9993. Precision studies showed that % relative standard deviation was within range of acceptable limits. The mean percentage recovery was found to be 99.26%. The proposed method have been validated as per ICH guidelines.

4. Dey S^[6] *et al.*, Have established a cost effective UV-Vis spectrophotometric method for the estimation of cefadroxil, a first generation cephalosporin an antibiotic drug, in bulk and pharmaceutical dosage form. The solvent used was methanol and distilled water (50:50) and the λ_{max} or the absorption maxima of the drug was found to be 264nm. A linear response was observed in the range of 1050µg/ml with a regression coefficient of 0.9999. The method was then validated for different parameters as per the I.C.H. (International Conference for Harmonization) guidelines. This method can be used for the determination of cefadroxil in quality control of formulation without interference of the excipients. Cefadroxil was subjected to stress degradation under different conditions recommended by I.C.H.

5. Shantier SW^[7] *et al.*, Have established a simple spectrophotometric method has been developed for the determination of cefadroxil in pure bulk and in capsules forms. The method is based on a direct reaction between cefadroxil and sodium hydroxide (1 N). A product with λ_{max} at 342 nm and molar absorptivity of 7.9×10^3 L mol⁻¹ cm⁻¹ is formed after heating cefadroxil with sodium hydroxide (1 N) for 30 minutes. The absorbance-concentration plot was rectilinear over the range 5-25 µg/mL with correlation coefficient values not less than 0.999. The detection limit (LOD) and quantification limit (LOQ) were 0.693 µg/mL and 2.31 µg/mL. The method was validated using the BP liquid chromatographic method for cefadroxil assay. The results obtained by the developed method for the capsules dosage form were statistically compared with those of the BP liquid chromatography method and evaluated at 95% confidence limits.

6. Rao KG^[8] *et al.*, Have reported a new simple and precise reverse phase high performance liquid chromatographic method has been developed and validated for the estimation of cefadroxil monohydrate in bulk and its pharmaceutical dosage form. The chromatographic separation was performed by using mobile phase consisting of KH₂PO₄: acetonitrile in the ratio of 65:35 % v/v and the pH 3.5 adjusted with 0.2% orthophosphoric acid. The column used was Hypersil ODS C18 (250 × 4.6 mm, 5µ) with flow rate of 1 ml/min using PDA detection at 220 nm. The described method was found to be linear over the range of 20-80µg/ml and correlation coefficient was found to be 1 with a retention time of 3.257min. The assay of cefadroxil was found to be 99.98 %. The results of the study showed that the proposed RP-HPLC method is simple, rapid, precise,

reliable, accurate and economical which is useful for the routine determination of cefadroxil monohydrate in bulk and its pharmaceutical dosage form.

7. Bianca Aparecida De Marco^[9] *et al.*, Have developed a new and efficient method has been developed and validated for the identification and quantification of the cefadroxil monohydrate capsules by RP-HPLC, aiming the contribution to the green chemistry since it has low use of organic solvent and low production of toxic waste. The RP-HPLC method was performed in isocratic mode with temperature at 25°C. The mobile phase consisted of ethanol + acidified water with orthophosphoric acid 0.1% (8:92 v/v), on column ZorbaxSB C18 (150 mm x 4.6 mm, 5 µm) at a flow rate of 0.8 mL min⁻¹ with 10 µL of injected volumes, with UV/DAD detection at 230 nm. The method was linear over the concentration range of 20–120 µg/mL with ($r = 0.9999$) and retention time (RT) equal to 6.1 minutes. Statistical analysis provided reliable, safety and reproducible results. The method did not use buffering solutions, presented good analysis time and practicality in the execution making economic for the industry. The method is considered adequate and safe to be used in routine quality control analyzes for determination and quantification of cefadroxil monohydrate capsules.

8. Anjum A.^[10] *et al.*, Have reported a simple, precise, specific and accurate RP-HPLC method has been developed for the determination of cefadroxil monohydrate in bulk and pharmaceutical dosage forms. Chromatography was performed on a supelco RP C-18 column (250 mm × 4.6 mm) with 5µm particle size. The mobile phase consists of two solvents methanol and 0.05M disodium hydrogen orthophosphate buffer (60:40 v/v) and with pH 3.0 adjusted with ortho-phosphoric acid. At a flow rate of 0.75 mL/min. Detection was performed at 264 nm. The retention time of cefadroxil monohydrate was found to be 4.108 min. By adoption of this procedure cefadroxil monohydrate is eluted completely. Linear calibration plots were obtained between 20-100 µg/ml. The method of analysis was used for quantification in pharmaceutical preparations with a coefficient of variation < 2%. Results of analysis were validated statistically and by recovery studies. The method was validated according to the ICH guidelines with respect to specificity, linearity, accuracy, precision and robustness.

9. Rahim N.^[11] *et al.*, Have developed a High Performance Liquid Chromatographic (RP-HPLC) method for the analysis of cefadroxil in bulk material and oral solid dosage forms has been developed and validated. The chromatographic system consisted of Sil-20A auto sampler, LC-20A pump and SPD-20A UV/visible detector. The separation was achieved by C18 column at ambient temperature with a mobile phase consisting of methanol: Phosphate buffer (10: 90) at a flow rate of 1.5 ml/min. The method is reproducible, repeatable (%RSD for intra-day and inter-day ranged

between 1.75-5.33% and 0.58-2.69%) and linear ($R^2=0.9935$). The LOD and LOQ of the method were 0.5 and 1.0 $\mu\text{g/ml}$, respectively. The present RP-HPLC method was found to be sensitive, accurate, precise, rapid and cost effective that can be efficiently used in QC/QA laboratories for routine analysis of the raw materials as well as oral dosage formulations of cefadroxil.

10. Shukla RS^[12] *et al.*, Have established a rapid, accurate, and sensitive method has been developed and validated for the quantitative determination of cefadroxil (first generation) in bulk form. An Inertsil ODS, 4.60×250 mm², 5 μm analytical column was used with an eluting system consisting of a mixture of phosphate buffer (pH 6.5)-methanol 78-32% (v/v) at a flow-rate 1.5 ml/min. Detection was performed by UV-Vis detector at 210 nm, resulting in limit of detection of 0.06 ppm for cefadroxil per 20- μl injection. A linear relationship was observed up to 0.2 ppm for cefadroxil. Analysis time was less than 10 min. The statistical evaluation of the method was examined by means of within-day repeatability ($n = 6$) and day-to-day precision ($n = 7$) and was found to be satisfactory with high accuracy and precision. The method may be applied for the determination of the cefadroxil in bulk formulation in future.

11. Vasuda B. Pisal^[13] *et al.*, Have reported a new simple High Performance Thin Layer Chromatographic (HPTLC) method for determination of Potassium Clavulanate and Cefadroxil in combined tablet dosage form has been developed and validated. The mobile phase selected was Methanol: Ethyl acetate: Formic acid (1.5: 8: 0.8, v/v/v) with UV detection at 230 nm. The retention factor for Potassium Clavulanate and Cefadroxil were found to be 0.77 ± 0.011 and 0.39 ± 0.007 , respectively. The method was validated with respect to linearity, accuracy, precision and robustness as per the International Conference on Harmonisation (ICH) guidelines. Results found to be linear in the concentration range of 2000-12000 ng/band for Potassium Clavulanate and 500-3000 ng/band for Cefadroxil respectively. The method has been successfully applied for the analysis of drugs in pharmaceutical formulation. The % assay (Mean \pm S.D.) was found to be 100.06 ± 0.916 for Cefadroxil and 99.93 ± 0.996 for Potassium Clavulanate. The method can be used for routine analysis of these drugs in combined tablet dosage forms in quality-control laboratories.

12. Vittaladevaram V.^[14] *et al.*, Have developed a rapid, accurate and sensitive method has been developed for the quantitative determination of Cefadroxil (first generation) in different pharmaceutical formulations. An C-18 ODS, 4.60×250 micro meter analytical column was used with an eluting system consisting of a mixture of phosphate buffer (pH 4.8)-Methanol-Acetonitrile 95-3-2% (v/v) at a flow rate 1ml/min. Detection was performed by UV-Vis Detector at 230nm, for Cefadroxil per

20microlitre injection. The proposed method is suited both for the determination of Cephalosporins in a wide variety of commercial dosage forms and for the investigation of related compounds and other impurities in Cephalosporins.

13. Dhoka MV^[15] *et al.*, Have developed a rapid, precise, accurate, specific, and sensitive high performance liquid chromatographic method and high performance thin layer chromatographic methods have been developed for simultaneous determination of cefadroxil monohydrate and ambroxol hydrochloride in their tablet formulation. The HPLC method was standardized using Purospher BDS C18 column (25cm X 4.6mm, 5 μm) with mobile phase constituted of 0.5M ammonium acetate buffer- acetonitrile (50:50v/v), pH adjusted to 7 using orthophosphoric acid delivered at the flow rate of 1.0 mlmin-1 and detection was performed at 247nm. For HPTLC analysis separation was carried out on precoated TLC plates, coated with silica gel 60F-254 and using mobile phase methanol- potassium dihydrogen phosphate (0.067M) (35:65v/v) scanned at 254nm with CAMAG TLC scanner controlled by Cats Software. Different analytical performance parameters such as linearity, accuracy, precision, repeatability, robustness LOD and LOQ were determined according to International conference of Harmonization ICH Q2B guidelines.

14. Musty S^[16] *et al.*, Have established a simple, sensitive, accurate, precise and selective stability indicating reverse phase high performance liquid chromatographic method has been developed and validated for the determination of ambroxol and cefadroxil in bulk drug and pharmaceutical dosage form. Separation and quantification were achieved on a Phenomenex C18, 5 μm , 150 x 4.6 mm i. d. column using PDA detector. The mobile phase was 0.1% OPA: methanol (50:50 v/v), at a flow rate of 1 ml/min and injection volume was 10 μL . Detection was carried out at a wavelength of 249 nm. The method was validated for precision, accuracy and robustness. Good linear relationship in the concentration range of 12-36 $\mu\text{g/ml}$ for ambroxol with correlation coefficient of 0.999 and 60-180 $\mu\text{g/ml}$ for cefadroxil with correlation coefficient of 0.999. The LOD and LOQ for Ambroxol were found to be 0.0680 mg/ml and 0.2268 mg/m for cefadroxil were found to be 0.244mg/ml and 0.813mg/ml, respectively. The precision was less than 2% RSD for both analytes.

15. Kumar CA^[17] *et al.*, Have reported a simple, rapid and selective method has been developed for the spectrophotometric determination of cefadroxil and ceftriaxone using 1, 2- naphthaquinone-4- sulfonic acid sodium

CONCLUSION

Literature survey signifies that the various HPLC, UV and few HPTLC methods were published 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 Cefadroxil in pure and pharmaceutical dosage form.

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