REVIEW OF LITERATURE

There are many methods available on the analysis of these Cephalosporins. They include both classical and instrumental methods. The methods have been developed keeping in view the requirements. Consequently, certain methods are also focused on the analysis of the drug from biological fluids.

- **Okamoto Y et al (1990)**[12] reported hydrolytic degradation products of cefdinir were studied in acidic (pH 1), neutral (pH 6), and basic (pH 9) solutions. Seven major degradation products were isolated by preparative and/or high-performance liquid chromatography and characterized by UV, IR, 1H-NMR, and mass spectra. To clarify degradation pathways in each pH solution, kinetic and product analyses during hydrolysis of cefdinir were carried out along with the followup reaction of representative degradation products. Cefdinir was shown to degrade via two major degradation routes: beta-lactam ring-opening and pH-dependent isomerizations (lactonization, epimerization at C-6 or C-7, syn-anti isomerization of N-oxime function).

- **Okamoto Y et al (1996)**[13] reported The validation of the HPLC method used for the determination of cefdinir and its related substances is described. The developed method was specific and stability-indicating and provided a linear response with concentration. The system and method precision, expressed as relative standard deviations, were not greater than 1%, and the reproducibilities within and between laboratories were acceptable for the assay method. The procedure can quantitate related substances greater than approximately 0.05% of the principal cefdinir peak.

- **Kees F et al (1996)**[14] reported In a cross-over study on twelve healthy volunteers cefpodoxime proxetil (CAS 87239-81-4) and acetylcysteine (CAS 616-91-1) were evaluated for possible pharmacokinetic interactions. After a standardized breakfast, the subjects received p.o. either 200 mg cefpodoxime administered as cefpodoxime proxetil (reference) or 200 mg cefpodoxime and 200 mg acetylcysteine (test). To determine the pharmacokinetic profile of cefpodoxime the plasma concentrations were determined by HPLC. The plasma concentration-time curve of cefpodoxime was very similar after both regimens, and with respect to cefpodoxime bioequivalence has been proven. The
narrow range of 90% confidence intervals for the quotient test/reference for Cmax and AUC indicate reliable bioavailability of cefpodoxime proxetil independent of co-administered acetylcysteine.

- **F Camus et al (1994)**[^15] reported selective HPLC method is described for the determination of cefpodoxime levels in plasma and sinus mucosa. Sample preparation included solid-phase extraction with a C8 cartridge. Cefpodoxime and cefaclor (internal standard) were eluted with methanol and analyzed on an optimised system consisting of a C18 stationary phase and a ternary mobile phase (0.05 M acetate buffer pH 3.8-methanol-acetonitrile, 87:103, v/v) monitored at 235 nm. Linearity and both between- and within-day reproducibility were assessed for plasma and sinus mucosa samples. Inter-assay coefficients of variation were lower than 13.6% (n = 10) for plasma (0.2 micrograms/ml) and lower than 12.4% (n = 5) for sinus mucosa (0.25 micrograms/g). The quantification limit was 0.05 micrograms/ml for plasma and 0.13 micrograms/g for tissue. The method was used to study the diffusion of cefpodoxime in sinus mucosa.

- **N. H. Vadia et al (2009)**[^16] reported new, simple, cheap, fast, accurate, sensitive and precise colorimetric methods that can be used for the determination of cefetamet pivoxil hydrochloride. The first proposed method is colorimetric method using folin ciocalteu reagent and sodium hydroxide, color of newly formed complex was measured at room temperature within one hour; while the second method is derivative spectrophotometric method, first derivative spectra at sensitivity 2 were obtained for different standard drug solutions and the amplitude was calculated between maxima and minima. The developed methods were successfully applied to the determination of this drug in synthetic mixtures and commercially available tablets.

- **T. Madhusudana Reddy et al (2003)**[^17] reported Electrochemical reduction behavior of cephalosporins, Cefixime (CF) and Cefpodoxime Proxetil (CP) have been studied by using different voltammetric techniques in Britton-Robinson buffer system. Two well defined cathodic waves are observed for both the compounds in the entire pH range. Number of electrons transferred in the reduction process was calculated and the reduction mechanism is proposed. The results indicate that the process of both the compounds is irreversible and diffusion-controlled. The peak currents for CF and CP are found to be linear over the range of concentration 6.0×10⁻⁸ to 1.2×10⁻⁵ mol l⁻¹ and
8.8×10^{-8} to 1.1×10^{-5}\text{mol l}^{-1}, respectively. The lower detection limits are found to be 4.6×10^{-8} and 8.52×10^{-8}\text{mol l}^{-1} for the two compounds. A differential pulse voltammetric method has been developed for the determination of these drugs in pharmaceutical formulations and urine samples.

- **Silber Michael B, et al. (1987)**\(^{[18]}\) reported a simple, accurate and precise isocratic reversed-phase high performance liquid of a new cephalosporin in human serum and urine. Mobile phase was prepared fresh on the day of analysis. Mobile phase A was prepared by combining 170ml of acetonitrile, 1.36g of monobasic sodium phosphate, 2ml of 85\% phosphoric acid and 828ml of distilled water. Mobile phase B (used for urine assay) was prepared by combining 200ml of acetonitrile, 1.36g of monobasic sodium phosphate, 2ml of 85\% phosphoric acid and 798ml of distilled water at pH 2.7 with flow rate of 2.0ml/min.

- **Castillo M, et al. (1988)**\(^{[19]}\) reported the degradation rate constants for ampicillin and for dicloxacillin in the suspension filtrate, and their solubility coefficients (at 25\(^\circ\)) by spectrophotometry employing a multicomponent computer program.

- **Eric-jovanovic S, et al. (1998)**\(^{[20]}\) reported a HPTLC method for the determination of ceftriaxone, cefixime and ceftaxime, on a pre-coated silica gel HPTLC plates with concentrating zone (2.5x10cm) by developing mobile phase ethyl-acetone-methanol-water (5:2.5:2.5:1.5 v/v/v/v). at 270nm.

- **Gehad G. Mohamed, et al. (2006)**\(^{[21]}\) reported a simple rapid and accurate spectrophotometric method for the determination of β-lactum drugs, flucloxacillin and dicloxacillin in pure form and different preparations. The absorption of Fluclox and Diclox are recorded in different pH values ranged from 2 to 12 and the curves at pH 2-12 are characterized by two absorption bands at 225 - 270, and 225 - 274nm. for Fluclox and Diclox respectively.

- **Nanda RK, et al. (2009)**\(^{[22]}\) reported accurate, precise, rapid and economical methods for the estimation of cefixime and ornidazole in tablet dosage form. It is based on simultaneous equation and wavelengths selected for analysis were 290.0nm for cefixime and 312.0nm for ornidazole.

- **Shahnaz Gauhar, et al. (2009)**\(^{[23]}\) reported a RP-HPLC Method for the analysis of Cefixime in Bulk Material and in Capsule Consisting of a LC-10 AT VP pump, SPD-
10AVP UV/ visible detector with Column as Bondapak C18 with mobile phase consist of Methanol: Buffer solution (sodium dihydrogen phosphate) in the ratio of 35:65 at a flow rate of 1ml/min.

- **Dhoka Madhura V, et al. (2010)**[^24] reported a simple, precise, accurate and sensitive Reverse phase high liquid chromatographic method for simultaneous estimation of Cefixime trihydrate and Erdosteine in combined capsules dosage form. Drugs were resolved on a HiQ Sil C8 column (25x4.6mm) utilizing mobile phase of TetraButyl Ammonium Hydroxide (0.1N) pH adjusted to 6.5 with Orthophosphoric acid (10%aqueous) in a ratio of 2:1. Flow rate 1.0ml/min. at 254nm.

- **Kumudhavalli M.K, et al. (2010)**[^25] reported a reversed phase High performance liquid chromatographic for simultaneous estimation of cefixime and potassium clavanate in tablet dosage form by mobile phase consisting of 0.03M phosphate buffer and methanol in the ratio of 84:16 with wavelength is 220nm and flow rate is 1ml/min.


- **Yost RL et al (1985)**[^27] reported A reversed-phase high-performance liquid chromatographic assay for the simultaneous determination of cefotaxime and its metabolite desacetylcefotaxime in plasma and urine was developed. Plasma was deproteinized with small amounts of acetonitrile. After separation of the proteins the supernatant was extracted with a mixture of chloroform and 1-butanol. A phase separation was obtained leaving the cephalosporin and its metabolite in the aqueous part and extracting most of the interfering endogenous material. The aqueous phase was injected directly into the chromatograph. As part of the plasma water was dissolved in the acetonitrile--1-butanol--chloroform layer, the concentration of the cephalosporin in the aqueous phase was significantly higher than in the original plasma sample. Therefore, the usual diluting effect of the deproteinization could be avoided. In a similar way the assay was applicable to measure cefotaxime and its metabolite in urine. Calibration curves were set up and were linear up to 25
micrograms/ml for desacetylcefotaxime and 250 micrograms/ml for cefotaxime. The assay was applied to study the pharmacokinetics of cefotaxime and its metabolite in a healthy volunteer. In a similar way this deproteinization and extraction method was also applied to assay for ceftazidime, cephalexin, cephazolin and cefoxitin.

- **Ling SS et al (2003)**\(^{[28]}\) reported a high-performance liquid chromatographic method with ultraviolet (UV) detection was developed for measuring cefotaxime in rat and human plasma. The method used direct injection of the plasma supernatant after deproteinization with 70% perchloric acid. Degradation of cefotaxime in acidic medium was retarded by adding phosphate buffer before centrifuging the sample. The mobile phase was 0.05 M aqueous ammonium acetate-acetonitrile-tetrahydrofuran (87:11:2, v/v) adjusted to pH 5.5. Analysis was run at a flow-rate of 1.0 ml/min, and a detection wavelength of 254 nm was used. The method has a quantification limit of 0.20 microgram/ml. The within- and between-day coefficients of variation and accuracy values were less than 8% and +/-3%, respectively, while the recovery values were greater than 87% over the concentration range tested (0.20-50 microgram/ml). The speed, sensitivity, specificity and reproducibility of this method make it particularly suitable for the routine determination of cefotaxime in human plasma. Moreover, only a relatively small sample plasma volume (100 microliter) is required, allowing this method to be applied to samples taken from neonates.

- **Martinez LG et al (1998)**\(^{[29]}\) reported Cefotaxime was derivatised with 1,2-naphthoquinone-4-sulphonate (NQS), extracted into solid-phase cartridges (C18) and detected using a UV-visible detection system. Optimum conditions for this new procedure were: hydrogencarbonate-carbonate buffer, pH 10.5, 5-min reaction time at 25 degrees C and an NQS concentration of 7.1x10\(^{-3}\) mol l\(^{-1}\). The accuracy and the precision of the liquid-solid procedure were tested. The procedure was used to measure cefotaxime in pharmaceutical and urine samples. The results obtained were contrasted with those reported for a HPLC method for urine samples. The generalized H-point standard additions method was used to measure cefotaxime in urine samples.
• **Nuevas L et al (1998)** report Cefotaxime sodium is a broad spectrum third generation antibiotic. It is obtained by reaction of 7-aminocephalosporanic acid (7-ACA) and S-(2-benzothiazolyl)2-amino-alpha-(methoxyimino)-4-thiazoleethanethioate.

2-Mercaptobenzothiazole is a by-product of this reaction. A derivative spectrophotometric determination of cefotaxime is proposed for its determination in a reaction mixture in the presence of the related compounds from synthesis. With this method Beer's law is obeyed over a concentration range from 0.005 to 0.080 mg ml(-1) at 276.8 nm (r = 0.9995). This technique is accurate, precise (RSD = 0.4%), and has a sensitivity of 1.2% (differences in analytical response of 0.74 microg ml(-1) could be detected). Recovery experiments of cefotaxime from reaction mixtures include 100% for all assayed concentrations. For these reasons, this technique is found valid for the intended purposes.

• **Scanes T et al (2001)** reported A simple and sensitive HPLC method for the simultaneous determination of cefotaxime (I) and desacetylcefotaxime (II) in human plasma and cerebrospinal fluid (CSF) is described. The assay involves deproteinisation and subsequent separation on a reversed-phase HPLC column, with ultraviolet detection at 262 nm. Retention times were 6.8 and 2.2 min for cefotaxime and desacetylcefotaxime, respectively. Average recoveries for the analytes were 78% (I) and 88% (II) from both matrices. Linear responses were observed over a wide range (0.58-940 microg/ml for (I) in plasma, 0.80-55.8 microg/ml for (I) in CSF, 0.54-148 microg/ml for (II) in plasma and 0.50-36.0 microg/ml for (II) in CSF)

• **Dell D et al (1981)** reported a high-performance liquid chromatographic method is described for the analysis of the anti-bacterial agent cefotaxime and desacetylcefotaxime in physiological fluids. Plasma or serum samples were mixed with chloroform--acetone to remove proteins and most lipid material. The aqueous phase was then freeze-dried, reconstituted in mobile phase and chromatographed on a reversed-phase column using UV detection at 262 nm. Urine was analysed directly after centrifugation to remove particulate matter. The detection limit was 0.5--1.0 micrograms/ml for serum and 5 micrograms/ml for urine. The method has been
applied to the analyses of cefotaxime and desacetylcefotaxime in plasma, serum, urine, cerebrospinal fluid, saliva, and pus from infected wound secretions. Two additional metabolites, which are lactones in which the beta-lactam ring has been opened, could be separated by this method.

- **Dokladalova J et al (1983)[33]** reported a gradient high-performance liquid chromatographic (HPLC) procedure has been developed for the determination of microgram amounts of cefoperazone in human serum and urine. The method employs a muBondapak C18 column and gradient elution with two mobile phases. Excellent separation of the drug from potential degradation products as well as from representative penicillins (sodium ampicillin, sodium methicillin, potassium penicillin G) and aminoglycosides (tobramycin, gentamicin, kanamycin) has been demonstrated. Coefficients of variation of 7.3% or less were obtained for 25-100 micrograms/ml cefoperazone in both serum and urine. Average recoveries of the drug from spiked serum and urine samples corresponded to 97.6% and 98.6%, respectively. Amounts as low as 1 microgram cefoperazone per ml of sample can be estimated using sample volumes corresponding to 0.1 ml serum or 1 ml urine. Good correlation between the HPLC assay and a microbiological cylinder-plate assay employing Micrococcus luteus ATCC 9341 has been demonstrated for human serum and urine of patients treated with cefoperazone. While the microbiological method is less time-consuming, it lacks specificity in the presence of other antibiotics. The HPLC method can be used to analyze cefoperazone in the presence of penicillins and aminoglycosides which can potentially be co-administered with cefoperazone.

- **Li FS et al (2000)[34]** reported A reversed-phase, isocratic high performance liquid chromatographic method with acid mobile phase can separate sulbactam and cefoperazone within 12 minutes. Column packed with Hypersil ODS2(250 mm x 4.6 mm i.d., 5 microns) was manufactured by Dalian Elite Company. Mobile phase is composed of water (adjusted to pH 4.0 with 1% phosphoric acid) and acetonitrile (80:20, V/V). The detection was performed at 210 nm and the injection volume was 2 microL. Cefoperazone and sulbactam have good linearity in the ranges of 100 mg/L to 800 mg/L and 100 mg/L to 1,000 mg/L with the correlation
coefficients of 0.9991 and 0.9997 respectively. This method is easily to be operated and can be applied for manufacturing and medicinal study.