

## RESEARCH ARTICLE

# Detection of Ceftriaxone antibiotic and removal via complexation with Fe (III).

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### Abstract

Antibiotic pollution in the aquatic environment has emerged as one of the most serious concerns caused by the use of pharmaceuticals and personal care products (PPCPs). Antibiotic levels in wastewater from pharmaceutical factories and hospitals have been detected at varying levels. An effective method for the removal of ceftriaxone (a  $\beta$ -lactam antibiotic) in aqueous systems has been developed. The method uses Fe(III) to complex ceftriaxone and removes it from the solution. Ultraviolet (UV) and Fourier Transform Infra-Red (FTIR) detection techniques were used to identify the ceftriaxone-Fe(III) complex, while high-performance liquid chromatography (HPLC), was used to quantify the amount of ceftriaxone removed. Results showed that 99.7 % of ceftriaxone was removed in 3 h by Fe (III) ions in a 1:1 concentration ratio at pH 3.3 and at room temperature. The study demonstrated that reaction time, and concentration ratio of the reactants are critical parameters for effective complexation. The complexation reaction technique has the potential to be used in a treatment process for the removal of ceftriaxone chemically from industrial wastewater. However, a neutralization step is required to process the waste aqueous phase.

**Key words:** Ceftriaxone; Ferric chloride; UV; FTIR; HPLC.

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### Introduction

Antibiotics may end up in municipal sewage or hospital wastewater in their original form or as metabolites after being consumed by humans and animals (Yuan et al. 2011). Antibiotics, have become a type of 'pseudo-persistent' pollutant in the aquatic environment due to their widespread and continuous use in daily life, despite the fact that they have relatively short half-lives are relatively shorter than those of persistent organic pollutants (POPs) (Wang et al. 2011). Antibiotic residue in the environment is partly to blame for the emergence of drug-resistant bacteria (Jian et al. 2021)

Ceftriaxone sodium is a third-generation cephalosporin broad-spectrum antibiotic with higher bactericidal activity against one type of bacteria (gram-positive) and less activity against another type of bacteria (gram-negative) (Kusumaningrum et al. 2020; Alaa et al. 2011). Ceftriaxone sodium exerts its antibacterial effects by binding to a protein found in the bacterial cell wall (Kondaiah et al. 2017). A metal complex of ceftriaxone, such as the ceftriaxone-Fe(III) has antimicrobial activity against a variety of bacteria, including *Salmonella enterica* (*S. enterica*), *Escherichia Coli* (*E. coli*), *Proteus mirabilis* (*P. mirabilis*), and *Klebsiella pneumoniae* (*K. pneumoniae*) (Alaa et al. 2011; Yuan et al. 2011). The determination of ceftriaxone is not only necessary for human health, and the environment, but also for quality control in the food industry as it is added in refined sugar and food products as an antibiotic.

Unfortunately, ceftriaxone is not readily biodegradable, and so traditional wastewater treatment processes may not be effective for its removal (Wang et al. 2018). As a result, the risk of the emergence of various types of resistant bacteria high, and so is a critical environmental problem, and a threat to public human health (Moreira et al. 2016; Kong et al. 2015; Liu et al. 2012). There are many techniques and deferent methods for the removal of antibiotics from

industrial wastewater such as the classical biological treatment (Gulkowska et al. 2008; Costanzo et al. 2005; Lin et al. 2009; Minh et al. 2009; Li et al. 2009; Li et al. 2011; Sim et al. 2011; Leung et al. 2012; Julia et al. 2014; Yu et al. 2016; Tamuraa et al. 2017; Guo et al. 2015), the use of activated carbon derived from agriculture wastes (Samarghand et al. 2015; Ahmed et al. 2012; Nazari et al. 2016), photolysis and oxidation-based processes (Khorsandi et al. 2019). Photolytic transformation results in products with increased acute toxicities (Wang et al. 2012), and the removal of cephalosporins by chlorination has also been investigated and shown to increase genotoxicity (Bing et al. 2013).

As Fe(III) form a metal complex with ceftriaxone, and is a good coagulant for the removal of contaminants in wastewater stream, this project studied the extent of its effectiveness in the removal of ceftriaxone in an aqueous system (as a model for pharmaceutical industrial wastewater) by varying its ratio to that of ceftriaxone. The ceftriaxone-Fe(III) complex formed was examined by both FTIR and UV analysis. The quantity of residual ceftriaxone remaining after complexation/precipitation with Fe(III) was determined by HPLC to establish the preferred operating condition for the removal of ceftriaxone from an aqueous system.

## 2. Materials and Methods

Fresh solutions of ceftriaxone sodium powder from Zhuhai united-lab. India and FeCl<sub>3</sub> from oxford laboratory reagents, India were prepared. For mobile phase preparations, monobasic potassium phosphate and dibasic sodium phosphate were obtained from Scharlau laboratotries, Spain, and tetradecyl ammonium bromide was obtained from Sisco research Lab. Private Limited, India.

UV-spectrophotometer (Perkin Elmer) made in Germany was used for spectrophotometric study and FTIR-spectrophotometer (Perkin Elmer L1600400) spectrum two FTIR/DTGS, made in Germany, used for obtaining IR spectrum for drug and its complexes and Mettler Toledo pH-meter (Seven Multi), made in Japan that used for measuring and pH adjustments.

The HPLC used is a Hewlett Packard, 1100 series (hp), made in America, with column type (C18, BDS), size is ( length 25cm, Internal diameter 4.6 mm) stationary phase C18(BDS)(5µm), column temperature is 30°C, flow rate 1.5 ml/min., injection volume 20 µL and detector type UV-spectrophotometer and detection at 254 nm and the chromatographic system as per United state pharmacopeia (USP 43):

Mode: LC, Detector: UV 254 nm, Column: 4.6-mm × 25-cm; 5-µm packing L1, Flow rate: 1.5 mL/min and Injection volume: 20 µL. The mobile phase was prepared by preparation of:

- Solution A: 9 g/L of monobasic potassium phosphate in water.

- Solution B: 24 g/L of dibasic sodium phosphate, and dodecahydrate in water.

- Solution C: 20 g/L of citric acid in water. Adjust with 10 N sodium hydroxide to a pH of 5.0 prior to final dilution.

- Buffer solution: Combine 389 mL of Solution A and 611 mL of Solution B. Adjust with 10 N sodium hydroxide TS or phosphoric acid to a pH of 7.0.

Mobile phase: Dissolve 2.0 g each of tetradecyl ammonium bromide and tetraethylammonium bromide in a mixture of 440 mL of water, 55 mL of buffer, 5.0 mL of Solution C, and 500 mL of acetonitrile.

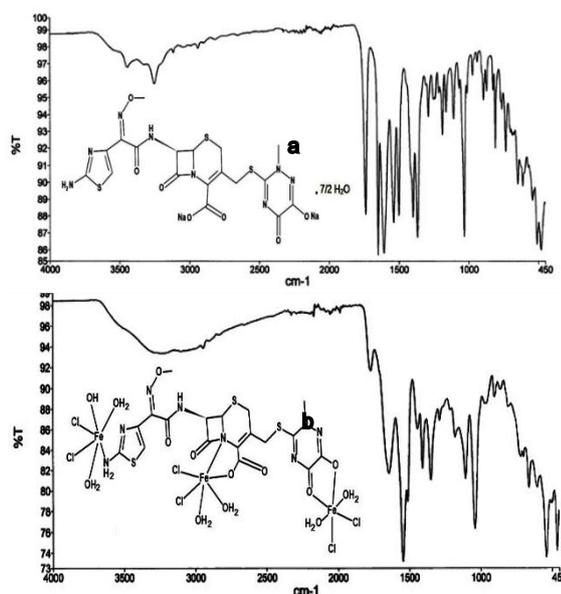
Addition of freshly prepared FeCl<sub>3</sub> solution dropwise with constant stirring in one direction to ceftriaxone sodium solution with concentration ratios of 1:1 and 10:1. The reaction time varied between 1 to 24 h. at pH=3.3 at room temperature. The mother liquor was filtered through 0.4 µm filter paper, and the solution was analyzed by HPLC to obtain the peak area of Ceftriaxone. The concentration of ceftriaxone has been determined from the calibration curve equation ( $a = 4e-8 b + 4e-6$ ) with relative error (2%),  $R^2 = 0.999$  in which (a) is the concentration of Ceftriaxone-Na and (b) is the absorbance peak area.

## 3. Results and Discussion:

### 3.1. FTIR spectrophotometry study

FTIR spectrophotometry study was carried out to identify intensities of the vibrational bands of ceftriaxone sodium and ceftriaxone-Fe(III) complex. The vibrational band measurements was then compared with those obtained from previous studies (Alaa et al. 2011; Gunasekaran et al. 2008). The main frequencies of amine, lactam (C=O) and amide or ester (C=O) in the spectra of ceftriaxone-Na have been shifted as a red shift (Bathochromic shifting) when compared with the spectra of ceftriaxone-Fe complex which indicates formation of the complex (Figure (1) and Table (1))





**Figure 1.**

- a) Infrared spectrum and molecular structure of Ceftriaxone-Na  
 b) Infrared spectrum and molecular structure of ceftriaxone-Fe(III) complex.

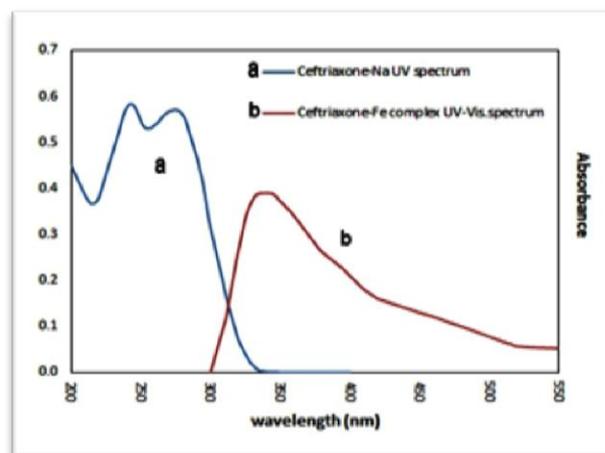
**Table 1.** Functional groups of ceftriaxone-Na and ceftriaxone-Fe (III) complex.

Compound	$\nu$ (NH <sub>2</sub> ) Amine group	$\nu$ (CO) Lactam ring	$\nu$ (CO)amide / $\nu$ (CO) ester	$\nu$ (COO) asymmetric
Ceftriaxone-Na	3454	1737	1648	1607
[Fe <sub>3</sub> (ceftriaxone)OHCl <sub>6</sub> ].6H <sub>2</sub> O	3241	1768	1641	1543

According to the previous studies,  $\beta$ -lactam antibiotics (e.g., ceftriaxone) can be coordinated with metal ions such as Fe<sup>3+</sup>, Cu<sup>2+</sup>, Co<sup>2+</sup>, Mn<sup>2+</sup>, and Cd<sup>2+</sup> (Alaa et al. 2011; Gunasekaran et al. 2008). Three metal ions donors are bond with the ceftriaxone ligand molecule to form the complex. The coordination occurs between the ceftriaxone anion and the metal ions through the oxygen atom of the lactam ring carbonyl group or the carboxylate group and the amide group. In case of Fe(III), the suggested ceftriaxone ligand molecule to form the complex. The coordination occurs between the ceftriaxone anion and the metal ions through the oxygen atom of the lactam ring carbonyl group or the carboxylate group and the amide group. In case of Fe(III), the suggested formula is [Fe<sub>3</sub>(ceftriaxone)OHCl<sub>6</sub>].6H<sub>2</sub>O and is shown in (Fig.1 (b)) (Alaa et al. 2011). The best conditions for complex formation of ceftriaxone-Fe(III) complex were in acidic aqueous media at pH=3.3 at room temperature.

### 3.2. UV spectrophotometry study

The maximum absorption of ceftriaxone-Na was obtained at wavelength ( $\lambda_{max}$ ) = 242 nm (Fig.2 (a)) and reduces because of the addition Fe(III) ions that cause complexation reaction with the ceftriaxone molecules (Fig.2 (b)). The maximum absorption of 2x10<sup>-5</sup> M of ceftriaxone-Na,  $A_{max}$  = 0.587, and it dropped by addition of 2x10<sup>-5</sup> M of FeCl<sub>3</sub> after the 1st h. This shows that ceftriaxone-Na concentration reduced and ceftriaxone-Fe complex formed due to the complexation reaction as shown in (Fig.2(b)).



**Figure 2.**

- a) Ceftriaxone-Na UV-spectrum at conc. 2x10<sup>-5</sup> M and ( $A_{max}$ ) = 0.587 - ( $\lambda_{max}$ ) = 242 nm  
 b) Ceftriaxone- Fe complex UV-Vis. Spectrum ( $A_{max}$ ) = 0.390 - ( $\lambda_{max}$ ) = 334 nm

### 3.3. HPLC Study

The HPLC study was carried out to determine the optimum condition for the removal of ceftriaxone by FeCl<sub>3</sub>. Ceftriaxone-Na is the salt of ceftriaxone antibiotic and it is a powder that contains not only the antibiotic, but water and other components. So, in this study the ceftriaxone concentration was calculated based the HPLC calibration curve using a standard ceftriaxone. Variations in the concentrations of FeCl<sub>3</sub> and ceftriaxone, and the reaction time were studied at constant pH of 3.3 and ambient temperature.

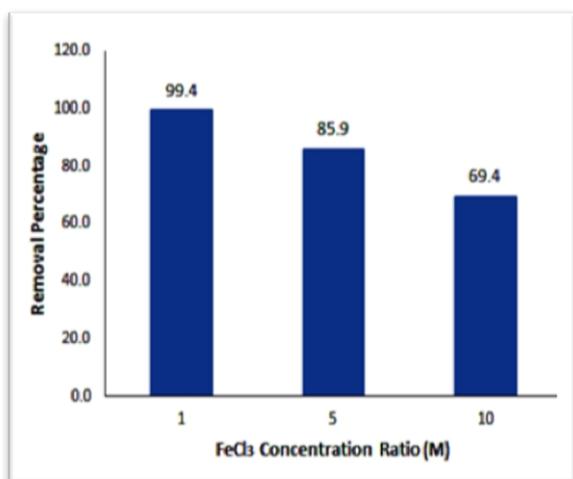
#### 3.3.1. Effect of Fe(III) concentration

Table 2, and Figures 3 show that at 2.00 x 10<sup>-3</sup> M ceftriaxone, 99.4% is removed at a 1:1 ratio with FeCl<sub>3</sub> after 6 h. The amount of the antibiotic removed drops as FeCl<sub>3</sub> concentration increases beyond the 1:1 ratio.

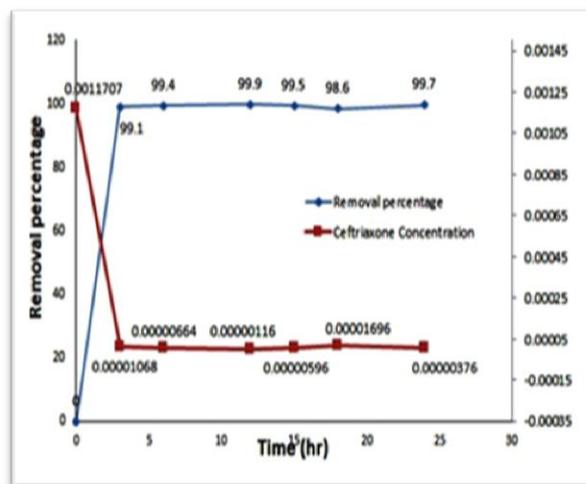
**Table 2.**

Effect of Fe(III) concentration on ceftriaxone removal

#	Initial Ceftriaxone Conc. (M)	FeCl <sub>3</sub> Conc. (M)	Peak area of Ceftriaxone	Ceftriaxone Conc. (M)	Ceftriaxone Average conc. (M) ± SD	Removal % of Ceftriaxone	Conc. ratio	Reaction Time
1.	1.00E-03	0	29366	0.00117064				
2.	1.00E-03	0	29370	0.0011708	0.001171 ±0.0000001	0	-	0
3.	1.00E-03	0	29367.5	0.0011707				
4.	1.00E-03	1.00E-03	324.23	0.0000090				
5.	1.00E-03	1.00E-03	266.00	0.0000066	0.0000075 ±0.0000013	99.4	1:1	6 h
6.	1.00E-03	1.00E-03	270.12	0.0000068				
7.	1.00E-03	5.00E-03	4174.59	0.00016				
8.	1.00E-03	5.00E-03	4225.00	0.00017	0.0001649 ±0.0000019	85.9	1:5	6 h
9.	1.00E-03	5.00E-03	4268.83	0.00017				
10.	1.00E-03	1.00E-02	9189.66	0.00036				
11.	1.00E-03	1.00E-02	8923.35	0.00035	0.0003582 ±0.0000053	69.4	1:10	6 h
12.	1.00E-03	1.00E-02	9055.7	0.00036				



**Figure 3.** Effect of FeCl<sub>3</sub> concentration on the percentage removal of Ceftriaxone

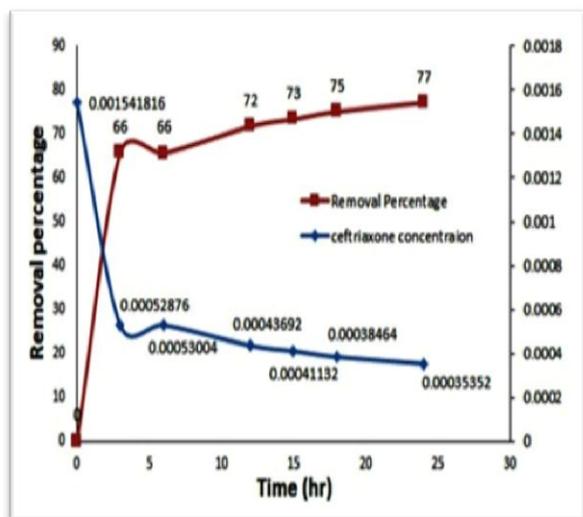


**Figure 4.** Effect of complexation time by FeCl<sub>3</sub> on Removal percentage and concentration of Ceftriaxone-Na (Concentration Ratio 1:1).

**3.3.2. Effect of reaction time on Ceftriaxone sodium concentration by Fe (III).**

The effect of reaction time at constant concentration ratio (1:1) of ceftriaxone and Fe(III) was studied at room temperature as shown in **Figure 4**. The maximum amount of ceftriaxone removed was 99.7% in 3 h, and thereafter remained constant.

At a higher Ceftriaxone to Fe (III) ratio of 1:10, the amount of Ceftriaxone steeply increased to the first 3 h then slowly increased to a value of 77% by 24 h at pH=3.3 at room temperature (Figure 5). So, the antibiotic ratio to Fe (III) of 1:10 is the optimum ratio for effective removal of the antibiotic.



**Figure 5.** Effect of complexation time by FeCl<sub>3</sub> on Removal percentage and concentration of Ceftriaxone-Na (Concentration Ratio 1:10)

Also, at a higher concentrations ratio of Ceftriaxone to Fe (III), precipitate of ceftriaxone-Fe complex appeared and obtained by traditional filtration by filter paper. As shown in (Figure 6):



**Figure 6.** Ceftriaxone-Fe complex formation and precipitate obtaining.

Table 3 shows different strategies reported for the removal of the antibiotic. While the method reported in the present is very effective, the waste is acidic and will cause environmental issues.

**Table 3.** Methods used for the removal of ceftriaxone antibiotic in comparison with this study.

Examples for some Antibiotic removal techniques	Removal Efficiency	Potential defects
1. Removal of ceftriaxone sodium in aquatic environment by photo degradation with Bi <sub>2</sub> WO <sub>6</sub> /g-C <sub>3</sub> N <sub>4</sub> photo catalyst (Zhao et al. 2018)	94%	The photolytic transformation products of some antibiotics increased acute toxicity to <i>Vibrio fischeri</i> (Microtox test) (Jiang et al. 2010; Wang et al. 2012).
2. Photodegradation of ceftriaxone in aqueous solution by using UVC, UVC/H <sub>2</sub> O <sub>2</sub> oxidation processes (Khorsandi et al. 2019)	61%, 100% respectively	Effective strategy but takes a long time of 48 h (Guo et al. 2015).
3. A combined system using green algae and active sludge (Guo et al. 2015)	95%	Less effective than this complexation technique by Fe(III).
4. Sorption of cephalosporins to activated carbon prepared produced from walnut shells, agricultural waste, lotus stalks and wine wood (Ahmed et al. 2012; Liu et al. 2011; Pouretedal et al. 2014)	80% to 89%	Very effective but the waste stream is acidic with a pH of 3.3.
5. Ceftriaxone removal by Fe(III) (Concentration Ratio 1:1) (This study)	99.7%	

**Conclusion**

The method of using Fe(III) as a complexing agent for ceftriaxone was found to be simple and effective for its removal. The addition of FeCl<sub>3</sub> to ceftriaxone at a concentration ratio of 1:1 removed 99.7 % of the antibiotic at pH=3.3 at room temperature after only 3 h. FeCl<sub>3</sub> works both as a coagulant and a flocculant, and so is expected to be effective in a wastewater that is contaminated with antibiotics with similar structural properties as ceftriaxone. This approach of forming a complex will avoid the occurrence of some antibiotics in the aqua environment and keep us safe. A neutralization process should be developed as the waste solution after the removal of ceftriaxone is acidic.

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