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Research Paper

Preparation, physicochemical characterization and biological evaluation of cefodizime metal ion complexes

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Abstract

Objectives Cefodizime is a broad spectrum cephalosporin belonging to the third generation agents. In this study, attention has been paid to the preparation, physicochemical characterization and biological evaluation of new Cu^{2+}, Zn^{2+}, Fe^{3+}, Co^{2+} and Al^{3+} complexes of cefodizime.

Methods The stoichiometrics and the mode of bonding of the complexes were deduced from their elemental and metal analysis, electrical conductivity measurements, UV–vis, infrared and Raman spectroscopic investigations. Study of the stoichiometry of these complexes referred to the formation of 1 : 1 ratios of metal to ligand. Antimicrobial activity of the complexes was determined using two strains of Gram-positive (*Bacillus subtilis* and *Proteus vulgaris*) and two strains of Gram-negative (*Escherichia coli* W3110 and *Pseudomonas putida*) bacteria. The minimal inhibitory concentration was determined as the lowest concentration inhibiting bacterial growth on solid Luria Bertani medium.

Key findings The spectra gave evidence as to the position of binding. In addition, the aqueous solubility of cefodizime was strongly reduced by complexation.

Conclusions The antibacterial activity of cefodizime was not affected by complexation with Al^{3+} but it was reduced by complexation with the other tested metal ions against the bacteria under study.

Keywords antibacterial activity; cefodizime; metal complexes; physicochemical characterization

Introduction

The cephalosporin antibiotics are semisynthetic antibacterials derived from cephalosporin C, a natural antibiotic produced by the mould *Cephalosporium acremonium.*[1] The most widely used system of classification of cephalosporins is by generations. According to their antimicrobial spectrum of activity, they are classified into four generations. The first generation cephalosporins are very active against Gram-positive cocci. They have limited activity against Gram-negative bacteria.[2] The second generation cephalosporins have somewhat increased activity against Gram-negative microorganisms but are much less active than the third and fourth generation agents.[3,4]

Cefodizime is a broad-spectrum, third-generation, parenteral cephalosporin which possesses a prolonged elimination half-life, of more than 3.5 h.[5,6] The chemical structure of cefodizime disodium salt is shown in Figure 1.

Cephalosporin antibiotics have long been known to behave as relatively efficient chelating agents.[7] A list of clinically used chelating agents may be found in most pharmacopoeia, while new chelating agents continue to be sought.[8,9]

The medicinal uses of metal complexes are of increasing clinical and commercial importance. Fluorouracil–oxaliplatin complex is used in Europe and the USA for treatment of colorectal cancer.[10,11] Ranitidine–bismuth citrate complex is marketed in the USA as ranitidine bismutrex for the management of peptic ulcer and ulcers associated with *Helicobacter pylori.*[12] Gold and ruthenium complexes of chloroquine and clotrimazole have been investigated for their antiparasitic activity.[13,14] Furthermore, it was found that some chloroquine complexes are useful even in chloroquine-resistant cases. Iqbal *et al.*[15] reported that copper–cephalexin complex exhibited a good anti-inflammatory activity and

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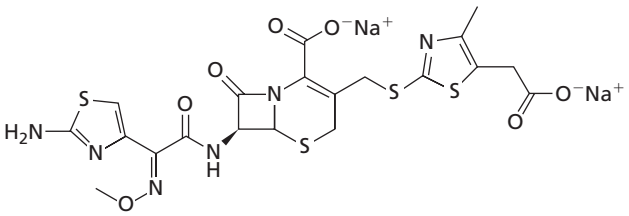

Figure 1 The chemical structure of cefodizime disodium

had more antibacterial effect than the free cephalexin. The effect of metal ions on drug activity was confirmed by several studies.[16,17]

The aim of this work was the preparation and physicochemical characterization of cefodizime metal complexes as well as the investigation of their antibacterial activity.

Materials and Methods

Chemicals

All chemicals were of reagent grade and were used without any further purification. Cefodizime disodium was obtained from Hoechst (Frankfurt, Germany). $CuSO_4$ and $ZnSO_4.7H_2O$ were purchased from Sigma-Aldrich GmbH (Seelza, Germany). $FeCl_3.6H_2O$ was supplied by Roanal (Budapest, Hungary). $Co(NO_3)_2.6H_2O$ was obtained from Gruessing (Filsum, Germany). $NiCl_3.7H_2O$ and $AlCl_3$ were purchased from Germed (Dresden, Germany). Dimethyl sulfoxide (DMSO) was obtained from Carl Roth GmbH & Co. (Karlsruhe, Germany). Ethylene diamine tetraacetate (EDTA), nitric acid, dipotassium hydrogen phosphate and potassium dihydrogen phosphate were supplied by E. Merck (Darmstadt, Germany). Methanol, ethanol, diethyl ether, acetonitrile, acetone and dimethylformamide were obtained from Riedel-de Haen AG (Seelze, Germany).

Complex preparation

Cefodizime disodium (2 mmol) was dissolved in 20 ml methanol. Metal salts, $CuSO_4$, $ZnSO_4.7H_2O$, $FeCl_3.6H_2O$, $Co(NO_3)_2.6H_2O$ and $AlCl_3$ (1 mmol) were separately dissolved in 10 ml methanol. The two solutions were mixed while stirring for 30 min. Coloured products precipitated and were isolated by filtration. The products were washed with water, acetone and dimethyl ether, and dried in a desiccator.

Physicochemical characterization

FT-infrared spectroscopy

The FT-infrared (IR) spectra of cefodizime and its metal complexes were recorded using an FTIR spectrometer Vertex 70 by Bruker Optics (Ettlingen, Germany). The samples were diluted with an adequate amount of KBr and compressed to pellets. The pellets were measured in the range from 370 to 4000 cm^{-1} in transmission mode.

FT-Raman spectroscopy

The FT-Raman measurements of cefodizime and its Zn^{2+} and Al^{3+} complexes were acquired by using the RFS 100/S spectrometer (Bruker Optics, Karlsruhe, Germany). Due to their colours the other complexes were not suitable for the Raman measurements.

UV–vis spectroscopy

An HP 8452 A (Hewlett-Packard, Waldbronn, Germany) was used to determine the UV–vis spectra of cefodizime and its metal complexes in phosphate buffer (pH 7.4).

Elemental analysis

C, H, N and S contents were analysed using an elemental analyser, CHN-932, Leco Corporation (St Joseph, MI, USA).

Metal analysis

Metal contents were determined by direct titration against standard EDTA (for the Zn^{2+} complex) or by a back titration technique using standard Zn solution (for the remaining complexes) after complete decomposition of the complexes achieved by boiling with concentrated nitric acid for 10 min.

Water content determination

Water content in the prepared complexes was determined using the Karl-Fischer method using the Karl-Fischer-Titrator AQUA 40.00 instrument, Elektrochemie Halle (Halle, Germany).

Quantitative solubility

Quantitative solubility of the complexes was determined spectrophotometrically in phosphate buffer (pH 7.4) by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of the material in the solvent for a prolonged period until equilibrium is achieved. At 270 nm and room temperature the extinction coefficient was between 6.51 and 6.70 l/mmol per cm.

Preparation of phosphate buffer, pH 7.4

The buffer solution was prepared by dissolving 1.237 g dipotassium hydrogen phosphate and 0.394 g potassium dihydrogen phosphate in 600 ml distilled water, and then adding distilled water to reach a volume of 1000 ml. The pH of the buffer was measured at 25°C using a microprocessor pH meter obtained from Testo GmbH and Co. (Lenzkirch, Germany).

Preparation of saturated solution

Saturated solutions of cefodizime and its complexes were prepared by adding an excess mass of powder to a constant volume (2 ml) of phosphate buffer, pH 7.4. Saturated solutions of cefodizime and its complexes were kept on a magnetic stirrer in closed glass tubes for 24 h at 25°C. Before the analysis all samples were filtered through 0.45-mm Millipore PTFE filters (Millipore Corp., Bedford, MA, USA).

Antimicrobial activity

Antimicrobial activity of the complexes was determined using two strains of Gram-positive (*Bacillus subtilis* and *Proteus vulgaris*) and two strains of Gram-negative (*Escherichia coli* W3110 and *Pseudomonas putida*) bacteria. The minimal inhibitory concentration (MIC) was determined as the lowest concentration inhibiting bacterial growth on solid Luria Bertani medium (DifcoTM Lennox; Becton Dickinson,

Germany). A preculture for each bacterium was incubated at 30°C, 250 rev/min, for 17 h. This was then diluted 1 : 400 in fresh medium and incubated for 2 h at 30°C, 250 rev/min. This 2 h-culture was used for streaking onto plates containing the complexes (dissolved in DMSO) in different concentrations. The plates were incubated at 30°C for 17 h.

Using the paper disc diffusion method on solid Luria Bertani medium another technique was performed. The complexes were tested at a concentration of 3 mg/ml in DMSO. As a control, DMSO alone was applied to the paper discs. A preculture and a 2 h-culture (as described above) were done. A 500 μl sample of the 2 h-culture was plated onto nutrient agar (Carl Roth, Germany), dried and paper discs with 10 μl of the complex solution were applied. After 17 h at 30°C the inhibition zone was measured.

Statistical analysis

The one-way analysis of variance post-hoc test was used for the determination of significant differences in the study (OriginPro 7.5). The analysis of variance post-hoc Tukey's test was used to compare all the samples with each other (antibacterial activity of cefodizime and its complexes against different bacteria).

Results

Initial complex data

The Fe^{3+} and Co^{2+} complexes were brown and rose, respectively. The Zn^{2+} and Al^{3+} complexes were white, while the Cu^{2+} complex was green. Microanalytical and complexometric titration data (Table 1) confirmed the formation of 1 : 1 metal to ligand ratio. Water content determined by the Karl-Fischer method showed that the Cu^{2+} complex was tetrahydrated, the Al^{3+} complex was pentahydrated, whilst the Zn^{2+}, Fe^{3+}, and Co^{2+} complexes were hexahydrated. UV–vis spectra showed no significant difference between cefodizime and its metal complexes.

FT-infrared spectroscopy

Evidence for complex formation was obtained by comparing the most characteristic IR spectral bands of the free cefodizime and its complexes. In general, cephalosporins have three characteristic C=O absorptions for the stretching vibrations of the β-lactam ring, the carboxylate and amide I. Cephalosporins have a zwitterionic character. Thus, their spectra of free ligand show bands of antisymmetric (υ_{as}) and symmetric (υ_s) vibrations of the carboxylate group. Disappearance of one or more of such bands may indicate the participation of it or them in metal coordination. The important IR frequencies of cefodizime and its metal complexes along with their assignments are given in Table 2.

FT-Raman spectra

The main Raman spectra of cefodizime and its Zn^{2+} and Al^{3+} complexes are listed in Table 3. Due to their colours the rest of the complexes were not suitable for Raman investigation.

Quantitative solubility

Five-point standard calibration curves of cefodizime and its complexes in phosphate buffer, pH 7.4, gave linearity correlation coefficients ranging from 0.996 to 0.999. The compounds were determined spectrophotometrically at λ_{max} = 270 nm using the same solvent medium as the blank (Table 4).

Antibacterial activity tests

The results of the MIC test are shown in Table 5. Cefodizime interferes with cell-wall synthesis of bacteria, leading to lysis of the infectious microorganisms. In-vitro antibacterial activity of cefodizime and its complexes were tested using the MIC and the paper disc diffusion method using two strains of Gram-positive (*B. subtilis* and *P. vulgaris*) and two strains of Gram-negative (*E. coli* W3110 and *P. putida*) bacteria. Antibacterial activity of cephalosporin metal ion

Table 1 Elemental analysis data of cefodizime metal complexes

Compound	H	C	N	S	Metal
(Cu(cefodizime)).4H_2O	33.4 ± 0.2 (33.4)	3.5 ± 0.3 (3.6)	11.4 ± 0.5 (11.7)	17.7 ± 1.3 (16.8)	8.8 ± 0.3 (8.9)
(Zn(cefodizime)).6H_2O	32.2 ± 0.9 (31.8)	3.9 ± 0.2 (3.9)	11.6 ± 0.6 (11.2)	16.0 ± 1.02 (16.9)	8.2 ± 0.3 (8.4)
(Fe(cefodizime)).6H_2O	31.9 ± 0.6 (32.1)	3.9 ± 0.4 (4.0)	11.9 ± 1.1 (11.3)	16.2 ± 0.3 (16.4)	8.9 ± 0.5 (8.5)
(Co(cefodizime)).6H_2O	32.0 ± 0.3 (32.0)	4.0 ± 0.2 (4.0)	11.2 ± 0.5 (11.2)	16.7 ± 0.5 (17.0)	8.4 ± 0.9 (7.9)
(Al(cefodizime)).5H_2O	34.1 ± 0.4 (34.3)	4.0 ± 0.1 (4.0)	11.5 ± 0.7 (11.9)	17.9 ± 0.6 (18.3)	3.7 ± 0.4 (3.9)

Values are contents in % ± SE, n = 4, found (calculated).

Table 2 The main FT-infrared spectra of cefodizime and its metal complexes

Compound	υ(C=O) lactam (cm^{-1})	υ(C=O) amide (cm^{-1})	υ(COO) antisymmetric (cm^{-1})	υ(COO) symmetric (cm^{-1})	Δ υ(COO) (cm^{-1})
Cefodizime	1777	1659	1588	1375	213
(Cu(cefodizime)).4H_2O	1767	Shoulder	1624	1378	246
(Zn(cefodizime)).6H_2O	1772	Shoulder	1625	1391	234
(Fe(cefodizime)).6H_2O	1770	Disappeared	1623	1399	224
(Co(cefodizime)).6H_2O	1776	Shoulder	1623	1384	239
(Al(cefodizime)).5H_2O	1771	Shoulder	1619	1377	242

Table 3 The main FT-Raman spectra of cefodizime and its Zn^{2+} and Al^{3+} complexes

Compound	υ(C=O) lactam (cm^{-1})	υ(C=O) amide (cm^{-1})	υ(COO) antisymmetric (cm^{-1})	υ(COO) symmetric (cm^{-1})
Cefodizime	1764	1623	1585	1397
(Zn(cefodizime)).6H_2O	1770	1630	1587	1398
(Al(cefodizime)).5H_2O	1766	1627	1581	1400

Table 4 The aqueous solubility of cefodizime and its complexes in phosphate buffer

Compound	Solubility (mg/ml)	SE
Cefodizime	164.41	4.35
(Cu(cefodizime)).4H_2O	2.181	0.009
(Zn(cefodizme)).6H_2O	2.496	0.006
(Fe(cefodizime)).6H_2O	1.963	0.011
(Co(cefodizime)).6H_2O	2.582	0.009
(Al(cefodizime)).5H_2O	2.301	0.013

Phosphate buffer was pH 7.4. SE, standard error.

complexes depends mainly on the type of cephalosporin used, the type of metal ion and the type of microorganism under investigation.[18]

Discussion

In the FT-IR spectra (Table 2) of cefodizime, a characteristic band arising from stretching vibrations of the carbonyl group of the β-lactam ring appeared at 1777 cm^{-1}. This band appeared in all studied complexes almost at the same wave number. This may suggest that the carbonyl oxygen atom from the β-lactam ring was not engaged in metal binding. Furthermore, the FT-IR spectra of cefodizime revealed a band at 1659 cm^{-1} due to stretching vibrations of the amide carbonyl group. This band either vanished or appeared as a shoulder in metal complexes, suggesting the coordination of metals through this carbonyl group.

The bands of antisymmetric (υ_{as}) and symmetric (υ_s) vibrations of the carboxylate group arose at 1588 and 1375 cm^{-1}, respectively. In spectra of metal complexes, these two bands were shifted towards the higher wave number. This suggested interaction between the metal ions and the carboxylate group of cefodizime.[19] On the other hand, a carboxylate ligand could bind to the metal atom either as a monodentate or a bidentate ligand, giving changes in the relative positions of the antisymmetric and symmetric stretching vibrations.[4] The FT-IR spectra of the complexes gave a separation value of >200 cm^{-1}, suggesting monodentate bonding for the carboxylate group.[20]

The band due to υ(C-S) was observed in the FT-IR spectra of cefodizime at 1041 cm^{-1} which showed no significant changes in any of the complexes, suggesting that there was no coordination through this group to the metal ion.[21] In addition, IR spectra of cefodizime exhibited a band at 1356 cm^{-1} due to υ(C–N) of the β-lactam and thiazole ring nitrogen atom.[22] This band appeared in all studied complexes without further change, indicating that the β-lactam and thiazole ring nitrogen atom were not participating in the bonding. Bands at 3191 and 3310 cm^{-1} in the spectra of cefodizime were due to antisymmetric and symmetric NH stretching of the carbamate NH_2 group. These bands appeared relatively at the same position in the spectra of all the complexes with the exception of the Co^{2+} complex. This may provide evidence for the participation of this group in the coordination only in the case of the Co^{2+} complex and its inertness towards coordination in the other complexes.

Similar to the IR spectra, Raman spectra of cefodizime showed a characteristic band arising from stretching vibrations of the carbonyl group of the β-lactam ring at 1764 cm^{-1} (Table 3). This band appeared in all the studied complexes almost at the same wave number. It may indicate that the carbonyl oxygen atom from the β-lactam ring was not engaged in metal binding. Raman spectra of cefodizime revealed a band at 1623 cm^{-1} due to stretching vibrations of the amide carbonyl group. This band was significantly shifted in metal complexes, suggesting the coordination of metals through this group. The bands of antisymmetric (υ_{as}) and symmetric (υ_s) vibrations of carboxylate groups of cefodizime arose at 1585 and 1397 cm^{-1}, respectively. Although the shift of these bands in the Raman spectra of metal complexes was small, they gave a significant shift in

Table 5 Antibacterial activity of cefodizime and its complexes against different bacteria[a]

Compound	Minimal inhibitory concentration (μg/ml)			
	Bacillus subtilis	*Proteus vulgaris*	*Escherichia coli*	*Pseudomonas putida*
Cefodizime	20	0.006	0.15	150
(Cu(cefodizime)).4H_2O	40	0.020	0.20	450
(Zn(cefodizime)).6H_2O	30	0.020	0.20	300
(Fe(cefodizime)).6H_2O	30	0.035	0.35	300
(Co(cefodizime)).6H_2O	40	0.020	0.35	>550
(Al(cefodizime)).5H_2O	20	0.007	0.15	175

[a]Bacteria were incubated (30°C) in solid Luria Bertani medium containing increasing concentrations of cefodizime or its complexes. Minimal inhibitory concentration, the lowest concentration that inhibited the formation of single colonies. The experiment was performed in triplicate.

the FT-IR spectra. This may suggest interaction between metal ions and the carboxylate group of cefodizime.

The solubility values of complexes that were calculated from these determinations showed significant decrease when compared with the solubility of cefodizime. These values are listed in Table 4. The solubility of cefodizime in the phosphate buffer (pH 7.4) was 164.41 mg/ml while the solubility of complexes ranged from 1.963 to 2.58 mg/ml. The decreased solubility of metal complexes may have been attributed to the decrease in their hydrophilicity compared with cefodizime.[23] According to this study we could arrange the solubility of complexes in phosphate buffer (pH 7.4) in the following order, with the highest solubility for the cefodizime–Co^{2+} complex and the least solubility for the cefodizime–Fe^{3+} complex: cefodizime–Co^{2+} > cefodizime–Zn^{2+} > cefodizime–Al^{3+} > cefodizime–Cu^{2+}> cefodizime–Fe^{3+}.

Except for the cefodizime–Al^{3+} complex, all tested metal ion complexes were shown to be less active than cefodizime against the bacteria investigated. Cefodizime–Al^{3+} complex exhibited an antibacterial activity similar to the parent drug against *B. subtilis, P. vulgaris* and *E. coli* and 1.16-times less than cefodizime against *P. putida.* The antimicrobial activity of the other complexes ranged from 1.3 to 5.8-times less active than the pure antibiotic. Cefodizime–Zn^{2+} and cefodizime–Fe^{3+} complexes had a middling activity, while the cefodizime–Cu^{2+} and cefodizime–Co^{2+} complexes had the lowest activity.

On the other hand, the inhibition zone of cefodizime and its metal ion complexes against the same bacteria was measured using the paper disc diffusion method on solid Luria Bertani medium. The following inhibition zones (diameter in mm) were measured, for *B. subtilis*: cefodizime 14, cefodizime–Cu 9, cefodizime–Zn 11, cefodizime–Fe 12, cefodizime–Co 8, cefodizime–Al 12; for *P. vulgaris*: cefodizime 17, cefodizime–Cu 14, cefodizime–Zn 15, cefodizime–Fe 15, cefodizime–Co 13, cefodizime–Al 17; for *E. coli*: cefodizime 26, cefodizime–Cu 25, cefodizime–Zn 24, cefodizime–Fe 25, cefodizime–Co 23, cefodizime–Al 25; for *P. putida*: no inhibition zone. The results showed a similarity in antibacterial activity between the cefodizime–Al complex and the parent cefodizime. However, the other complexes showed less activity than cefodizime against the bacteria under investigation. These results were in accordance with those obtained by Anacona and Acosta,[24] who studied the antibacterial activity of cephradine metal complexes. Resistance of *Pseudomonas* species to cefodizime was reported by some authors.[25] In comparison with the free ligand, lower antibacterial activity of their complexes was attributed to their insolubility.[26]

In contrast with these results, it has been reported that for some cephalosporins their metal complexes showed higher antibacterial activity than the free uncomplexed cephalosporins.[15,27] Until now, the relationship between chelation and antibacterial activity has been very complex and is expected to be a function of steric, electronic and pharmacokinetic factors, along with mechanistic pathways.[24]

The analysis of variance post-hoc test (Tukey's test) was used to compare all samples with each other (antibacterial activity of cefodizime and its complexes against different bacteria). The analysis of variance test (Tukey's test) exhibited significant differences at the 0.05 level only for *B. subtilis*, *B. vulgaris* and *E. coli* with *P. putida*. The population means were significantly different (one-way analysis of variance).

Conclusions

Cefodizime formed complexes with different metal ions. The stoichiometric ratio of these complexes was 1 : 1 metal to ligand. Furthermore, the coordination of ligand with metal ions occurred through carboxylate and amide carbonyl groups. In addition, the aqueous solubility of the cefodizime was strongly affected by complexation. With the exception of the cefodizime–Al complex, all tested metal ion complexes were less active than cefodizime against the bacteria under study.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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