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Physicochemical Stability of Cefotaxime Sodium in Polypropylene Syringes at High Concentrations for Intensive Care Units

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Abstract

Background: Cefotaxime sodium is an antibiotic used to treat severe infections such as in intensive care units (ICUs). The recommended dose of cefotaxime sodium can vary from 3 grams (g) to 24 g per day and publications have demonstrated that continuous administration of cefotaxime sodium is the preferred mode of administration. In ICUs, a minimum volume is used for patients requiring fluid restriction, leading to high concentrations of cefotaxime sodium.

The objective was to study the stability of cefotaxime sodium solutions at 83.3 mg/mL and 125 mg/mL, diluted in 0.9 % sodium chloride (0.9 % NaCl) or in 5 % glucose (G5 %), stored in polypropylene syringes, after the preparation and after a 6-hour and a 12-hour storage at 20–25 °C.

Methods: Three syringes for each condition were prepared. At each time of the analysis, three samples for each syringe were prepared and analysed by high performance liquid chromatography (HPLC) coupled to a photodiode array detector. The method was validated according to the International Conference on Harmonisation Q2(R1). Physical stability was evaluated by visual and subvisual inspection (turbidimetry by UV spectrophotometry at 350, 410 and 550 nm as recommended by the European Consensus Conference). pH and osmolality values were measured at each time of the analysis.

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Results: For each solvent, cefotaxime sodium solutions at 83.3 mg/mL and 125 mg/mL retained more than 90 % of the initial concentration after 12 hours. During the stability study, pH values decreased slightly, the intensity of the yellow colour increased and values of absorbance increased progressively for each wavelength and each condition. An additional peak with a relative retention of 3.01 was also observed after the forced degradation gradually increased up to 4.01 % and 3.17 % of the total of surface area of the peaks present on the chromatogram after 12 hours in 0.9 % NaCl and in G5 % respectively.

Conclusions: In view of the results and despite the fact that solutions retained more than 90 % of the initial concentration after HPLC analysis, we propose to limit the stability of cefotaxime sodium in 0.9 % NaCl and G5 % at 83.3 and 125 mg/mL at 6 hours. These stability data of highly concentrated solutions provide an additional knowledge to assist ICUs in daily practice. This work also demonstrates that highly concentrated cefotaxime sodium solutions are physically unstable after a 6-hour storage and cannot be administered as a daily infusion.

Keywords: cefotaxime sodium, intensive care unit, HPLC, stability

Introduction

Cefotaxime sodium (Figure 1) is a semi-synthetic antibiotic of the β -lactam family, of the third-generation cephalosporin group (C3G). This drug is a broad-spectrum antibiotic with activity against numerous gram-positive and gram-negative bacteria. Cefotaxime sodium is a time-dependent antibiotic [1].

This antibiotic is commonly used to treat severe infections caused by cefotaxime sodium-sensitive organisms, such as septicemia, endocarditis and meningitis, with the exception of *Listeria monocytogenes*, which is naturally resistant to C3G. In these indications, the recommended dose of cefotaxime sodium can vary from 3 grams (g) to 24 g per day. For meningitis

Figure 1: Chemical structure of cefotaxime sodium.

infections caused by *Streptococcus pneumoniae*, the recommended dose of cefotaxime sodium can be 300 mg/kg/day if the minimum inhibitory concentration (MIC) for C3G is greater than or equal to 0.5 mg/L [2].

Van Zanten *et al.* compared continuous vs intermittent cefotaxime sodium administration in patients. They recommended continuous administration of cefotaxime sodium as the preferred mode of administration [3]. In clinical practice in intensive care units (ICUs), nurses use a final volume of 48 mL in syringes to have an accurate flow rate of 2 mL/h over 24 hours. They often use high concentrations of drug solutions with a minimum volume to avoid fluid overload. In our hospital, in clinical practice, 4 g or 6 g of cefotaxime sodium were usually added in a syringe with a final volume of 48 mL, which obtained concentrations studied at 83.3 and 125 mg/mL.

Das Gupta *et al.* determined a 24-hour stability for cefotaxime sodium solution at 50 mg/mL diluted in 0.9% sodium chloride (0.9% NaCl) in polypropylene syringes, stored at 25 °C [4]. They observed that after a 2-day storage at 25 °C, the concentration of cefotaxime sodium was less than 90 % of the initial concentration and the pH value had decreased from 5.3 to 4.7. As for the visual aspect, they observed that the intensity of the light yellow colour increased during storage at 25 °C. Muller *et al.* determined equally a 24-hour stability for cefotaxime sodium solutions at 20 mg/mL diluted in 0.9% NaCl in polyolefin bags, at 25 °C [5]. Barthes *et al.* studied the influence of pH on the cefotaxime sodium's stability. They observed a better stability for cefotaxime sodium solutions with a pH between 4.5 and 6.5 and they didn't observe degradation products during their stability study [6].

Berge *et al.* [7] and Fabre *et al.* [8] have described the mechanism of degradation of cefotaxime sodium with the formation of desacetylcefotaxime sodium or desacetylcefotaxime sodium lactone after opening of the β -lactam ring. Desacetylcefotaxime sodium is the

main metabolite of cefotaxime sodium with a broad antibacterial spectrum [9]. Berge *et al.* have demonstrated the formation of this product at pH = 5.52 [7]. Das Gupta [10] and Yamana *et al.* [11] observed the formation of desacetylcefotaxime sodium lactone for a pH less than 4.

The preliminary objective was to study the stability of cefotaxime sodium solutions over 24 hours. After 24 hours, the concentration of cefotaxime was around 85 % of the initial concentration. In view of these results, we decided to shorten the stability study to 12 hours with an analysis after a 6-hour and 12-hour storage. The objective was to study the stability of cefotaxime sodium solutions at 83.3 mg/mL and 125 mg/mL, diluted in 0.9 % NaCl or in glucose 5 % (G5 %), in polypropylene syringes after the preparation and over 12 hours at room temperature.

Materials and methods

Chemicals and reagents

Di-sodium hydrogen phosphate Na_2HPO_4 (VWR Chemicals, batch: 17D104101), orthophosphoric acid 85 % (batch: 15D200503) and methanol for HPLC isocratic grade (Carbo Erba; batch: V8B441218B) were used for the mobile phase. Hydrochloric acid 1M (VWR Chemicals, batch: 17110005), Hydrochloric acid 0.1M (VWR Chemicals, batch: 17110001), sodium hydroxide 1M (VWR Chemicals, batch: 17110003), sodium hydroxide 0.1M (VWR Chemicals, batch: 17110003) and hydrogen peroxide 30 % (Merck; batch: K48743810713) were used. Water for chromatography was obtained from a reverse osmosis system (Millipore Iberica, Madrid, Spain). Cefotaxime sodium 2g, Powder for Solution for Infusion Concentrate (Cefotaxime sodium Mylan[®], batch: R3052), 0.9 % NaCl 250 mL glass vial (Chaix et du Marais, Lavoisier, batch: 7F289) or G5 % 250 mL glass vial (Chaix et du Marais, Lavoisier, batch: 4F193) and Water for injection 500 mL (Chaix et du Marais, Lavoisier, batch: 8F341) were used for test solutions. Cefotaxime sodium 500 mg, Powder for Solution for Infusion Concentration (Cefotaxime sodium Mylan[®], batch R1045) was used for the forced degradation and the validation of the analytical method. 3-desacetylcefotaxime sodium (Santa Cruz Biotechnology; batch: B1618) was used for the identification of a degradation product.

Preparation of test solutions

Stability study in polypropylene syringes: for the preparation of the concentration at 83.3 mg/mL, two vials of cefotaxime sodium 2 g were reconstituted with 10 mL of 0.9 % NaCl 0.9 % or G5 % and then diluted with the same solvent used for the reconstitution to obtain a final volume of 48 mL. For the preparation of the concentration at 125 mg/mL, three vials of cefotaxime sodium 2 g were reconstituted with 10 mL of 0.9 % NaCl or G5 % and then diluted with the same solvent used for the reconstitution to obtain a final volume of 48 mL. These solutions were stored in polypropylene syringes (BD Plastipak™, 50 mL Luer-lock). Three syringes were prepared for each concentration and each solvent.

The syringes were stored at room temperature (20–25 °C), not protected from light.

HPLC assay

Cefotaxime sodium solutions were analysed by a stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) method with photodiode array detection adapted from the Japanese Pharmacopoeia [12].

The HPLC system consisted of an ELITE LaChrom VWR/Hitachi plus autosampler, a VWR photodiode array (PDA) detector L-2455 and a VWR L-2130 HPLC-pump. Data was acquired and integrated by using EZChrom Elite (VWR, Agilent). The column used was LiChrospher® 100 RP-18, LiChroCART® 125–4, 12.5 cm length and 5 µm particle size (Analytical Chromatography, Merck). The mobile phase was in gradient mode constituted of a phase A: 86 % Na₂HPO₄ buffer 0.05 M, adjusted at pH = 6.25 with orthophosphoric acid 85 % (VWR Chemicals) and 14 % of methanol (VWR Chemicals) and a phase B: 60 % Na₂HPO₄ buffer 0.05 M, adjusted at pH = 6.25 with orthophosphoric acid 85 % (VWR Chemicals) and 40 % of methanol (VWR Chemicals).

The flow rate was set at 1.3 mL/minute, with an injection volume of 10 µL. The detection wavelength was set at 235 nm. The temperature of the injector was set at 15 °C and the temperature of the column oven at 30 °C. The calibration curve was constructed from plots of peak area versus concentration. The linearity of the method was evaluated with five concentrations (50, 75, 100, 125 and 150 µg/mL).

A solution of cefotaxime sodium 1 mg/mL was prepared with 100 mg of cefotaxime sodium diluted with 100 mL of ultrapure water. We used a vial of 500 mg of cefotaxime sodium. This solution at 1 mg/mL of cefotaxime sodium was used to realise standard curves by dilution with ultrapure water. The intra-day reproducibility was evaluated as

recommended by the International Conference on Harmonisation (ICH) Q2 (R1) [13], using three determinations for each concentration at 50, 100 and 150 µg/mL. For interday precision, three determinations for each concentration at 50, 100 and 150 µg/mL of cefotaxime sodium solutions were assayed daily on three different days.

The evaluation of the stability in the autosampler was performed. Solutions of cefotaxime diluted in ultrapure water were stored in the automatic injector at 25 °C. Chemical stability was evaluated at different times over 12 hours.

The Diode Array Detector allows the evaluation of the UV spectrum of the chromatographic column effluent every 0.4 second, thus allowing evaluation of the UV purity of an eluting peak. Variations in the UV spectrum over the elution profile of the peak of interest would indicate that the peak is contaminated, that the analytical method does not separate cefotaxime from its degradation products, and that the method is therefore unsuitable [14].

The stability-indicating capability was evaluated by analysing forced degraded cefotaxime sodium solutions.

Acidic conditions: one mL of a cefotaxime sodium 400 µg/mL solution was diluted with 1 mL HCl 0.5 M, stored at 20–25 °C for 3 hours, neutralised by 1 mL of NaOH 0.5 M and diluted with 1 mL of ultrapure water to obtain a theoretical concentration of 100 µg/mL.

Alkaline degradation: one mL of a cefotaxime sodium 400 µg/mL solution was diluted with 1 mL NaOH 0.01 M, stored at 20–25 °C for 5 minutes, neutralised by 1 mL of HCl 0.01 M and diluted with 1 mL of ultrapure water to obtain a theoretical concentration of 100 µg/mL.

Oxidative degradation: one mL of a cefotaxime sodium solution 400 µg/mL was diluted with H₂O₂ 0.3 % 1 mL stored at 20–25 °C and diluted with 2 mL of ultrapure water to obtain a theoretical concentration of 100 µg/mL.

Heat degradation: a solution of 400 µg/mL cefotaxime sodium was exposed to a temperature of 40 °C for 7 hours. The solution was diluted to obtain a final concentration of 100 µg/mL.

Sample dilution for analysis by RP-HPLC

During the analysis, 5 mL were removed from each syringe. The solutions were diluted before analysis with ultrapure water to obtain a concentration of 100 µg/mL (middle of the standard curve).

Samples were prepared in triplicate for each syringe. After dilution, each sample was analysed by RP-HPLC. This process was repeated after 6 and 12 hours.

Total run time was set at 35 minutes. We adapted the analysis time after forced degradation. According to the Japanese Pharmacopoeia, the analysis time was 50 min but no peak of degradation was observed after 27 min during the forced degradations.

Chemical stability was defined as not less than 90 % of the initial cefotaxime sodium concentration and in relation with the evolution of potential degradation products [13, 15].

pH measurement

pH measurement was performed using a Bioblock Scientific pH meter. Analysis was carried out for each concentration and each solvent after preparation and after 6 and 12 hours. pH values were considered to be acceptable if they did not vary by more than 1 pH unit from the initial measurement [15]. We measured pH for each syringe, for each condition.

Identification of 3-desacetylcefotaxime sodium

A solution of desacetylcefotaxime sodium at 100 µg/mL was prepared with 5 mg of desacetylcefotaxime sodium diluted in 50 mL of ultrapure water. This solution was analysed by RP-HPLC.

Determination of physical stability

Physical stability was defined as the absence of particulate formation, haze, colour change and gas evolution [16]. The samples were visually inspected against a white/black background with unaided eye at each analysis time. The subvisual aspect was assessed by using a Safas Monaco UV mc² spectrophotometer. The absorbance light was scanned at 350, 410 and 550 nm [16].

Results

Reversed phase HPLC

The calibration curve was linear, the determination coefficient was 0.9997. The equation of the calibration curve was $y = 71,869.99 \times -147,428$. The intra-day precision expressed as relative standard deviation (RSD) was between 0.08 % and 1.81 %. The intermediate precision

expressed as relative standard deviation (RSD) was 1.66 % at 50 µg/mL, 1.25 % at 100 µg/mL and 1.09 % at 150 µg/mL.

For the evaluation of the stability in the automatic injector, solutions at 100 µg/mL were stable with a degradation rate less than 3 %.

The UV spectral purity of the cefotaxime peak in chromatograms of the degraded samples was compared with the spectrum of the undegraded sample of cefotaxime obtained at time 0. These procedures were in accordance with the acceptance standard.

Stability-indicating capacity was proved by using various stressed conditions. The retention time of cefotaxime sodium is close to 9 minutes. The chromatogram of cefotaxime sodium without stressed degradation is presented in Figure 2 and after alkaline stressed conditions in Figure 3 for example.

After acidic, alkaline, oxidative and heat stressed degradations, 17 %, 19 %, 48 % and 13 % of cefotaxime sodium were degraded respectively. The mass balance was evaluated and is presented in Table 1.

Chemical stability of solutions

HPLC assay

The percentage of cefotaxime sodium diluted in 0.9 % NaCl or G5 % at 83.3 mg/mL and 125 mg/mL after storage at 20–25 °C for various time points is shown in Table 2. After 12 hours, cefotaxime sodium solutions in 0.9 % sodium chloride retained more than 90 % of the initial concentration.

During the stability study, we observed peaks n° 3, 5 and 8 of the forced degradation. Peak n°3 and peak n°5 are constant and less than 0.72 % and 0.33 % of the total of surface area of the peaks present on the chromatogram respectively. The percentage of surface area of peak n°8 relative to the main peak of cefotaxime sodium increases by to 2.66 % in 0.9 % NaCl and 2.15 % in G5 % after a 6-hour storage and 4.01 % in 0.9 % NaCl and 3.17 % in G5 % after a 12-hour storage.

pH measurements

pH measurements are presented in Table 3. pH measurements decrease slightly during the stability study. The maximum of variation is 0.48 pH units which is less than 1 pH unit which is our acceptable limit.

Figure 2: Chromatogram of a 100 µg/mL cefotaxime sodium solution in sodium chloride 0.9% without stressed conditions.

Figure 3: Chromatogram of a 100 µg/mL cefotaxime sodium after alkaline stressed conditions (NaOH 0.01 N, 5 min).

Table 1: Mass balance of cefotaxime sodium solutions after various stressed degradations.

Peaks (n°)	Retention time (minutes)	Relative retention	Without stressed degradation	Area									
				Acidic degradation			Alkaline degradation			Oxydative degradation		Heat degradation	
				HCl	0.5M	3h	NaOH	0.01M	5 min	H ₂ O ₂	0.30 %	40 °C	7h
Cefotaxime sodium	8.97	1.00	6,876,018	5,599,725			5,599,725			3,615,128		5,989,383	
1	1.37	0.15	11,897	37,382			218,156			100,040		282,245	
2	1.95	0.22	33,961	–			774,532			244,839		199,455	
3	2.28	0.25	81,329	535,589			21,417			1,539,918		587,761	
4	3.17	0.35		37,429			–			–		–	
5	4.20	0.47	20,764	17,320			18,030			–		20,185	
6	5.50	0.61		557,405			–			–		21,664	
7	12.50	1.39		15,467			156,680			–		–	
8	26.95	3.01	29,355	20,988			13,818			–		28,121	
Mass balance			7,053,324	6,976,282			6,802,358			5,499,925		7,128,814	
% degradation				17 %			19 %			48 %		13 %	

Table 2: Stability of cefotaxime sodium diluted in 0.9 % sodium chloride (NaCl 0.9 %) or in 5 % glucose (G5 %).

Solvent	Concentration	Syringe	Mean % of initial concentration ± SD*%		
			0 hour	6 hours	12 hours
NaCl 0.9 %	83.3 mg/mL	S1	100.00 ± 0.66	97.20 ± 0.37	92.83 ± 0.34
		S2	100.00 ± 0.82	93.77 ± 2.62	92.04 ± 1.61
		S3	100.00 ± 0.63	94.76 ± 0.51	91.73 ± 0.42
	125 mg/mL	S1	100.00 ± 0.74	95.36 ± 0.28	94.55 ± 1.24
		S2	100.00 ± 1.11	95.79 ± 1.26	94.91 ± 0.53
		S3	100.00 ± 0.82	(1)	96.27 ± 0.20
G5 %	83.3 mg/mL	S1	100.00 ± 0.21	97.29 ± 1.12	95.38 ± 0.41
		S2	100.00 ± 1.36	95.68 ± 0.93	93.56 ± 0.18
		S3	100.00 ± 0.69	93.16 ± 0.33	90.11 ± 0.97
	125 mg/mL	S1	100.00 ± 0.55	100.42 ± 0.11	95.24 ± 0.76
		S2	100.00 ± 1.33	96.11 ± 0.22	94.32 ± 1.03
		S3	100.00 ± 1.53	95.67 ± 0.08	95.18 ± 0.95

Note: Drug concentrations in samples taken at time zero were designated as 100 %. *SD = Standard Deviation. Samples were prepared in triplicate for each syringe. ⁽¹⁾Technical problem with HPLC.

Identification of 3-desacetylcefotaxime sodium

The chromatogram obtained for the solution of desacetylcefotaxime sodium at 100 µg/mL is presented in Figure 4. The relative retention of desacetylcefotaxime sodium is 0.24 which corresponds to peak n°3 observed in other chromatograms.

Physical stability of solutions

Visual aspect

Cefotaxime sodium solutions are yellow after the preparation. The yellow colour intensifies in all the conditions of the study over time. The solutions were limpid with no precipitation or gas formation during the study.

Table 3: pH measurements.

Solvent	Concentration	Syringe	0 hour	6 hours	12 hours
NaCl 0.9 %	83.3 mg/mL	S1	5.32	5.00	4.82
		S2	5.32	5.00	4.87
		S3	5.33	4.99	4.85
	125 mg/mL	S1	5.32	5.05	5.09
		S2	5.32	5.08	5.09
		S3	5.33	5.06	5.09
G5 %	83.3 mg/mL	S1	5.36	5.09	4.99
		S2	5.37	5.10	5.00
		S3	5.37	5.10	4.99
	125 mg/mL	S1	5.59	5.24	5.11
		S2	5.56	5.20	5.12
		S3	5.57	5.22	5.13

Subvisual evaluation

NaCl 0.9 %

At 350 and 550 nm, there is no modification of the average absorbance value after a 12-hour storage.

At 450 nm, the initial average absorbance value was less than 0.44 AU and 0.69 AU for solutions at 83.3 mg/mL and

125 mg/mL respectively. After a 12-hour storage, the average absorbance value was 1.07 AU and 1.40 AU respectively.

G5 %

At 350 nm, the initial average absorbance value was less than 2.22 AU and 3.10 AU for solutions at 83.3 mg/mL and 125 mg/mL respectively. After a 12-hour storage, the average absorbance value was 3.03 AU and 3.21 AU respectively.

At 450 nm, the initial average absorbance value was less than 0.48 AU and 0.70 AU for solutions at 83.3 mg/mL and 125 mg/mL respectively. After a 12-hour storage, the average absorbance value was 1.20 AU and 1.27 AU respectively.

At 550 nm, there is no modification of the average absorbance value after a 12-hour storage.

Discussion

Reversed phase HPLC

Cefotaxime sodium solutions were analysed by a stability-indicating reversed-phase high-performance

Figure 4: Chromatogram of a 100 µg/mL desacetylcefotaxime sodium in ultrapure water.

liquid chromatography (RP-HPLC) method adapted from the Japanese Pharmacopoeia. The stability indicating capacity of this method has been proved with forced degradation of cefotaxime sodium solutions in extreme conditions (acidic, alkaline, oxidative and heat conditions). For the oxidative degradation, the percentage of degradation obtained was 48 %. The mass balance in comparison with the undegraded cefotaxime sodium solution is not optimal. That can be explained by the loss of chromophores after the addition of 0.3 % H_2O_2 .

Stability study of cefotaxime sodium solutions

Diluted in 0.9 % NaCl or in G5 % and stored at 20–25 °C, cefotaxime sodium solutions at 83.3 mg/mL and 125 mg/mL retained more than 90 % of the initial concentration after 12 hours. For syringe S3 at 83.3 mg/mL in G5 %, the solution was at the acceptance limit with a concentration at 90.11 % of the initial concentration and a standard deviation of 0.97 %.

Peak n°8 with relative retention at 3.01 was also observed after the forced degradation in acidic, alkaline and heat conditions, increased during the study, up to 4.01 % in 0.9 % NaCl and 3.17 % in G5 % of the total of surface area of the peaks present on the chromatogram after 12 hours.

During the stability study, pH values decreased slightly as observed in the stability study by Das Gupta *et al.* [4].

The intensity of the light yellow colour of solutions increased as observed in the stability study by Das Gupta *et al.* [4]. No visual particles or precipitation were observed after the visual examination. As for the subvisual evaluation, values of absorbance increased gradually for each wavelength and each condition of analysis after a 12-hour storage.

Despite demonstrated chemical stability of the solutions for 12 hours for each condition, the increase in the surface area of the additional peak n°8 and the changes in the physical stability of the solutions constrains to limit the stability time of the diluted cefotaxime sodium solutions 83.3 and 125 mg/mL in 0.9 % NaCl and G5 % at 6 hours.

Conclusion

In view of the results and despite the fact that solutions retained more than 90 % of the initial concentration after

HPLC analysis, we propose to limit the stability of cefotaxime sodium in 0.9 % NaCl and G5 % at 83.3 and 125 mg/mL at 6 hours. These stability data of highly concentrated solutions provide additional knowledge to assist intensive care services in daily practice. This work also demonstrated the limit of the stability of highly concentrated solutions of cefotaxime sodium.

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