Asian Journal of Chemistry; Vol. 25, No. 13 (2013), 7596-7598

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.15454

Stability of Cefoselis Sulfate in Intravenous Solutions

PRZEMYSLAW ZALEWSKI*, JUDYTA CIELECKA-PIONTEK and ANNA JELINSKA

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Poznan University of Medical Sciences, Grunwaldzka 6, 60-780 Poznan, Poland

*Corresponding author: E-mail: pzalewski@ump.edu.pl

(*Received*: 8 March 2013; *Accepted*: 1 July 2013) AJC-13760

The stability of cefoselis sulfate in various intravenous solutions was studied. 20 mg mL^{-1} solutions of cefoselis sulfate were prepared by using a variety of intravenous diluents and stored in poly(vinyl chloride) minibags for up to 24 h at room temperature (20 ºC) and at 5 ºC and for up to 30 days at -20 ºC. Cefoselis sulfate concentrations were determined by high-performance liquid chromatography. The stability of cefoselis sulfate was affected to the highest degree by storage temperature, composition of intravenous solutions used as diluents and the concentrations of their components. When cefoselis sulfate was stored for 24 h in glucose solution (5 and 10 %) at room temperature, its stability was above 99.5 % of the initial value whereas the medium of mannitol reduced its concentration to 91.6 % after only 2 h.

Key Words: Cefoselis sulfate, Stability in intravenous solutions, HPLC.

INTRODUCTION

The class of cephalosporins came in exist in 1954[1]. Since the isolation of the first cephalosporin, they have been increasingly applied in the treatment of various types of infections. At the moment, there are over twenty cephalosporins divided into five generations available commercially[2], which are characterized by low allergenicity and toxicity as well as a broad spectrum of activity[3]. The first-generation cephalosporins are active especially against Gram-positive bacteria and the successive generations have an increased activity against Gram-negative bacteria. The mechanism of action of the cephalosporins involves inhibiting the synthesis of bacteria cell wall[4]. Resistance to the cephalosporins may be due to poor permeability of the drug into bacteria, lack of penicillin-binding proteins, or degradation by β-lactamases. The cephalosporins consist of a β-lactam ring attached to a dihydrothiazoline ring. The β-lactam moiety is essential for antibacterial activity but it is very vulnerable to chemical degradation. It has been found that the cephalosporins are prone to degradation in aqueous solutions[5-8] and in the solid state[9-13]. Cefoselis sulfate (Fig. 1) is a new, fourth-generation cephalosporin with a broad spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*[14]. The drug contains a 3-non-acetoxy group (pyrazylmethyl group) at the C3 position determining antibacterial activity against methicyllin-resistant *Staphylococcus aureus*. Cefoselis sulfate is susceptible to degradation in aqueous solutions[15]. Its degradation was studied at 353 K and pH 0.44-13 and was found to be a pseudo-first-order reaction. The influence of buffers, ionic strength, temperature, light and oxidizing agents on the degradation of cefoselis sulfate was also described[16]. It was proved that cefoselis sulfate was the most stable at a pH range of 4 to 6.5 and the least stable above pH 11.24. As cefoselis sulfate, similarly to other fourth-generation cephalosporins, must only be administered intravenously, it is important to evaluate how intravenous solutions used to dilute the drug affect its stability.

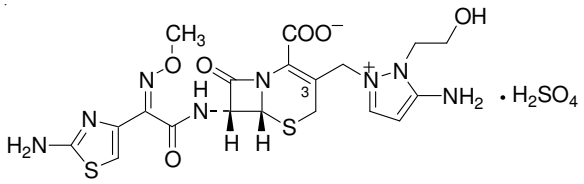

Fig. 1. Chemical structure of cefoselis sulfate

The aim of this study was to determine the stability of cefoselis sulfate in different kinds of intravenous solutions stored at -20, 5 and 20 ºC.

EXPERIMENTAL

Cefoselis sulfate was obtained from Xingcheng Chempharm Co., Ltd. Taizhou, Zhejiang, China. It is white,

crystalline powder containing 99.5 % cefoselis sulfate, 0.1 % related substances and complies with the Chinese Pharmacopoeia 2005 regulations. Water for injections was obtained from Polpharma SA, Poland. Sodium chloride (0.9 %), glucose (5 %, 10 %) and Ringer's solution were products of Baxter Manufacturing Sp. z o. o., Poland. Jonosteril Basic solution and mannitol were obtained from Fresenius Kabi, Italy.

All other chemicals and solvents were obtained from Merck KGaA, Germany and were of analytical grade. High quality pure water was prepared by using a Millipore purification system (Millipore, Molsheim, France, model Exil SA 67120).

Chromatographic separation and quantitative determination of cefoselis sulfate were performed by using a high-performance liquid chromatograph equipped with an LC-6A pump (Shimadzu), a UV-visible (SPD-6AV) detector (Shimadzu) and a Rheodyne with a 50 µL loop. As the stationary phase a Lichrospher RP-18 column, 5 µm particle size, 250 mm × 4 mm (Merck, Darmstadt, Germany) was used. The mobile phase consisted of 5 volumes of acetonitrile and 95 volumes of ammonium acetate, 12 mmol L^{-1}, the mobile phase pH was 7.15. The flow rate of the mobile phase was 1.0 mL min^{-1}. The wavelength of the detector was set at 260 nm. The HPLC method was evaluated and validated for the determination of cefoselis sulfate in previous stability studies[16].

Sample preparation: During the stability study poly(vinyl chloride) minibags were filled with a solution containing 5 mg of cefoselis sulfate and diluted to 20 mg mL^{-1} with water for injections, sodium chloride (0.9 %), glucose (5 %, 10 %), Ringer's solution, Jonosteril Basic solution or mannitol (20 %), depending on the test conditions. The solutions for the study were stored at room temperature (20 ºC, protected and unprotected from light) for 2, 6 and 24 h, refrigerated (5 ºC, protected from light) for 6 h and 24 h or frozen (-20 ºC, protected from light) for 30 days and then defreezed at room temperature.

At specified time intervals, samples of the reaction solutions were collected, diluted and 50 µL of the solutions were injected onto the column.

RESULTS AND DISCUSSION

The HPLC method with UV detection used in this study was previously found suitable for the determination of cefoselis sulfate under the stress conditions of hydrolysis (acid and base), oxidation, photolysis and thermal degradation[16]. The selectivity of this method for the determination of cefoselis sulfate in the presence of degradation products formed during hydrolysis was confirmed. The symmetrical peak of cefoselis sulfate (t_R = 14.58 min) was clearly separated from the peaks of the degradation products formed in the whole pH range (Fig. 2).

All infusion solutions of cefoselis sulfate were transparent. The greatest pH change relative to the initial pH was 0.03. Solutions of cefoselis sulfate were defined as stable when the substrate loss was not greater than 10 % relative to the initial value.

Cefoselis sulfate was stable over a period of 2 h at room temperature in sterile water, sodium chloride (0.9 %), glucose (5 % and 10 %), Ringer's solution, Jonosteril Basic. At room temperature, cefoselis sulfate was the most stable in glucose (5 % and 10 %) and the least stable in a 20 % solution of mannitol. Due to the fact that in mannitol (20 %) precipitate was observed at room temperature (Table-1). Table-2 summarizes the data of the stability of cefoselis sulfate stored at 5 ºC in poly(vinyl chloride) minibags protected from light.

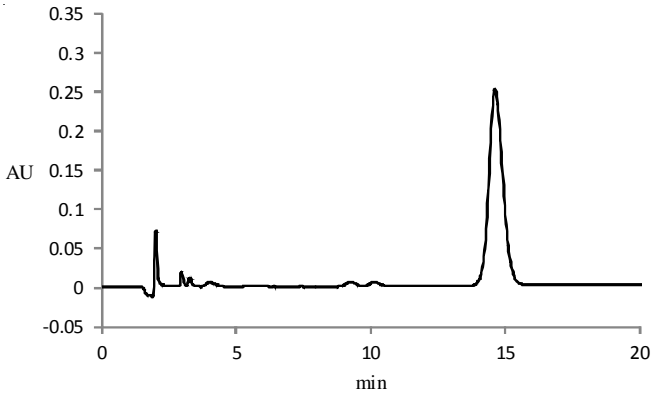

Fig. 2. HPLC chromatogram of cefoselis sulfate in 0.9 % sodium chloride (retention time 14.58 min) in the presence of degradation products (retention time from 1.95 to 9.97 min) after incubation 24 h at 20 ºC

TABLE-1
STABILITY OF CEFOSELIS SULFATE STORED AT ROOM TEMPERATURE IN POLY(VINYL CHLORIDE) MINIBAGS

Unprotected from light			Protected from light		
Intravenous solution	t (h)	c (%)	Intravenous solution	t (h)	c (%)
Sodium chloride 0.9 %	0	100.00	Sodium chloride 0.9 %	0	100.00
	2	98.75		2	97.43
	4	96.91		4	95.87
	24	91.42		24	89.32
Water for injections	0	100.00	Water for injections	0	100.00
	2	92.40		2	93.96
	4	95.99		4	95.02
	24	89.08		24	91.12
Glucose 10 %	0	100.00	Glucose 10 %	0	100.00
	2	100.00		2	100.00
	4	100.00		4	100.00
	6	100.00		6	100.00
	24	99.68		24	99.90
Glucose 5 %	0	100.00	Glucose 5 %	0	100.00
	2	100.00		2	100.00
	4	100.00		4	100.00
	6	100.00		6	100.00
	24	99.53		24	100.00
Mannitol 20 %	0	100.00	Mannitol 20 %	0	100.00
	2	91.66		2	98.74
	4	83.78		4	98.10
	6	80.99		6	97.34
	24	Precipitate		24	95.46
Ringer's solution	0	100.00	Ringer's solution	0	100.00
	2	95.69		2	96.12
	4	94.13		4	95.29
	6	91.23		6	93.76
	24	90.76		24	92.79
Jonosteril Basic®	0	100.00	Jonosteril Basic®	0	100.00
	2	99.72		2	100.00
	4	95.24		4	99.96
	6	92.36		6	99.48
	24	90.07		24	97.92

TABLE-2
STABILITY OF CEFOSELIS SULFATE STORED AT 5 ºC IN POLY(VINYL CHLORIDE) MINIBAGS PROTECTED FROM LIGHT

Intravenous solution	t (h)	c (%)	Intravenous solution	t (h)	c (%)
Sodium chloride 0.9 %	0	100.00	Glucose 5 %	0	100.00
	6	100.00		6	99.45
	24	100.00		24	97.94
Water for injections	0	100.00	Ringer's solution	0	100.00
	6	100.00		6	98.50
	24	94.79		24	91.58
Glucose 10 %	0	100.00	Jonosteril Basic®	0	100.00
	6	98.52		6	100.00
	24	97.53		24	100.00

Table-3 summarizes the data of stability of cefoselis sulfate stored for 30 days at -20 ºC in poly(vinyl chloride) minibags protected from light.

TABLE-3
STABILITY OF CEFOSELIS SULFATE STORED FOR 30 DAYS AT -20 ºC IN POLY(VINYL CHLORIDE) MINIBAGS PROTECTED FROM LIGHT

Intravenous solution	c (%)	Intravenous solution	c (%)
Sodium chloride 0.9 %	100.00	Glucose 5 %	100.00
Water for injections	98.27	Ringer's solution	99.62
Glucose 10 %	100.00	Jonosteril Basic®	90.30

The greatest impact on the stability of cefoselis sulfate in intravenous solutions applied in this work was demonstrated by the temperature at which they were stored and by their components as well as their concentrations. Since cefoselis sulfate is stable at room temperature, it may be administrated intravenously for 2 h without being protected from light as protection against light has negligible effect on its stability, except when Jonosteril and mannitol are used as intravenous solutions. This cephalosporin, dissolved in intravenous solutions such as these used in this study, may be stored at a temperature of 5 ºC for up to 24 h.

ACKNOWLEDGEMENTS

This study was supported by a grant from the State Committee for Scientific Research, Poland (no. N N405 683040).

REFERENCES

1. L. Zaffiri, J. Gardner and L.H. Toledo-Pereyra, *J. Invest. Surg.*, **25**, 67 (2012).
2. E. Akaho and H. Nakayama, *J. Antibiot. (Tokyo)*, **56**, 379 (2003).
3. S.J. Dancer, *J. Antimicrob. Chemother.*, **48**, 463 (2001).
4. P. Zalewski and J. Cielecka-Piontek, *Ann. Acad. Med. Siles*, **65**, 77 (2011).
5. G. Patel and S. Rajput, *Acta Chromatogr.*, **23**, 215 (2011).
6. Y. Ikeda, J. Ban, T. Ishikawa, S. Hashiguchi, S. Urayama and H. Horibe, *Chem. Pharm. Bull.*, **56**, 1406 (2008).
7. T. Sugioka, T. Asano, Y. Chikaraishi, E. Suzuki, A. Sano, T. Kuriki, M. Shirotsuka and K. Saito, *Chem. Pharm. Bull.*, **38**, 1998 (1990).
8. J.O. Fubara and R.E. Notari, *J. Pharm. Sci.*, **87**, 1572 (1998).
9. B. Medenecka, A. Jelinska, M. Zajac, M. Baldyka, K. Juszkiewicz and I. Oszczapowicz, *Acta Pol. Pharm.*, **66**, 563 (2009).
10. A. Jelinska, B. Medenecka, M. Zajac and M. Knajsiak, *Acta Pol. Pharm.*, **65**, 261 (2008).
11. M. Zajac, A. Jelinska and P. Zalewski, *Acta Pol. Pharm.*, **62**, 89 (2005).
12. A. Jelinska, I. Dudzinska, M. Zajac, I. Oszczapowicz and W. Krzewski, *Acta Pol. Pharm.*, **62**, 183 (2005).
13. P. Zalewski, J. Cielecka-Piontek, P. Garbacki, A. Jelinska and M. Karazniewicz-Lada, *Chromatographia*, **76**, 387 (2013).
14. P. Zalewski, J. Cielecka-Piontek, A. Jelinska and P. Marczak, *Curr. Issues Pharm. Med. Sci.*, **25**, 306 (2012).
15. P. Zalewski, J. Cielecka-Piontek and A. Jelinska, *React. Kinet. Mech. Catal.*, **108**, 285 (2013).
16. P. Zalewski, J. Cielecka-Piontek and A. Jelinska, *Cent. Eur. J. Chem.*, **10**, 121 (2012).