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Stability of cefotaxime sodium in solid state

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The influence of temperature and relative humidity on the stability of cefotaxime sodium in the solid state was investigated. Changes in the concentration of cefotaxime sodium were followed by a HPLC method with UV detection. The kinetic and thermodynamic parameters of the decomposition reaction were calculated.

1. Introduction

Cefotaxime is a third generation cephalosporin with a 2-amino-4-thiazolyl side chain and α-methoxyiminogroup in the syn position. Cefotaxime is effective against a wide variety of Gram-positive and Gram-negative microorganisms. The α-methoxyimino group is responsible for the stability of the drug against most beta-lactamases. Previously, the stability of cefotaxime sodium was investigated in solutions [1, 2] and the effect of pH was examined [3]. One of the most useful analytical methods for determination of cefotaxime sodium concentrations is HPLC, but other methods such as microbiological, iodometric or colorimetric methods have been used as an alternative [2]. Castaneda compared capillary electrophoresis with HPLC in monitoring the purity of cefotaxime sodium and impurity level during synthesis and in the final product [4]. HPLC methods, with different detection methods have been used for monitoring the amount of cefotaxime sodium and its metabolites in plasma and aqueous humour [5, 6]. In the solid state, photodegradation of cefotaxime was investigated [7] but the influence of humidity and temperature on stability was not examined. However, the stability of cefotaxime sodium in solid state is an important problem due to the possibility of degradation of lyophilized substance for injection during storage at room temperature. In the present work, we determined the effect of temperature and humidity on the stability of cefotaxime sodium in solid state.

2. Investigations and results

A chromatogram of the standard solution was recorded at wavelength 235 nm. A calibration curve of the peak height was plotted. The correlation coefficients of the linear regression analysis were 0.9992. Precision was tested with 3 replicates and found to have a coefficient of variation of 2.739×10^{-4}. The proposed procedure therefore allows a satisfactory determination for the kinetic studies.

The investigation of thermal degradation in dry air atmosphere was carried out at five temperatures. During the experiment the colour of substance changed from white through yellow to brown; all products of degradation were soluble in water. In dried air the degradation of cefotaxime sodium proceeded according to first order reaction $c_0 \rightarrow 0$. The plots $\ln c_i = f(t)$ are linear and the observed rate constant were calculated by the least squares method according to equation $\ln c_i = \ln c_\infty + kt$ (Table 1). The thermodynamic parameters of degradation of cefotaxime sodium in dried air have been calculated for a temperature of 293 K (Table 1).

The influence of temperature in 76.4% humidity on the stability of cefotaxime sodium was examined. During storage the colour of the substance changed from white through yellow to brown but, opposite to decomposition in dried air, some products of reaction were insolubile in water. The concentration of cefotaxime sodium changed according to the pseudo-first order reaction model $c_\infty \rightarrow 0$ (Table 1). The thermodynamic parameters of degradation of cefotaxime sodium in dried air have been calculated for 293 K (Table 1). In this study the dependence between the kinetic parameters of decomposition of cefotaxime sodium and relative humidity was also investigated. Stability was examined at 358 K for a relative humidity from 25.0% to 76.4%. The results are shown in Table 2.

Table 1: First-order rate constants and thermodynamic parameters for the decomposition of cefotaxime sodium in solid state in dry air RH = 0% and in relative humidity RH = 76.4%

T	10^6 k ± Δk (s^{-1})	r	n	Thermodynamical parameters
RH = 0%				
371	0.148 ± 0.009	0.9939	13	
373	0.171 ± 0.009	0.9929	19	Ea = 151.25 ± 11.05 ($kJ \cdot mol^{-1}$)
378	0.352 ± 0.032	0.9921	9	$\Delta H^{\neq}$ = 148.81 ± 11.05 ($kJ \cdot mol^{-1}$)
383	0.619 ± 0.146	0.9765	6	$\Delta S^{\neq}$ = 31.67 ± 29.19 ($J \cdot K^{-1} \cdot mol^{-1}$)
388	1.237 ± 0.055	0.9974	11	
RH = 76.4%				
338	1.035 ± 0.092	0.9991	5	
343	1.269 ± 0.914	0.9935	4	Ea = 45.27 ± 7.92 ($kJ \cdot mol^{-1}$)
353	2.131 ± 0.222	0.9971	6	$\Delta H^{\neq}$ = 42.84 ± 7.92 ($kJ \cdot mol^{-1}$)
358	2.289 ± 1.645	0.9936	4	$\Delta S^{\neq}$ = −225.52 ± 22.60 ($J \cdot K^{-1} \cdot mol^{-1}$)
363	3.256 ± 0.508	0.9935	6	

Table 2: First-order rate constants for the decomposition of cefotaxime sodium in solid state in different humidity, 358 K

RH (%)	10^7 k ± Δk (s^{-1})	r	n
25.0	0.247 ± 0.029	0.9915	7
50.9	1.18 ± 0.21	0.9810	7
56.2	1.46 ± 0.20	0.9887	7
60.5	1.69 ± 0.16	0.9944	7
66.5	1.98 ± 0.20	0.9921	8
76.4	2.29 ± 1.65	0.9936	4

3. Discussion

Degradation of cefotaxime sodium in solid state was studied in the absence and in the presence of humidity. The thermodynamic parameters E_a $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated at room temperature (293 K).

The values of the thermodynamic parameters obtained for relative humidity = 0% and relative humidity = 76.4% are considerably different, which shows that the mechanism of the decomposition reaction of cefotaxime sodium in solid state in dry air is different from the mechanism in the presence of humidity. Negative entropy of activation in the presence of moisture suggests a double partial model of reaction with participation of a water molecule. The small value for the activation energy of reaction in relative humidity = 76.4% ($Ea = 45.27 \pm 7.92\ kJ \times mol^{-1}$) is a good reason to protect the substance from excess humidity even at room temperature. In the absence of humidity, cefotaxime displays very good stability. In conclusion, this substance should be protected from excess humidity and kept in tightly closed containers in a refrigerator.

4. Experimental

4.1. Material and reagents

Cefotaxime sodium (CEFO-Na for i.v. injection) (Hoechst AG) – lyophilized substance for injection. All chemicals were analytical grade reagents.

4.2. Methods

Decomposition was followed by a HPLC method previously described by Villanova et al. [1] and modified for our needs. The liquid chromatograph was equipped with a variable-wavelength UV detector set at 235 nm, a Waters Spherisorb RP 18 10 μm, a Rheodyne 20 μl syringe loading injector. The mobile phase was 0.1 mol phosphate buffer pH 7.6 – methanol (83 : 17), the flow was 1.0 ml/min. As an internal standard salicylamide (0.1424 mg/ml) was used.

4.3. Kinetic procedure

Weighed samples (10 mg) of substance in open glass vials were placed in an automatically controlled dry chamber at the appropriate temperature. To investigation the effect of humidity, samples were placed in desiccators containing aqueous saturated solutions of appropriate inorganic salts and placed into the dried chamber. Tests for stability in solid phase without humidity were carried out in the temperature range 371–388 K or 338–363 K at humidity values 25–76.4% [8]. For analysis, samples were cooled to room temperature, dissolved in water, transfered to a volumetric flask and diluted to 25.0 ml with the same solvent. Before the HPLC-analysis, 1.0 ml of this solution was mixed with 2.0 ml of internal standard solution.

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