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The Effect Of Storage Temperature On The Level Of Cefotaxim Injection After Dissolution With 0.9% NaCl By HPLC

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Abstract
Cefotaxime sodium is a β-lactam antibiotic belonging to the third-generation cephalosporin class that can undergo hydrolysis when dissolved. Cefotaxime must be dissolved in an appropriate solvent. Once dissolved, cefotaxime must be used immediately. The purpose of this study was to determine the effect of storage temperature on the concentration of cefotaxime sodium injection with 0.9% NaCl solvent.
Cefotaxime sodium injection was dissolved in 0.9% NaCl solvent and then stored at refrigeration (2-8°C) and room temperature (25-30°C) for storage periods of 0, 1, 3, 5, 7, and 10 days. Quality tests were then conducted, including organoleptic and pH measurements, and the determination of concentration using HPLC.
The results of the study showed that cefotaxime sodium injection was more physically stable in organoleptic and pH quality tests at 2-8°C than at room temperature. The decrease in the level of cefotaxime injection occurred at refrigeration temperatures of less than 10% after being stored for 10 days, this decrease in level is still acceptable according to the provisions of the active substance level in the preparation of 95-110%, while the level of cefotaxime sodium injection was reduced by 10% after only 1 day. The effect of storage temperature on the level of cefotaxime sodium injection preparations shows that at refrigeration temperatures it is more stable than at room temperature.
Keywords: Cefotaxime Sodium; temperature; concentration; HPLC

I. Introduction

Infectious diseases are a public health problem, especially in developing countries like Indonesia. Antibiotics are the most widely used drugs in the treatment of infections caused by bacteria [1]. Antibiotics are used to treat infectious diseases by inhibiting the growth of or killing pathogenic bacteria [1].2].

Cefotaxime is a β-lactam derivative of the cephalosporin antibiotic class. β-lactam antibiotic preparations in practical applications in hospitals are available in the form of dry powder injections. The instability factor in water causes injectable preparations of β-lactam derivative antibiotics such as the cephalosporin group that are available in powder form to be dissolved with a suitable solvent before use [3]. Mixing drugs with incompatible solutions will cause incompatibility in the form of physical incompatibility (cloudiness) and chemical incompatibility (color changes and decreased levels). A drug that is changed in its dosage form such as being dissolved and added with other ingredients or modified by environmental factors such as storage conditions can result in changes in the stability of the drug [4].

Cefotaxime sodium preparations are available in the form of dry powder for injection of 500 mg, 1 gram and 2 grams, so that it can be used after being dissolved.must be used immediately. Intravenous infusion of cefotaxime sodium is dissolved using a compatible solvent, namely 50-100 ml of 0.9% NaCl solution [5]. Cefotaxime Sodium is also compatible with the use of aqua pro injection solvent, 5% dextrose solution and after being dissolved is stable for 12-24 hours at room temperature and 7-10 days at refrigerator temperature and 13 weeks when frozen [6].

Preparations stored at refrigeration or room temperature (the effect of storage temperature) show that the storage temperature of the preparation affects the stability of the active substance. The active substance content of a drug preparation must meet the content requirements as stated in the Indonesian Pharmacopoeia. The content requirements for cefotaxime sodium preparations according to the 6th edition of the Indonesian Pharmacopoeia are not less than 90% and not more than 115% [7]. Previous research conducted a stability test of Cefotaxime Sodium injection preparations after being dissolved with aqua proinjection solvent experienced a decrease in content of more than 10% after storage for more than five days at 4°C and 1 day at 30°C [8].

To support the assurance of efficacy, safety and quality of drug use, this study was conducted with the aim of determining the changes in the levels of cefotaxime sodium injection preparations after being dissolved using a compatible solvent, namely 0.9% NaCl solution with different temperature treatments, namely at

refrigeration temperature and room temperature with storage periods of 0, 1, 3, 5, 7, and 10 days using the High Performance Liquid Chromatography (HPLC) analysis method.

II. Research Methods

The type of research used was a laboratory experimental study to determine changes in cefotaxime levels after reconstitution which were influenced by refrigerator temperature and room temperature using a High Performance Liquid Chromatography (HPLC) instrument.

The population used in this study was a 1 gram generic cefotaxime injection preparation obtained from a hospital in Surakarta. The sample used in this study was a 1 gram generic cefotaxime injection preparation dissolved in 0.9% NaCl solvent.

Tools And Materials

The tools used include KCKT (Alliance 2695 PDA 2998 Waters), UV-vis spectrophotometry (Hitachi U-2900), analytical balance (AG 245 Mettler Toledo), dropper pipette, volumetric pipette, micropipette, measuring cylinder (Pyrex), measuring flask (Iwaki), beaker glass (pyrex), glass funnel (pyrex), stirring rod, pH meter (Mettler Toledo), refrigerator, injection syringe, 0.45 µm GHP Acrodisl GF filter, and HPLC vial.

The materials used in this study were 1 gram of generic cefotaxime injection (CV. Dankos Farma), 0.9% NaCl, standard cefotaxime sodium, sterile aqua bidest, phosphate buffer, disodium hydrogen phosphate (Merck), pro-chromatography methanol, and phosphoric acid (Merck).

Ways Of Working

The sample used in this study was a 1 g generic product of cefotaxime injection from PT Dankos Farma. The 1gram generic cefotaxime sodium preparation was dissolved in 100 ml of 0.9% NaCl (10,000 ppm). The sample preparation to be studied was stored atrefrigerator temperature (2-8oC) and room temperature (25-30oC). At each temperature, organoleptic, pH, and concentration were determined on days 0, 1, 3, 5, 7, and 10. Determination of cefotaxime concentration was carried out using HPLC.

Organoleptic testing is carried out by testing periodically, namely on the dayto-0, 1, 3, 5, 7, and 10. Cefotaxime sodium standard was used as a control to compare with the test results on days 0, 1, 3, 5, 7, and 10. Observations were made by observing changes in pH, color, odor, and dosage form.

Samples were pH tested at time 0 and on days 1, 3, 5, 7, and 10 after reconstitution. Ten ml samples were taken using an injection syringe and placed into a beaker. The pH was measured using a pH meter.

Standard solution 1000µg/ml is made by weighing 50 mg of cefotaxime sodium dissolved in 0.9% NaCl then transferred quantitatively into a 50 ml measuring cylinder and added with 0.9% NaCl to the mark. From the standard solution, solutions with a series of concentrations of 2, 10, 20, 30, and 40 µg/ml are made.

Determination of optimum conditions for KCKT, using standard solution 20µg/mlcefotaxime sodium, with variations in the mobile phase of phosphate buffer pH 6.2: methanol 86:14; 81:19 and 76:24 (v/v), with mIsocratic method, with a 25 cm x 3.99 mm C18 column, a flow rate of 1 mL/min, using a Photo Diode Array detector, with a wavelength of 232 nm. The HPLC instrument automatically adjusts the mobile phase ratio for each optimization determination.

Making a Standard CurveThe relationship between concentration and area was determined by measuring the area of the cefotaxime sodium chromatogram. A calibration curve was created using cefotaxime sodium concentration ranges of 2, 10, 20, 30, and 40 ppm. Each concentration of solution was injected into the HPLC system as much as 10 ppm.µl and eluted with the selected mobile phase. The data obtained were then plotted as a relationship curve between the concentration (x) and the chromatogram area (y) after which the linear regression equation was determined.

Validation of Analysis Method

Determination of Linearity.A relationship curve between concentration and area was created by measuring the area of the cefotaxime sodium chromatogram to determine linearity. The concentrations used were 2, 10, 20, 30, and 40 µg/ml. This was measured using HPLC and a relationship curve was created between concentration and area to obtain the equation $y = bx + a$.

Accuracy Determination. Accuracy testing was carried out by preparing standard solutions with concentrations of 16, 20, and 24µg/ml then the solution was filtered using a 0.45 µm filter and each standard solution was injected 3 times in replication into the HPLC apparatus with a mobile phase of phosphate buffer pH 6.2: methanol. The accuracy value is expressed as percent recovery.

Precision Determination. This test was carried out by injecting a standard solution with a concentration of 20 µg/ml 6 times in replication into the HPLC instrument, then calculating the standard deviation value and the relative standard deviation (RSD) from the retention time and peak area of the detected cefotaxime.

Determination of Specificity. This was done by making a standard solution of cefotaxime 20 µg/ml, a cefotaxime sample solution, and 0.9% NaCl solvent. Then, it was injected into the HPLC instrument. The chromatogram results and retention time of the standard solution of cefotaxime 20 µg/ml, the cefotaxime sample solution, and the 0.9% NaCl solvent were compared.
LOD Determination And**LOQ.**Prepare standard cefotaxime solutions with concentrations of 2, 10, 20, 30, and 40 µg/ml, then inject each solution into the HPLC and create a linear regression equation between concentration and area. Calculate the calculated Y value and slope.

Determination of Test Solution Level

Determination of the levels of this test solution is carried out for each storage condition at refrigerator temperature and room temperature.with the storage time specified in the sample testing being on days 0, 1, 3, 5, 7 and 10, repeating the measurement three timesreplication.The test solution is injected into the instrumenthigh performance liquid chromatography as much as10µl and eluted with a mobile phase of phosphate buffer pH 6.2: Methanol at a flow rate of 1 ml/min.

III. Results And Discussion

Organoleptic Testing
The results of organoleptic tests on refrigerator and room temperature storage can be seen in table 1.

Table1. Organoleptic test of changes in color, shape and odor of cefotaxime injection on days 0, 1, 3, 5, 7, and 10 at refrigerator temperature and room temperature after reconstitution

Storage temperature	Storage time	Color	Form	Smell
Refrigerator temperature	0	Light yellow	Liquid	Cefotaxime has a distinctive odor.
	1	Light yellow	Liquid	Cefotaxime has a distinctive odor.
	3	Light yellow	Liquid	Cefotaxime has a distinctive odor.
	5	Light yellow	Liquid	Cefotaxime has a distinctive odor.
	7	Light yellow	Liquid	Cefotaxime has a distinctive odor.
	10	Light yellow	Liquid	Cefotaxime has a distinctive odor.
Room temperature	0	Light yellow	Liquid	Cefotaxime has a distinctive odor.
	1	Light yellow	Liquid	Cefotaxime has a distinctive odor.
	3	Light yellow	Liquid	Cefotaxime has a distinctive odor.
	5	Light yellow	Liquid	Smells rancid
	7	Yellow	Liquid and foamy	Smells rancid
	10	Yellow	Liquid and foamy	Smells rancid

Based on table 1 above, observations of the color, shape, and odor of cefotaxime injection preparations at refrigerator temperature did not reveal any changes during the storage period, so it can be concluded that the cefotaxime injection preparation after being reconstituted at refrigerator temperature is physically stable during storage until the 10th day because it can maintain its physical characteristics since the time the sample was reconstituted.

Observations of the color, shape, and odor of cefotaxime sodium injection at room temperature revealed changes. Color observations revealed a yellow color change on days 7 and 10. The dosage form showed a change in shape on days 7 and 10 of storage, indicated by the presence of foam. A rancid odor developed on days 5, 7, and 10 of storage..These changes indicate that the cefotaxime sodium injection has deteriorated and lost its physical stability. Temperature and light exposure from the storage location can cause hydrolysis, which can lead to physical changes in the cefotaxime injection.

pH testing
The results of the pH test for storage at refrigerator and room temperature can be seen in table 2.

Table2. pH of the preparation injectioncefotaxime after reconstitution at refrigerator temperature and room temperature

Storage time	pH Refrigerator temperature	pH Room temperature
0	5.02	5.01
1	5.02	4.92
3	5.01	4.87
5	4.97	4.78
7	4.97	4.72
10	4.92	4.61

The pH test results showed a decrease in pH values during refrigerated and room temperature storage. This decrease in pH during storage may be due to the increase in temperature, which increases the rate of hydrolysis reactions, making the pH more acidic.

Optimization of High Performance Liquid Chromatography conditions

OptimizationThe mobile phase used is a ratio of phosphate buffer pH 6.2: methanol86 : 14; 81 : 19 and 76 : 24 (v/v) withThe isocratic system uses one elution solution as the mobile phase with a C18 column of 25 cm x 3.99 mm, 5 µm, a flow rate of 1 mL/min, using a Photo Diode Array Detector, a temperature of 30o, with a wavelength of 232 nm and an injection volume of 10 µl.The results obtained from this optimization are in the form of chromatogram peaks which can be seen in Figure 2.

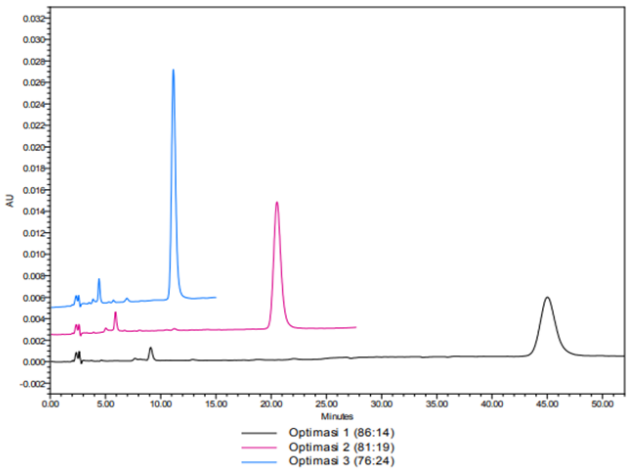


Figure 2. Optimization of the mobile phase of phosphate buffer pH 6.2: Methanol with ratio 86: 14; 81:19; 76: 14

Determination of optimum conditions is done by looking at several parameters, namely the Tr value (retention time), N (theoretical plate), HETP (*Height Equivalent Theoretical Plate*and Tf (tailing factor). The results obtained in all comparisons have an N value > 2000, a small HETP value and a Tf value < 2.These parameters meet the existing criteria, namely Tf < 2, and N > 2000 [9].

The retention time value obtained from the time difference where the mobile phase ratio of 76: 14 produced a shorter time of 11.158 minutes so that the determination of a good mobile phase was Phosphate buffer pH 6.2: Methanol (76: 24). The selected mobile phase comparison was based on the orientation where the peak that appeared was the cefotaxime sodium peak that was separated from the degradant with the smallest retention time of 11.158 minutes.

Determination of the Standard Curve

The preparation of a standard curve for cefotaxime sodium showed a linear correlation between concentrations of 2, 10, 20, 30 and 40 ppm.The data obtained is then used to create a relationship curve between the content (x) and the area (y) after which the regression line equation is determined.The results of the standard curve graph can be seen in Figure 3.

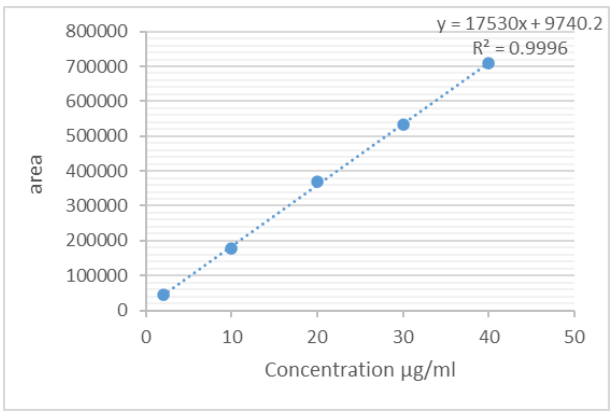


Figure 3. Standard curve graph

The linear regression equation of cefotaxime sodium using 0.9% NaCl solvent between concentration and area obtained a regression equation of y = 17530x + 9740.2 with a correlation value of 0.9997. The correlation coefficient results show a linear relationship between the detector signal and the amount of cefotaxime narium analyte in the sample.

Method Validation

Determination of Linearity

The linear regression equation of cefotaxime sodium using 0.9% NaCl solvent between concentration and absorption obtained a regression equation of y = 17530x + 9740.2 with a correlation value of 0.9997.The acceptance criteria for the r value in the linearity test according to the United States Pharmacopeia (2021) is ≥ 0.998, which means that the results of the linearity test carried out meet the specified requirements.

Accuracy Determination

Accuracy testing was carried out by injecting standard cefotaxime solutions with 3 different concentrations, each repeated 3 times. Cefotaxime accuracy resultsWhichobtained can be seen in table 3.

Table 3. Cefotaxime sodium accuracy results

Concentration (ppm)	Area	X	%recovery	%Average recovery
16	291566	16.07677125	100.48	100.26 ± 0.002
16	290483	16.01499144	100.09	
16	290792	16.03261837	100.20	
20	363185	20,1622818	100.81	100.33 ± 0.004
20	360352	20,00067313	100.00	
20	360970	20.03592698	100.18	
24	430591	24.00746149	100.03	100.23 ± 0.002
24	431645	24.06758699	100.28	
24	432005	24.08812322	100.37	

Based on Table 3, accuracy testing was carried out by calculating the % recovery value. The accuracy test results were 100.23-100.33%, which meets the requirements. criteriathe acceptability of the recovery percentage, namely % recovery, is 98 – 102% [10].

Precision Determination

Testing was conducted using the repeatability method, injecting the sample six times. The results of the precision test can be seen in Table 4.

Table 4. Cefotaxime sodium precision results

Concentration (ppm)	Replication	Area	X
20	1	363185	20,16228
	2	360352	20,00067
	3	360970	20.03593
	4	360970	19.98122
	5	360011	20,0924
		Average	20.03421
		Elementary School	0.082489
		RSD	0.41%

Based on table 5, the precision results from 6 replicated readings of the area of the 20 ppm cefotaxime standard solution obtained an RSD value of 0.41%. Precision is declared good because it has an RSD value of less than 2%.

Determination of Specificity

Selectivity testing of the validated method was performed by injecting standard solutions, samples, and solvents using the analytical method to be validated. The specificity test results showed no peak response from the solvent injection, while the sample and standard injections produced the same peak response at the same retention time. The results of the cefotaxime sodium specificity determination can be seen in the overlay of Figure 4.

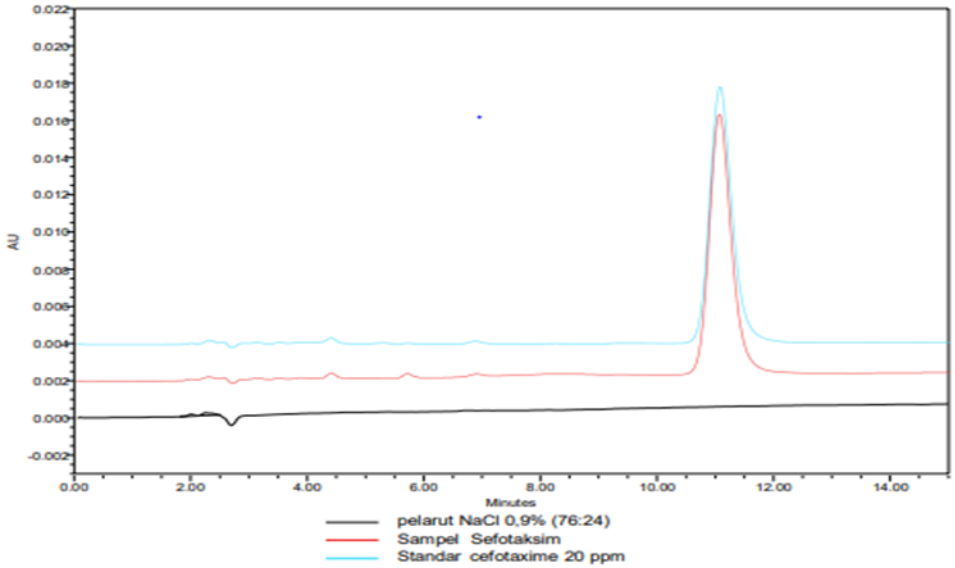


Figure 4. Specificity overlay

Determination of LOD and LOQ

Statistically, the calculation of the detection limit and quantitation limit is obtained through a linear regression line from the standard calibration curve. The measurement value will be the same as the b value in the linear equation y = a + bx.

The results of determining the LOD and LOQ of cefotaxime sodium can be seen in table 5.

Table 5. LOD and LOQ results of cefotaxime sodium

Concentration (ppm)	Area	y′	y − y′	$(y - y')^2$
2	45836	44800.2	1035.8	1072882
10	178777	185040.2	-6263.2	39227574
20	368691	360340.2	8350.8	69735861
30	533789	535640.2	-1851.2	3426941
40	709665	710940.2	-1275.2	1626135
			$\sum(y - y')^2$	115089493
			$\sum$/N-2$(y - y')^2$	38363164
			S(y/x)	6193,8005
			LOD	1,165975
			LOQ	3.5332575

The results of the LOD and LOQ calculations against the standard curve are LOD = 1.165975 µg/ml, LOQ = 3.5332575 µg/ml. This result is stated as good because the LOD value obtained is below the smallest concentration of the standard curve and the standard curve concentration series solutions all have values above the LOQ value.

Determination of Test Solution Level

Cefotaxime sodium injection was tested at different temperatures and storage times. The temperatures used were refrigerator and room temperature, with storage times specified in the sample testing on days 0, 1, 3, 5, 7, and 10.From the resultstestingcefotaxime sodium injection preparation after reconstitution with 0.9% NaCl obtained a leveland percentage levels during storage time at refrigerator temperature and room temperature.The results of the percentage of cefotaxime sodium injection levels during refrigerator temperature storage can be seen in table 6 and room temperature storage can be seen in table 7.

Table 6. The results of the percentage of cefotaxime sodium injection levels at refrigerator temperature storage (2oC-8oC)

Storage time	Area	Level	% content	Average % content
0	364393	20.23	101.16	103.28
	372460	20.69	103.46	
	367546	20.41	102.06	
1	358334	19.89	99.43	99.78

	360231	19.99	99.97	
	360113	19.99	99.94	
3	357095	19.81	99.07	99.29
	357940	19.86	99.32	
	358540	19.90	99.49	
5	351411	19.49	97.45	97.61
	351547	19.50	97.49	
	352926	19.58	97.89	
7	348058	19.30	96.50	96.68
	348662	19.33	96.67	
	349387	19.38	96.88	
10	343220	19.02	95.12	95.30
	344059	19.07	95.36	
	344290	19.08	95.42	

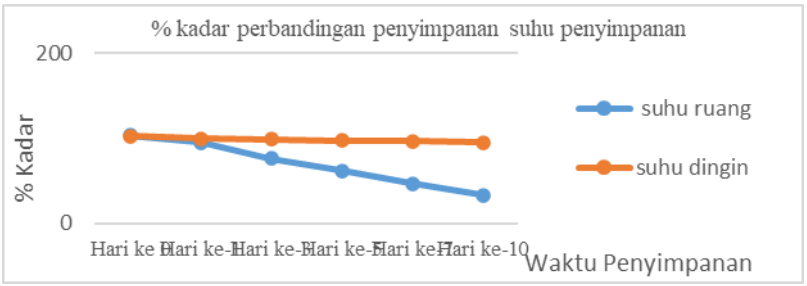
Based on table 6, the average percentage of cefotaxime sodium injection stored at refrigerator temperature on day 0 to day 10 showed a decrease in levels, butacceptable because it is in accordance with the provisions in the literature, namely not less than 90% and not more than 115%. Based on the paired-samples t-test using SPSS statistics, it shows that the percentage results of cefotaxime sodium injection levels at refrigerator temperature on day 0 compared to days 1, 3, 5, 7, and 10 show no significant difference, namely having a significance value of >0.05.

Table 7. The results of the percentage of cefotaxime sodium injection levels at room temperature storage (25OC -30OC)

Storage time	Area	Level	% content	Average % content
0	371976	20.66	103.32	103.04
	370019	20.55	103.16	
	371049	20.61	103.05	
1	335272	18.50	95.35	95.04
	333694	18.41	94.90	
	334571	18.41	94.88	
3	280102	15.42	77.11	76.61
	279351	15.38	76.18	
	278094	15.31	76.54	
5	230509	12.59	62.97	62.27
	228689	12.49	61.19	
	229352	12.53	62.64	
7	173352	9.33	46.67	46.71
	173082	9.32	46.59	
	174125	9.38	46.89	
10	126490	6.66	33.79	33.46
	126161	6.64	33.21	
	126285	6.68	33.40	

Based on table 7, there was a decrease in the level of storage at room temperature where pThe average concentration of the storage samples from day 3 to day 10 was no longer within the content range based on the provisions of the Indonesian Pharmacopoeia edition VI. Based on the paired-samples t test using SPSS statistics, it shows that the percentage results of cefotaxime sodium injection concentration on day 0 compared to days 1, 3, 5, 7 and 10 showed a significant difference, this can be seen from the resulting significance value of <0.05. This significant difference occurs because the increasing temperature, namely room temperature, makes the decomposition of the active substance in the drug greater so that the resulting concentration is small.

Decreased levels at room storage temperatureThere was a significant decrease, different from the relatively smaller decrease in levels at refrigerated storage temperatures. From the results of data processing using an independent sample t-test to see the comparison of levels at refrigerated storage temperatures and room temperature, there was a significant difference, as seen from the significance value obtained, which was <0.05.A comparison graph of storage temperature against storage time can be seen in Figure 5.



Picture1. Comparison chart of storage temperature against storage time

The decrease in the level of cefotaxime sodium injection in the reconstituted preparation is due to the decomposition of cefotaxime sodium in it.

Cefotaxime sodium is chemically derived from 7-aminocephalosporanic acid (7-ACA), and its matrix structure consists of a β-lactam ring fused to a six-membered dihydrothiazine ring, and is susceptible to side reactions and degradation.

Cefotaxime contains a lactam group and is therefore easily hydrolyzed. Hydrolysis occurs due to a reaction between cefotaxime and the H+ group.

OH^-which is present in the carrier fluid and the results have a significant impact on stability because it causes the β-lactam ring to break, resulting in decomposition into deacetylcefotaxime (active form), 7-epimer deacetylcefotaxime and methylene ester in the inactive form.

ConditionDifferent storage and temperatures of cefotaxime sodium injection can cause instability of a pharmaceutical preparation.

Increasing and decreasing storage temperature affects the chemical decomposition of a drug.

Drug preparations that are added with a carrier liquid and then stored in an environment with an increased temperature, then there is a possibility of instability that causes degradation to occur more quickly [11]. Due to changes in temperature during storage, the amount of drug degradation can be determined by determining the level of the preparation [12].

Antibiotic preparations are generally injection powder preparations, which when applied to the body must be dissolved with a suitable solvent.

Based on the literature, cefotaxime sodium is compatible with 0.9% NaCl.Mixing drugs with incompatible solutions can lead to physical and chemical incompatibilities. Drug incompatibilities can cause changes in drug stability. Cefotaxime dissolved in NaCl will produce a clear, light-yellow solution.

The decrease in drug levels significantly impacts patient health, as the treatment objectives are not achieved. The decrease in the levels of cefotaxime sodium injection due to the influence of refrigerator temperature and room temperature on storage time causes a decrease in antibacterial activity in the injection preparation, thereby reducing the effectiveness of cefotaxime sodium. The levels of cefotaxime sodium injection stored for 10 days at refrigerator temperature are acceptable according to the provisions for the levels of active substances in the preparation and at room temperature can be stored for up to 1 day of storage. The effect of temperature on the levels of cefotaxime sodium injection preparations shows that at refrigerator temperature it is more stable than at room temperature.

IV. Conclusion

The higher the temperature and the longer the storage time of cefotaxime sodium after reconstitution with 0.9% NaCl solvent, the greater the decrease in cefotaxime sodium levels, this is in accordance with the theory of degradation reactions or other reactions.

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