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STABILITY OF RECONSTITUTED CEFADROXIL ORAL SUSPENSION USING THREE TYPES OF WATER AT DIFFERENT STORAGE CONDITIONS

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ABSTRACT: The study aimed to investigate the effect type of water for reconstitution and the temperature on stability of Cefadroxil dry oral suspension 250mg/5ml during the recommended in-use shelf life. This study was carried out by selection of three brands of Cefadroxil dry suspension (imported and local brands), exposed to different conditions (refrigerator conditions and ambient temperature) after reconstitution by three waters (distilled, boiled and ozone treated water) then the assay test was performed using HPLC for fourteen days at 0 day, 3rd, 7th, 10th, 12th, 14th day. Physical tests were done included pH test, color, odor, taste, viscosity and sedimentation rate. The results revealed that the distilled water was the best water used for Cefadroxil reconstitution. There is a significant effect of brand type used because Cefacure® from the 0 day was higher than the limit in pharmacopeia (90-120%), however, Cefradil® and Curisafe® were within the limit at beginning then became lower than the limit after 2 weeks from reconstitution. Moreover, the storage conditions of Cefadroxil samples after reconstitution affected the Cefadroxil quality significantly; therefore, the samples were stored in refrigerator had less degradation rate than that were stored at room temperature. Conclusion, Cefadroxil showed good stability after reconstitution by the three types of water especially D.W. and it must be stored at refrigerator conditions to decrease the degradation of Cefadroxil during the recommended period.

KEYWORDS: Cefadroxil, dry suspension, reconstitution, stability, HPLC.

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1. INTRODUCTION

Liquid pharmaceutical preparations are more suitable alternative for patients who have difficulty in taking the capsules and tablets. However, many drugs, e.g. antibiotics are physically or chemically unstable when formulated as a solution or suspension and to avoid this instability problem it will be better to prepare the drug as dry powder or granules for reconstitution by water immediately before use [1]. Cefadroxil, which is one member of cephalosporins, it prepared as dry powder for reconstitution by water, then it must be kept in specific storage conditions to maintain effectiveness and stability, also it should be used within 2 weeks to avoid degradation of the active ingredient then reduction in activity to get the optimal benefit from the drug and avoid toxicity. However, many patients do not apply this information for different reasons such as there is no refrigerator and irregular power supply that may result in various degrees of degradation of the product [2]. Stability testing of pharmaceutical products is a complex set of procedures involving considerable cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation. Scientific and commercial success of a pharmaceutical product can only be ensured with the understanding of the drug development process and the myriad tasks and milestones that are vital to a comprehensive development plan. The most important steps during the developmental stages include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products [3, 4]. Pre-requirement of drug products that should be chemically and pharmaceutically equivalent must be identical in strength, quality, purity, active ingredient release profile and in the same dosage form, for the same route of administration [5]. Because of the widespread use of this drug, quality control testing should be done for diclofenac marketed products to ensure safety; efficacy; accepted quality; rationality of use to protect public health [6]. In-vitro testing or quality control of drugs is a set of experiments undertaken during production in process and occasionally ought to be undertaken post production by regulatory agencies and researchers. Routine laboratory testing of drugs in the market is a crucial to protect public health especially in developing countries where counter-fit and substandard drugs have become a major challenge to health care services [7]. There is need to ascertain the chemical and biological equivalence of antibiotics due to global health problem posed by antibiotic and multi-drug resistance [8]. The multi-drug resistance by infective agents might be due to chemical in equivalence and bio-inequivalence. Though the problem is worldwide, Southeast Asia and Africa seem to be particularly plagued by counterfeited pharmaceuticals [9]. For example, a study done in Southeast Asia in 2001 showed that 38% of antimalarial on sale in pharmacies did not have any active ingredients [10]. In a WHO survey, 20-90% of antimalarial [11] and 28% of antibiotic [9] drugs failed quality specifications. This study was carried out on one of the most common used antibiotics that available in the market as dry powder for reconstitution as suspension. Many people used the mineral water for reconstitution, some used boiled water, few used the

distilled water for reconstitution, and some people used the tap water. This study was conducted to ensure what type of water is good for this drug and if there is a significant effect on stability because the type of water used or the storage conditions of this drug during the recommended shelf life after reconstitution, 14 days. This study included three different brands to exclude any error of quality because of manufacturing or transportation processes.

2. MATERIALS AND METHODS

2.1 Sample collection

Cefadroxil samples, of the same batch number, were collected from different pharmacies in the same city (Sana'a City) [12]. Three different brands were used in this study; one local brand (Yemen) and two imported brands (Egypt and Jordan).

1.2.Sample size

Eighteen samples from three brands were marketed in Yemen. Six samples from each brand were used. Two samples from each brand with the same batch number were reconstituted by each type of water boiling water, distilled water, and ozone treated water.

1.3.Sampling time points

In use-stability testing should be performed at initial (zero time), at intermediates time points, and at the end of the proposed in-use shelf life [13]. The sampling time points was as the following: 0 day, 3rd day, 7thday, 10th day, 12th day, and 14th day, after reconstitution then stored at 2-8°C (in the refrigerator) and inside a cupboard with room temperatures of 27-29°C for two weeks.

1.4.Preparation of suspension

Powder was loosen from the bottom by the tapping against a hard surface. The specified amount of type of water (boiling water, distilled water, or ozone treated water) was added, sometimes in two or more portions with shaking until all the dry powder was suspended and the amount of the suspension equivalent to 100mg of Cefadroxil was examined (for 18 samples) at zero time then stored in different condition for assay test at 3rd, 7th, 10th, 12th, 14th day.

The analytical procedures were performed in Modern Pharmaceutical Company in Yemen.

1.5.The project of the study

Three Cefadroxil brands were included in this study with the same batch number and the same manufacturing date and expiry date from each brand (Cefacure®, Cefadril®, and Curisafe®) as shown in table (1).

Table 1: Cefadroxil monohydrate dry suspension brands which used in this study.

Brand	Company	Origin	Batch N.O	M .D	EX. D
Local brand (Cefacure®)	Modern pharm	Yemen	16529	8/2016	8/2018
Imported brand(Cefadril®)	RAM pharm	Jordan	K344	9/2016	9/2019
Imported brand (Curisafe®)	Pharco-pharm	Egypt	01402415	2/2015	2/2018

All three different brands were evaluated according to the US pharmacopeia then the results were analyzed statically using SPSS.

1.6. Validation of the analytical method

Preparation of stock and standard solutions for calibration

500mg of Cefadroxil monohydrate was transferred into 100ml volumetric flask, then volume completed with buffer solution pH 5. The standard solutions 0.5mg, 0.75mg, 1mg, 1.25mg and 1.5mg of the working concentration standard were prepared and diluted to the final volume with buffer. Three replicate measurements of each solution by (HPLC).

The peak area response obtained for each solution was plotted against its corresponding theoretical concentration and a linear regression analysis was performed on the five coordinates.

1.6.1.Physical test

The color, taste, odor, general appearance, and pH were inspected over each reconstitution at zero time. In addition, the viscosity of all formulations was determined by visual inspection and usual methods.

1.6.2.Chemical test (Assay)

Assay test was performed using HPLC method as the following:

a) Mobile phase

The mobile phase was prepared from (Buffer: acetonitrile) (960:40). The buffer was prepared by dissolving 6.86g of KH_2PO_4 in1000ml of distilled water and adjusted with 10 N KOH to a pH of 5.0 [14,15].

b) HPLC conditions

Column: C18, 15cm; Flow rate: 2ml/min. Wavelength: 230nm; Sensitivity: 1; Pressure: 28 Mpa; End time: 3.5min

c) Preparation of standard solution

100 mg of Cefadroxil RS was weighed into 100 ml volumetric flask, then dissolved and diluted with buffer to make 1mg/ml solution [14,15].

d) **Preparation of sample solution**

5ml of the reconstituted suspension was transferred into 250ml volumetric flask, then dissolved and diluted with the buffer solution. The prepared solution was put in ultrasonic for a few minutes to dissolve and filtered. Finally, a small amount of 1mg/ml of Cefadroxil was transferred into the HPLC for assay.

1.6.3.Microbial test for three types of water

Microbial test was done for the three types of water (D.W., O.T.W. and B.W.) which used in reconstitution the samples to measure the ability of water to promote the microbial growth by inoculating different dilutions concentration from each types of water in nutrient agar.

Standard plate count method

This method was used to detect if the water is good for human consumption or not by count bacteria per 1 ml of water. The media was prepared according to manufacturing company. Then different five dilutions were prepared from each type of water (1:10, 1:100, 1:1000, 1:10000 and 1:100000) by serial dilution with distilled water.1ml from each test tube was diluted and cultured in nutrient agar for 24 hrs.

1.7. Data analysis

The IBM SPSS statistical software of version 22.0 was used in this study.

3. RESULTS AND DISCUSSION

1.1.Validation of analysis method

The calibration curve for Cefadroxil showed a good linear response between the peak area and the concentration as shown in figure (1).

Table 1: Reproducibility of calibration curve

Concentration in mg/ml	Average	SD
0.5	4513311.6	3039.031
0.75	6842379.7	2096.644
1	9959788.12	865.669
1.25	12463505.4	3180.246
1.5	14190667.7	2746.725

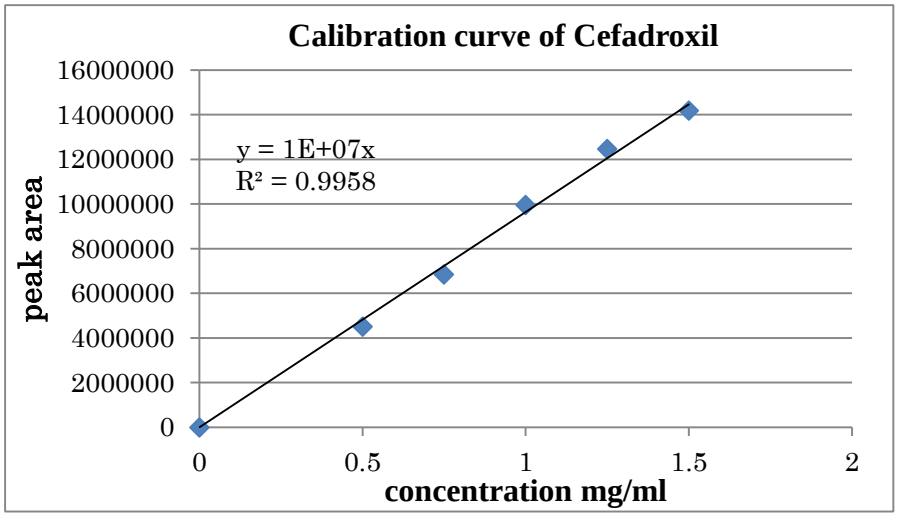

Figure 1: Reproducibility of Calibration Curve

The results of calibration for Cefadroxil illustrated the linearity that was demonstrated by plotting peak area vs concentration of Cefadroxil with regression equation y = 1E+07X. and the correlation coefficient R^2 = 0.9958 this indicates the validity of HPLC used in this study.

1.2. Quality control tests for Cefadroxil brands

1. Physical tests

The color, taste and odor were inspected at zero time of each brand after reconstitution with three different types of water as shown in table (2).

Table 2: Physical properties of the three brands after reconstitution by three types of water

	Physical properties	Type of water		
		Ozone treated water	Boiled water	Distilled. Water
Cefacure	Color	Milky	Milky	Milky
	Taste	Sweet with some	Sweet with some	Sweet with some
	Odor	Peppermint	Peppermint	Peppermint
	pH	5.9	6.11	5.72
Cefadril	Color	Orange	Orange	Orange
	Taste	Sweet	Sweet	Sweet
	Odor	Orange	Orange	Orange
	pH	4.53	4.54	4.52
Curisafe	Color	Orange	Orange	Orange
	Taste	Sweet	Sweet	Sweet
	Odor	Orange	Orange	Orange
	pH	5.74	6.06	5.32

The results of pH for the brands which reconstituted by distilled water were lower than the brands were reconstituted by boiled water and ozone treated water. The pH measurements for all three brands Cefadril®, Cefacure® and Curisafe® after reconstitution by three different types of water the measurement were within acceptance limit as shown in table (2). All the results of physical tests include pH, color, odor and taste were good and conform the specifications of pharmacopeia.

Viscosity test

Viscosity of Cefacure® (local brand) and Cefadril® (imported brand) after reconstitution was high in ozone treated water than the distilled water then boiled water. However, the viscosity of Curasife® (imported brand) after reconstitution by boiled water was more than reconstituted by ozone treated water then of distilled water. The sedimentation rate is inversely related to viscosity, an increase in the viscosity of the dispersion medium will decrease the settling. Yoshioka, S and Sttela [16] reported that hydrolysis rate was found to be proportional to the amount of water with high mobility rather than to the total amount of water.

2. Chemical tests (Assay test)

Table (4) shows the results of assay test for Cefadril® (Cefadroxil monohydrate 250mg/5ml) has the same batch no. (16529) after reconstitution by three different types of water during 14 days at different conditions. Cefadroxil monohydrate for oral suspension must contain not less than 90.0 percent and not more than 120 percent of labeled amount of Cefadroxil [15].

Table 4: Results of assay test for Cefadril® suspension at room temperature and refrigerator conditions after reconstitution by three types of water

Day	Room temperature						Refrigerator					
	D.W		O.T.W		B.W		D.W		O.T.W		B.W	
	Assay% ±SD	RSD	Assay% ±SD	RSD	Assay% ±SD	RSD	Assay% ±SD	RSD	Assay% ±SD	RSD	Assay% ±SD	RSD
0	103.76% ±0.13	0.141	95.15%± 0.24	0.266	96.82%± 0.25	0. 279	102.118 %±0.46	0.460	97.47%± 0.19	0.193	99.77%± 0.33	0 .33
3rd	99.91%± 0.09	0.141	92.07%± 0.07	0.083	92.46%± 0.03	0.038	101.20% ±0.10	0.106	96.23±0. 02	0.016	99.03±0. 06	0.061
7th	94.78%± 0.22	0.252	91.50%± 0.56	0.619	89.12%± 0.40	0.459	100.83± 0.17	0.113	94.05%± 0.42	0.420	96.80%± 0.18	0.187
10th	93.05%± 0.08	0.083	91.00%± 0.04	0.048	88.27%± 0.28	0.323	100.118 %±0.46	0.460	93.69%± 0.09	0.099	96.20%± 0.22	0.228
12th	92.94%± 0.72	0.745	90.21%± 0.07	0.075	87.61%± 0.22	0.245	100.02% ±0.22	0.210	93.04%± 0.13	0.131	94.11%± 0.10	0.104
14th	91.80%± 0.26	0.283	90.0%±0 .15	0.150	87.44%± 0.26	0.296	99.99%± 0.46	0.450	92.51%± 0.18	0.192	93.34%± 1.33	1.407

The results of assay test in table (4) show that all samples of Cefadril® brand which were reconstituted with three waters (D.W, O.T.W and B.W) at refrigerator during 14 days of studies are within the limit (90-120%) according USP. Since, the sample which was reconstituted with distilled water have better assay results than same samples reconstituted with (O.T.W and B.W). Moreover, the sample of Cefadril® brand which were reconstituted with boiled water at room temperature during 14 days of studies are lower than the limits according USP during 14 days. Almost this is because the high degradation in ambient temperature. However, the results of the assay test for the sample was reconstituted with distilled water were good during shelf life (14 days). Study, about effect of storage conditions on amoxicillin, reported that the rate of improper storage conditions of drugs was 26.0% and that there was a higher rate of unsuitable storage in rural areas due to the lack of refrigeration [17, 18]. The results of assay test for Curisafe® brand has the same batch no. (01402415) after reconstitution by three different types of water during 14 days stored at refrigerator

(2-8°C) and at room temperature are illustrated in table (5).

Table 5: Results of assay test for Curisafe® suspension at room temperature and refrigerator after reconstitution by three different types of water

Day	Room temperature						Refrigerator					
	D.W		O.T.W		B.W.		D.W		O.T.W		B.W.	
	Assay % ±SD	RSD	Assay%± SD	RSD	Assay % ±SD	RSD	Assay % ±SD	RSD	Assay%± SD	RSD	Assay%± SD	RSD
0	103.55% ±1.07	0.356	101.13% ±0.38	0.375	100.65% ±0.32	1.045	104.31% ±0.06	0.447	102.25% ±0.28	0.273	102.75% ±1.48	1.515
3rd	103.34% ±3.22	0.043	98.34%± 0.20	0.216	95.88%± 0.04	3.227	103.75% ±1.44	1.471	101.75% ±0.16	0.177	100.50% ±0.16	0.176
7th	102.05% ±0.32	0.209	97.25%± 1.33	1.364	92.15±0. 18	0.329	102.76% ±0.23	0.123	99.81%± 1.51	1.575	98.78%± 0.37	0.377
10th	101.03% ±0.07	0.019	94.92%± 0.04	0.042	89.78%± 0.02	0.069	100.57% ±0.05	0.048	98.62%± 0.08	0.081	97.61%± 0.05	0.047
12th	100.76% ±0.15	0.053	93.8%% ±0.06	0.057	88.54%± 0.05	0.143	99.60%± 0.45	0.062	97.97%± 0.03	0.025	98.83%± 0.12	0.120
14th	98.20%± 0.09	0.047	89.59%± 0.09	0.089	88.09%± 0.04	0.087	96.89%± 0.12	0.223	95.71%± 0.10	0.101	96.15%± 0.04	0.039

Table (5) above illustrates the result of assay test for Curisafe® brand samples after reconstitution after 14 days storage at room temperature that two samples which reconstituted with boiled water and ozone treated water were outside the pharmacopeial limit 89.59% and 88.09% respectively but the sample which reconstituted by distilled water was within the limit in assay 98.2% (90-120%). Regard to storage conditions, the samples were stored at refrigerator conditions showed good results and conform the pharmacopeia limit (90-120%) due to the degradation rate lower than that at room conditions. The assay test results for Cefadroxil monohydrate (250mg/5ml) oral suspension in the third brand (Cefacure®) has the same batch no. (16529) after reconstitution by three different types of water during 14 days stored at refrigerator (2-8°C) and at room temperature are found in table (6).

Table 6: Results of assay test for Cefacure® suspension at room temperature and refrigerator after reconstitution by three different types of water

Day	Room temperature						Refrigerator					
	D.W		O.T.W		B.W		D.W		O.T.W		B.W	
	Assay% ±SD	RSD	Assay% ±SD	RSD	Assay% ±SD	RSD	Assay% ±SD	RSD	Assay% ±SD	RSD	Assay% ±SD	RSD
0	128.96% ±0.21	0.179	126.94% ±0.24	0.196	130.67% ±0.21	0.165	130.41% ±0.75	0.628	131.57% ±0.08	0.065	131.53% ±0.22	0.182
3rd	126.08% ±0.06	0.048	124.04% ±0.11	0.095	129.40% ±0.12	0.101	129.90% ±2.56	2.173	131.04% ±0.12	0.111	130.01% ±0.16	0.132
7th	122.03% ±2.30	2.015	120.65% ±1.38	1.255	125.31% ±0.23	0.201	129.79% ±1.46	1.250	123.76% ±0.23	0.206	129.43% ±0.47	0.411
10th	119.46% ±0.21	0.172	116.87% ±0.11	0.093	124.00% ±0.09	0.064	128.39% ±0.18	0.145	122.08% ±0.16	0.126	127.73% ±0.03	0.027
12th	117.37% ±0.02	0.016	113.84% ±0.14	0.117	122.25% ±0.12	0.090	127.52% ±0.05	0.037	121.02% ±0.13	0.101	126.43% ±0.06	0.045
14th	115.42% ±0.12	0.095	109.90% ±0.19	0.154	121.61% ±0.22	0.164	126.62% ±0.10	0.073	120.48% ±0.16	0.118	126.06% ±0.08	0.059

All Cefacure® brand samples were stored at room temperature after reconstitution by three different types of water during 14 days, almost outside the pharmacopeial limit (90-120%). The samples of this brand consider rejected at zero point because of the assay result was above the upper limit 128.96, 126.94, 130.67 at room temperature and 130.41, 131.57, 131.53% at refrigerator, for the samples were reconstituted by distilled water, ozone treated water, and boiling water, respectively. This is may be because some problems in this brand itself may be during manufacturing or formulation or transportation and shipping of this brand. The samples had reconstituted by distilled water better than others. More so, the samples in refrigerator conditions has less degradation than that in room temperature conditions. As general, the above results assure the fact that the ideal condition for Cefadroxil storage is the standard storage condition of 2-8°C. Similar study was done by [19] on different brands of Co-amoxiclave oral powder after reconstitution by three types of water at different storage condition, and the results of this study showed no significant effect for the

type of water used in reconstitution. However, the storage condition did. Another Study by [20] on the effect of different storage condition on the stability of different brands of cefuroxime axetil oral powder after reconstitution and the results of this study show significant effect for brands which store at room temperature. Similar study on amoxicillin reconstitution, was conducted in Sanaa, has shown that both amoxicillin and clavulanic acid showed the use of bottled water resulted in better stability profiles compared to tap water for formulations stored in fridge or room temperature. These results could be due to the acidic pH of the tap water in Sana'a along with the high metal content reported in tap water. Both the presence of hydrogen ions and high concentration of metals are factors that promote hydrolysis. Furthermore, the storage of this antibiotic at room temperature has a high degrading effect on both amoxicillin and clavulanic acid [21].

3. Microbial test

Table 7: Result of microbial test for different dilutions of the three types of water (D.W., O.T.W and B.W.)

Water type	Dilution				
	10^1	10^2	10^3	10^4	10^5
D.W	No growth	No growth	No growth	No growth	No growth
O.T.W	No growth	No growth	No growth	No growth	No growth
B.W.	6	2	No growth	No growth	No growth

From the above table (7) different dilutions of three types of water were cultured in agar media did not promote microbial growth. Whereas, the boiling water was inoculated in 10^1 dilution grown 6 CFU/1ml and 10^2 dilution grown 2CFU /1ml and there is no microbial growth when it was inoculated the other dilutions. Counting was done by plate showing (25-250) colony forming units.

4. CONCLUSION

This study was performed on Cefadroxil oral dry powder for suspension. Cefadroxil is one of cephalosporin antibiotics first generation. Cefadroxil oral dry suspension needs reconstitution before use. The reconstitution process, storage conditions, type of water used in reconstitution are important factors for drug stability as much as the manufacturing process. This study included three brands of Cefadroxil, three types of water for reconstitution, and two different storage conditions then the assay test performed using HPLC system. The results revealed that there was a small effect of type of water used in this study on Cefadroxil in oral suspension during the shelf life after reconstitution but there was a significant effect of type of brand used and storage conditions of Cefadroxil samples during shelf life after reconstitution.

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CONFLICT OF INTEREST

Authors have no conflict of interest.

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