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Stability Study of the Co-amoxiclav Original Brand Oral Suspension (312.5/5ml) after Reconstitution at Recommended Conditions and at-Home Storage Conditions

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ABSTRACT

Co-amoxiclav for pediatric use comes as oral powder, which has to be reconstituted before administration. Concerns have been raised regarding the appropriateness of environmental conditions. A stability study was carried out on the original brand (Augmentin) suspension which were reconstituted and kept under the standard storage conditions of 2-8ºC and at home conditions (25ºC). Both compounds (amoxicillin and clavulanic acid) were considered stable if they retained 90% of their initial concentrations. From the study, it was found that the home conditions had no significant detrimental effect on the stability of amoxicillin but had a significant on stability of clavulanic acid, throughout the duration of therapy (10 days). However. The standard storage temperature should be adhered to stringently to guarantee maximum therapeutic benefit. This revealed that amoxicillin remained stable throughout the duration of therapy but clavulanic acid did not. Physical compatibility was assessed by visual observation for discoloration and precipitation throughout the duration of therapy. The chemical stability of the drug was analyzed by HPLC instrumental method. The various parameters analyzed include description, odor, color, taste, assay, water content, specific gravity, and pH. These parameters were evaluated at zero day, 3rd day, 7th day, 10th day intervals. The results of assay indicate that the samples are within the allow able limits (90-120%) for amoxicillin at recommended conditions and home conditions, but the storage of Augmentin suspension at home conditions (25ºC). showed that the clavulanic acid rapidly exposed to degradation directly after reconstitution of all batches after 3 days, the assay test were out the limit, however, when stored at refrigerator temperature (2-8ºC) the degradation of clavulanic acid is very low after prolong period (about 10 days). The results of amoxicillin concentration in all tested batches that were stored at 2-8ºC were very similar to the results of assay that were stored at room temperature.

Key words: stability evaluation, amoxicillin, clavulanic acid, degradation, reconstitution.

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INTRODUCTION

Amoxicillin belongs to the class of medications called penicillin-like antibiotics. The penicillin belong to the beta-lactam group of antibiotics [1], which are the dominant class of agents currently used for the chemotherapy of bacterial infections worldwide. Amoxicillin acts by inhibiting the synthesis of bacterial call walls [2]. It is usually the drug of choice within the class because it is better absorbed following oral administration and it is resistant to gastric acid [3]. Amoxicillin is susceptible to degradation by beta-lactamase-producing bacteria, and so may give with clavulanic acid to decrease its susceptibility[4]. Clavulanic acid a β-lactamase inhibitor [5], is added to amoxicillin to inhibit β-lactamase and increase the antibacterial effect of amoxicillin. Clavulanic acid has a similar structure to the beta-lactam antibiotics but binds irreversibly to the beta-lactamase enzymes [6]. Amoxicillin and clavulanic acid combinations are available in oral dosage form, powder for reconstitution as suspension and injectable. These two drugs act synergistically to produce the desired therapeutic effect. Their potency depends on content of the active moiety in these dosage forms.

One of the World Health Organization's (WHO's) main priorities is the quality of pharmaceuticals. The quality of pharmaceuticals is of importance not just on the global scale, but within nations as well. Unfortunately, administering counterfeit drugs could result in therapeutic failure, toxicity, allergic reactions due to their content, drug resistance, prolong illness, high cost of treatment and even mortality. Furthermore, other secondary implications are that the companies, pharmacies and distributors involved may lose their credibility, and a lot of financial resources may be lost in investigations and court cases. One should be aware that low quality medicines may not always be the results of problems at the manufacturing stage. They could be because of problems with packaging, transportation, storage conditions and the distribution system [7].

Whatever the case, low quality medicines are certainly not desirable on the market. Pharmacists, regulatory officials and health inspectors have to be vigilant and perform quality assurance tests on medications available locally. This gives the public confidence in available medications, and helps to take substandard medications out of the system. Increased quality assurance also prevents counterfeit drugs from penetrating the market: for fear that they will be detected[7].

Many reconstituted antibiotic suspensions are to be kept refrigerator in order to get the optimal benefits. However, many patients do not keep to the specified storage conditions for different

reasons like no refrigerator and irregular power supply resulting in various degrees of degradation of the product. In Yemen the power outage is common. Power supply is intermittent daily and outage can last for several hours to days at a stretch. This is not unique to Yemen, for example a work carried out in Basrah (Iraq) showed that there is extended power outage, an average of 14 hrs./day [8]. Antibiotic was chosen for this work because it needs refrigeration more often than not reconstituted antibiotic, a condition that may be difficult to meet in many resources limited environments as ours and also studies in Basrah (Iraq) and Sudan have shown that antibiotic is the most commonly encountered drug stored and consumed by patients in their homes and of the antibiotics stored, the beta-lactam antibiotics of penicillin and cephalosporin derivatives constituted the highest percentage at 26.43% and 22% respectively [8,9,10].

Suspensions of Co-amoxiclav (amoxicillin-clavulanate) are available for children and must be refrigerated at 2-8˚C to maintain effectiveness once reconstituted. Liquid formulations generally tend to have much shorter half-lives than solid formulations and once opened should be used within 2 weeks to avoid any microbial contamination or reduction in activity [11]. The expiry date depends on specified storage conditions. Not all drugs have the same rate of decomposition, thus expiry dates will differ. Reconstituted Co-amoxiclav oral suspension is stable for 7 days if stored at (2-8ºC), and if stored at room temperature its stability may be reduced to a week or less [12].

Stability testing provides information about the degradation mechanisms, potential degradation products, possible degradation pathways of drug as well as interaction between the drug and the excipients in drug product [13, 14,15]. Degradation processes include hydrolysis, oxidation and degradation by light because of the chemistry of many of the functional groups in drug molecules and the ubiquitous presence of water and oxygen. Even when factors such as water, oxygen and light have been controlled, degradation will still occur, but at a reduced rate. A forced degradation study is performed prior to commencing stability testing by exposing the drug to a variety of extreme conditions, such as pH, photolysis, oxidation and temperature, over a very short time period [16,17,18]. Climatic conditions can expose medications to dangerous temperatures that can potentially degrade the drug and often, unnoticed, example is Basrah where the summer heat can reach up to 50ºC[8], exceeding the U.S. Pharmacopeia's definition of room temperature (20-25ºC). High temperature and humidity accelerate deterioration, not only during transportation from overseas but also in warehouses and people's homes [12]. An appropriate storage condition for reconstituted antibiotics is keeping the medicines under refrigeration (2-8ºC). Many homes in rural areas of developing nation may not have refrigerators or lack power supply, and even where there is refrigerator and power supply there may be erratic supply.

Therefore medicines are stored at room temperature or kept in fridges that has no power supply for several hours in a day thereby exposing these drugs to excessive temperatures far more than the room temperatures which ultimately may cause decomposition of both the excipients and active ingredient (s). Yousif[9], in a Sudanese study reported that the rate of unsuitable storage conditions of drugs was 26%, compared to 31.8% in the Papua New Guinea study and that there was a higher rate of inappropriate storage in rural areas due to the lack of refrigeration.

Studies have shown different drug in-home storage practices, some store or keep their drugs on the dining table, top of the refrigerator, first aid boxes, in their bags, in the car, closed cupboard or drawer, suit case, in the kitchen and even the bathroom and these practices may result to degradation [19,11]. Instances of unsuitable storage often involve liquid preparations stored on open shelves, and reconstituted oral antibiotic powders stored for more than the recommended period after reconstitution or kept at freezing point [20].

A study carried out to determine the chemical stability of amoxicillin and potassium clavulanate (250/62 Co-amoxiclav) oral suspension stored at room temperature 20ºC and 8ºC over a period of 11 days showed amoxicillin is stable for 7 days at both temperatures. Potassium clavulanate maintains at least 90% of its initial concentration for 7 days at 8ºC but shows more than 40% degradation in the same time period at room temperature of 20ºC. the time taken for the original concentration of potassium clavulanate to drop to 90% of its value at room temperature of 20ºC is 2 days [12]. Another study by Tu et al. to determine the stability of amoxicillin trihydrate-clavulanate potassium in original containers and unit dose oral syringes showed that amoxicillin trihydrate is stable for at least 10 days in the original containers and all types of oral syringes at 5ºC whereas clavulanate-potassium is stable for 11 days in original containers and less than 5 days in all types of oral syringes at the same temperature [21]. All these studies pointed at the importance of storage conditions in the stability of both solid and liquid drug formulations.

This study assessed the impact of different home storage conditions on the stability of reconstituted Augmentin (the original brand of co-amoxiclav) oral suspension. It also enhances our knowledge on appropriate patients' council on drug storage in such environments.

MATERIALS AND METHOD

Materials

Amoxicillin trihydrate working stander powder was obtained from KDL laboratory, India; whilst the clavulanic acid potassium standard powder was obtained from Zhuhai, China; sodium di-

hydrogen phosphate and methanol obtained from Merck, India. Sodium hydroxide and phosphoric acid obtained from Scharlau, Spanish. Also HPLC 'PU-2089' obtained from Jasco, Jaban.

Methods

Sample collection

Samples was collected from pharmacies in Thamar City, the number of samples were taken is sufficient for the intended analysis and has the same batches and preferably from the same location [22], three batches of the Augmentin brand were collected from Thamar City, Yemen.

Procedure of sampling and assay

Stability study was performed at initial (zero) time, at intermediates time points and at the end of the proposed in-use shelf life (WHO). The sampling time points and testing the contents of Augmentin (312.5mg/5ml) oral suspension after reconstitution and stored at 2-8˚C and 25ºC, according to the following period intervals 0 day, 3rd day, 7th day, and 10th day. The analysis was carried out using HPLC instrument, and the concentration of amoxicillin and clavulanic acid elevated after reconstituted and stored in both conditions on 1st, 3rd, 7th , and 10th days [10].

Reconstitution of suspension powder

Powder was loosened from the bottom of the tapping against a hard surface. The specified amount of distilled water was added, in two portions, with shaking until all the dry powder is suspended.

The project of study

Three batches of Augmentin brand oral suspension (312mg/5ml) which used in this study was shown below in table (1), these batches used for study in refrigerator (2-8ºC) and at room temperature (25ºC)

All three different batches for this brand were evaluated according to the pharmacopeias USP and BP, then the results were analyzed statically.

Verification of analytical method:

Standard stock solution containing 2mg/ml of amoxicillin and 0.5mg/ml of clavulanate were prepared by dissolving amoxicillin (2mg) and clavulanate potassium (0.5mg) reference standard in distilled water. Five different concentrations (400, 440, 480, 520, and 560 µg/ml) of amoxicillin and (100, 110, 120, 130, and 140 µg/ml) of clavulanate mixtures were prepared from stock solution for calibration and linearity test. Three replicate measurements of each concentration were made using HPLC. The AUC is plotted against its corresponding theoretical concentration and a linear regression analysis is performed for the five coordinates[7,10].

Physical tests:

Organoleptic and appearance inspection:

The color, taste and odor were inspected for each reconstituted suspension at zero time and repeated during the interval time of stability evaluation.

pH test:

The sample was poured into a beaker and the electrode of pH meter was immersed in the sample and the result was recorded. The pH test was repeated during the interval time of stability evaluation [23].

Water content:

Determined using moisture analyzer at 80°C.

Specific gravity:

Clean and dry pycnometer was weighed and cleaned, then filled it with the sample at 25˚C, and removed any excess of the substance and weighed. Then the weight of sample was calculated. The previous step was repeated with water instead of the sample to get the weight of contained water. The specific gravity of the substance is the ratio of the contained weight of sample to that of water[24].

Chemical test:

Assay test was done using HPLC method as the following:

Mobile phase: Sodium di-hydrogen phosphate 7.4g was weighed then dissolved in 900ml distilled water, 100ml of methanol was added and filtered through 0.45µm micro-membrane filter.

HPLC conditions: Column: ODS1(C18) 15 * 0.45cm, flow rate: 1.0 ml/min, wavelength: 220nm, sensitivity: 1, pressure: 28 Mpa.

Preparation of standard:

Exactly 114.8mg of amoxicillin tri-hydrate which is equivalent to 100mg of anhydrous amoxicillin and 25mg of potassium clavulanate were weighed and transferred into volumetric flask, then dissolved and diluted to volume with water to obtained the concentration (0.5mg/ml of amoxicillin and 0.125mg/ml of potassium clavulanate) required for assay, after that the flask was put in sonicator to complete dissolution[7,24].

Preparation of sample:

An accurately measured portion of Augmentin (amoxicillin-clavulanate) oral suspension was transferred to a 250ml volumetric flask, freshly mixed and free from air bubbles, constituted as directed in the labeling, and equivalent to about 312mg of amoxicillin-clavulanate (about 5ml of

suspension). The volume complete to 500ml with water and to obtained the concentration (0.5mg/ml of amoxicillin and 0.125mg/ml of clavulanate) of complete dissolution [7,24]. A portion of this solution was filtered through a suitable filter of 0.45µm, and used the filtrate as the test preparation. Then separately equal volumes (about 20µl) was injected from each prepared solutions (standard preparations and the test preparations) into HPLC. The AUC was measured and recorded.

Assay % limit:

90.0-120.0% of labeled amount of amoxicillin (USP 30), 90.0-125.0% of the labeled amount of clavulanic acid (USP 30).

RESULTS AND DISCUSSION:

Results of verification of analysis method:

Linearity was demonstrated by plotting peak area vs. concentrations of amoxicillin, the result is linear, and the correlation coefficient (R^2 = 0.9992) was illustrated in table (2) and figure (1) below.

Table 1: illustrates the different batches of Augmentin brand (Co-amoxiclav).

Name of drug	Batch No.	Manufacturing date	Expiry date
Augmentin (original)	518918 (O_1)	04/2011	04/2014
	518919 (O_2)	04/2011	04/2014
	528924 (O_3)	08/2011	08/2014

Table 2: illustrates the average area for the concentration curve of amoxicillin.

Conc. (µg/ml)	Average of area	RSD%
400	173.27	0.33
440	190.59	0.32
490	207.53	0.13
520	224.62	0.05
560	240.59	0.50

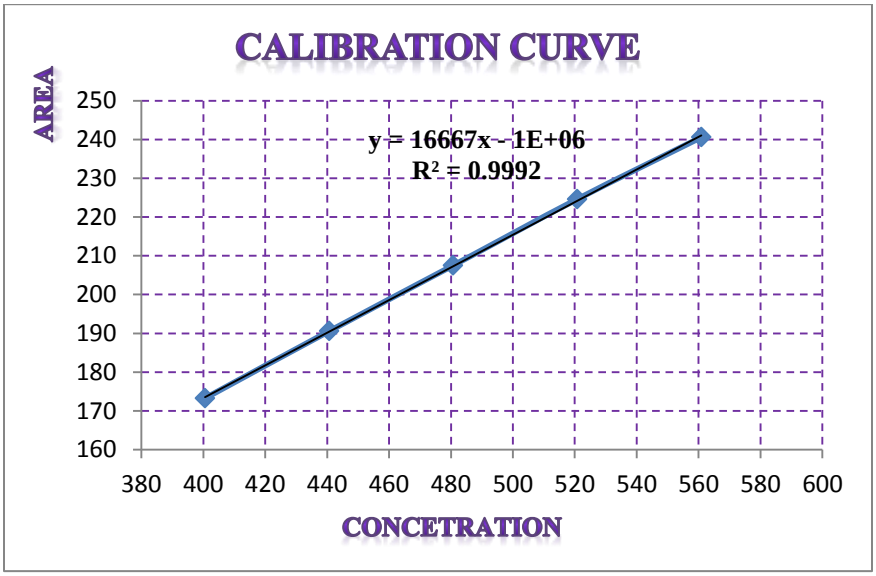

Figure 1: illustrates the linearity of calibration curve of amoxicillin.

Linearity for clavulanic acid

Linearity was demonstrated by plotting peak area vs concentrations of clavulanic acid, the result is linear and the correlation coefficient (R^2= 0.9999), was illustrated in table (3) and figure (2) below.

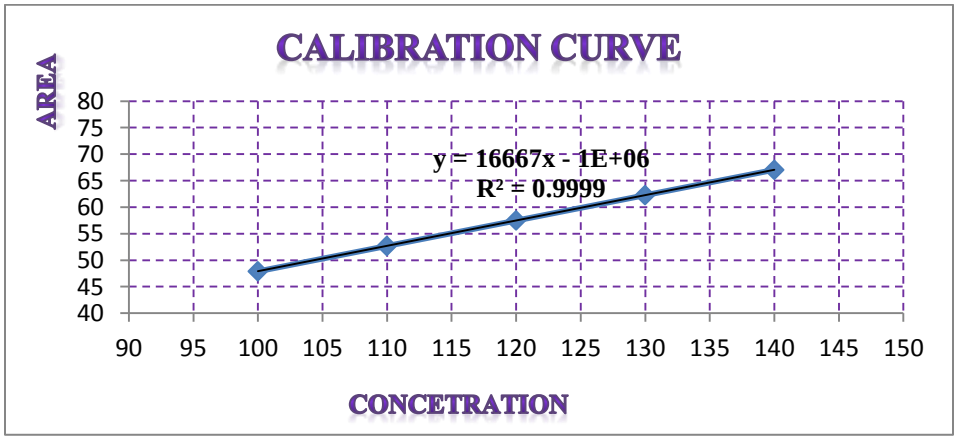

Figure 2: illustrates the linearity of calibration curve of clavulanic acid.

Table 3: illustrates the average area for the concentrations of clavulanic acid.

Conc. (µg/ml)	Average of area	RSD%
100	47.89	0.51
110	52.68	1.66
120	57.47	0.66
130	62.26	0.49
140	67.05	0.35

Results of quality control tests for Augmentin products:

Result of physical tests:

(a). Organoleptic and appearance inspection:

The Augmentin oral suspension was white free flowing powder. The reconstitution gave milky color with specific odor. The color, taste and odor were inspected at the following time points 0, 3rd, 7th, and 10th day and the result was illustrated in table (4). The physical test results of three different batches of Augmentin that stored at room temperature were highly different, especially the color, from the results of physical tests that obtained in the part one of stability study, but that stored in refrigerator (2-8ºC) were stable during study period as shown in table (4).

Table 4: shows the results of physical tests of Augmentin products after reconstitution and storage in refrigerator (2-8°C) and room conditions 25°C.

Conditions	**At Refrigerator(2-8 ^{0}C)**				**At Room Temperature (25^{0}C)**		
Stored times	Parameter	**O_1**	**O_2**	**O_3**	**O_1**	**O_2**	**O_3**
0 day	**pH**	4.23	4.2	4.22	4.19	4.22	4.33
	Color	Pale-milky	Pale-milky	Pale-milky	Pale-milky	Pale-milky	Pale-Milky
	Taste	Sweet	Sweet	Sweet	Sweet	Sweet	Sweet
	Odor	Fruity	Fruity	Fruity	Fruity	Fruity	Fruity
3rd day	**pH**	4.66	4.94	4.67	5.91	6.12	5.94
	Color	Pale-milky	Pale-milky	Pale-milky	Pale-yellow	Pale-yellow	Pale-yellow
	Taste	Sweet	Sweet	Sweet	Sweet with very slightly bitter	Sweet with very slightly bitter	Sweet with very slightly bitter
	Odor	Fruity	Fruity	Fruity	Fruity	Fruity	Fruity
7th day	**pH**	5.17	5.26	5.2	6.39	6.43	6.4
	Color	Pale-milky	Pale-milky	Pale-milky	Yellowish-brown	Yellowish-brown	Yellowish-brown
	Taste	Sweet	Sweet	Sweet with slight bitterness	Sweet with Slightly bitterness	slightly bitterness	bitterness
	Odor	Little fruity	Little fruity	Little fruity	Little fruity	Little fruity	Little fruity
10th day	**pH**	5.49	5.72	5.55	6.75	6.65	6.6
	Color	Pale-milky	Pale-milky	Pale-milky	Pale-brown	brown	Dark- brown
	Taste	Sweet with slight bitterness	Sweet with slight bitterness	Sweet with slight bitterness	bitter	bitter	bitter
	Odor	Little fruity with yeast odor	Fruity with yeast odor	Odorless	Fruity with yeast odor	Fruity with yeast odor	Fruity with yeast odor

(b). pH measurements

The results of pH for the brands are within acceptance limit (3.8-6.75) according to USP 30, at initial time point and throughout the period as illustrate in table (4).

(c). Water content and specific gravity:

The results of water content of three different Augmentin batches O_1, O_2, and O_3 were found within acceptance limit (not more than 7.5%) USP 30 as shown in table (5) below, but the results of specific gravity for the three Augmentin batches were found within acceptance limit (0.9-1.2) USP 30 as shown in table (5).

Table 5:shows The results of water content and specific gravity for three batches of Augmentin brand.

Augmentin	Batch No.	O_1(518918)	O_2(518919)	O_3(528924)
	Water content	6.01	5.91	5.98
	Specific gravity	1.03848	1.02299	1.02766

Results of chemical test:

Assay test:

The results of assay test of amoxicillin(250mg/5ml) in three different batches of Augmentin (O1, O2, and O3) after reconstitution during 10 days stored at (2-8ºC) and at 25ºC.are illustrated in table (6) and figure (3) which indicate that all batches have good results of amoxicillin assay during 10 days and within the USP limit. The result of this study is similar to the work done by Naidoo (2006), which showed that only amoxicillin suspension stored between 2°C and 8°C for 7 days showed the lowest level of degradation.

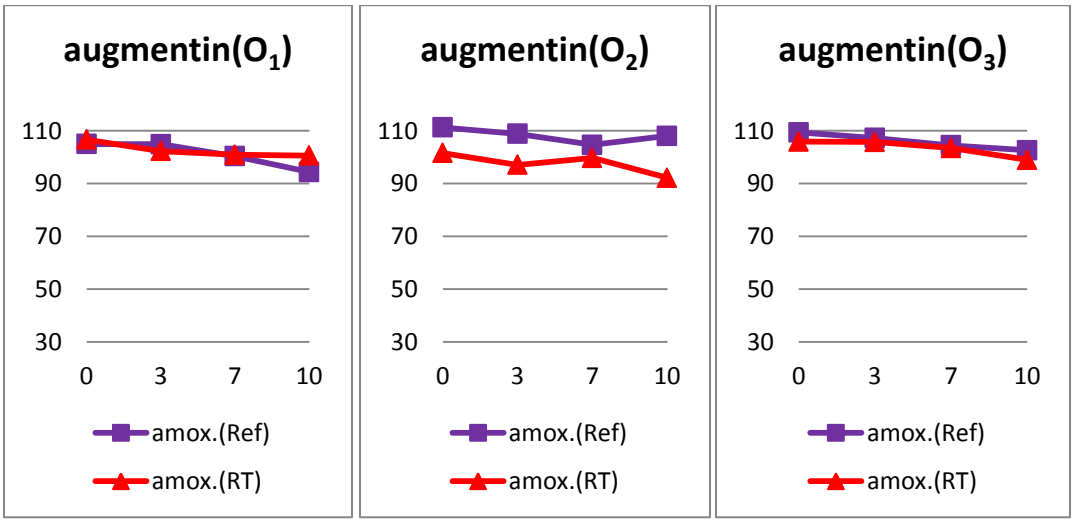

Figure 3: The results of comparative study of assay test of amoxicillin for original batches at refrigerator and room temperature

Table 6:illustrates the results of assay comparative study of assay test of amoxicillin for original batches at refrigerator and room temperature during 10 days.

Sampling point	Assay test % at refrigerator (2-8C^0)						Assay test % at room temp. (25C^0)					
	O_1		O_2		O_3		O_1		O_2		O_3	
	Mean±SD	RSD	Mean±SD	RSD	Mean±SD	RSD	Mean±SD	RSD	Mean±SD	RSD	Mean±SD	RSD
0day	105.8±.72	0.31	111.3±.15	0.06	109.4±.17	0.07	106.7±4	2.01	101.6±.06	0.03	105.9±.82	0.35
3rd day	104.9 ±.26	0.31	108.1 ±.49	0.20	107.3 ±.26	0.11	102.3±.49	0.22	97.1±1	0.47	105.8±.82	0.35
7th day	100.4± .69	0.11	104.7 ±1	0.86	104.5 ±.20	0.28	100.9±.20	0.09	99.7±.71	0.32	103.8±.40	0.18
10th day	104.9±.26	0.31	108.1±.49	0.20	107.3±.26	0.11	100.6±1	0.66	92.2±.95	0.46	99.0±.68	0.31

The results of assay test in table (6) showed that amoxicillin in all three different batches of Augmentin during all the results of amoxicillin were in the limit at different two conditions (2-8ºC) and (25ºC).

The result of comparative study of assay test for clavulanate in three batches of Augmentin brand when stored in room temperature (25ºC) and at refrigerator temperature (2-8ºC) are shown below in table (7) and figure (4).

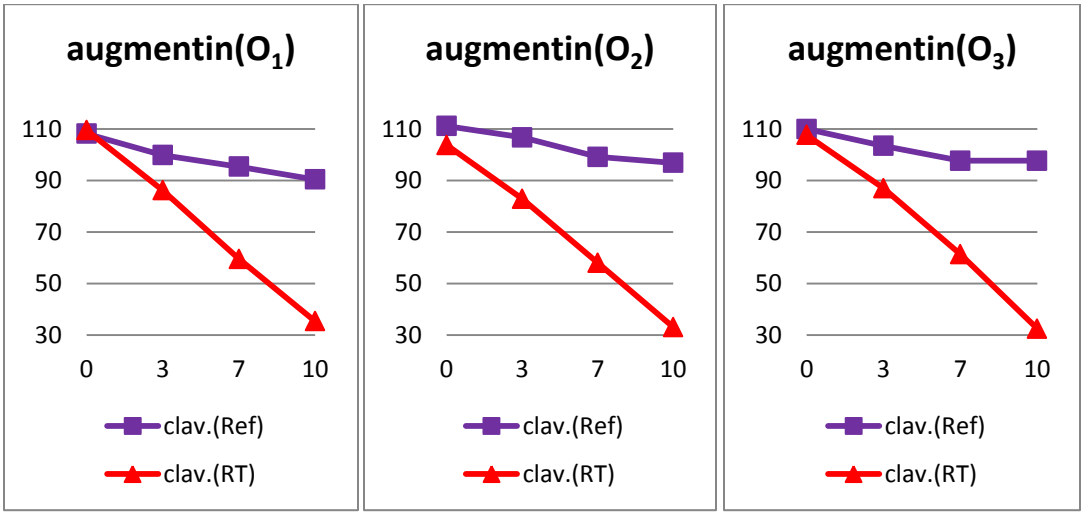

Figure 4: ***The results of comparative study of assay test of clavulanic acid in for Augmentin batches at refrigerator and room temperature.***

Table 7: The results of comparative study of assay test for clavulanate in original batches at refrigerator and room temperature during 10 days.

Batch	Assay test % at refrigerator (2-8C^0)						Assay test % at room temp. (25C^0)					
	O_1		O_2		O_3		O_1		O_2		O_3	
	Mean±SD	RSD	Mean±SD	RSD	Mean±SD	RSD	Mean±SD	RSD	Mean±SD	RSD	Mean±SD	RSD
0day	108.2±0.21	0.26	111.2±.06	0.07	110.0±0.10	0.12	109.6±0.56	0.67	103.8±0.55	0.70	107.7±0.15	0.19
3rd day	99.9±.15	0.21	106.8 ±.81	1.04	103.5±.20	0.26	86.2±0.20	0.31	82.9±0.26	0.43	87.0±0.10	0.16
7th day	95.4±.17	0.24	99.2±.55	0.76	97.7±.36	0.16	59.5±0.26	0.61	58.0±0.44	1.04	61.4±0.06	0.13
10th day	99.9±0.15	0.21	106.8±.81	1.04	103.5±0.2	0.26	35.3±0.25	0.97	33.0±0.15	0.63	32.4±0.12	0.49

From the above table (7) the results of assay for three different batches of Augmentin during 10 days stored at 25ºC as the following: The potassium clavulanate was showed higher rate of degradation in all batches of Augmentin, but all batches remained within the limit until 3rd day, from the period (3rd day – 10th day) all batches were become out of the limit and this not acceptable. While the samples were stored at refrigerator (2-8ºC) are within the USP limit during 10 days.

From the above results, the storage of Augmentin suspension at room temperature (25ºC) showed that clavulanic acid rapidly exposed to degradation directly after reconstitution all batches after 3rd day, the assay test are out of the limit, but if store at refrigerator temperature (2-8ºC) the degradation of clavulanic acid is very low after prolong period (about 10 days).

CONCLUSION

Amoxicillin and clavulanic acid in Augmentin suspension remain stable when oral powder for pediatric suspension is reconstituted with distilled water and stored under a standard storage conditions of 2-8ºC.over period of ten days. Amoxicillin is stable under a standard ambient room temperature (25ºC) throughout the ten days period of therapy whilst clavulanic acid is not. The amounts of both amoxicillin and clavulanic acid are reduced when oral suspension is brought into room temperature. Depending on the frequency and length of time with which suspension is kept out of the fridge, the therapeutic value of Augmentin may be affected, especially with regards to clavulanic acid.

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