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STABILITY STUDY FOR THREE BRANDS CO-AMOXICLAV ORAL SUSPENSION (312.5/5ML) AFTER RECONSTITUTION AT REFRIGERATOR (2-8^{O}C)

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ABSTRACT
Oral suspensions of antibiotics are mainly available as dry powders for reconstitution. Many reconstituted antibiotic suspensions are to be kept refrigerated in order to get the optimal benefits from the drug. However, many patients cannot keep to the specified storage conditions for different reasons like no refrigerator and irregular power supply that may result in various degrees of degradation of the product. The absence of quality analysis by the national drug regulatory authority for drugs that are manufactured in Yemeni Companies and for drugs imported and the absence of health education about the correct method for storage and use of drug according to the specifications that ensure the drug maintains its therapeutic effect during the period of use. All of these enforce us to do stability study for one of the most common used antibiotics (amoxicillin-clavulanate potassium) as oral suspension for two brands compare with reference brand (the original) when stored at refrigerator (2-8^{O}C) after reconstitution. Assay test was done for three different batches of each brand according to pharmacopeial tests at period time 10 days start from zero time using HPLC and the main results for original brand (Augmentin) was within the limits (90%-120% for amoxicillin and 90%-125% for clavulanic acid). The imported brand (Augmenta) was within the limit for amoxicillin (96%-107.8%) along the recommended period and the clavulanic acid for two days only within the limit (93%-103%) and after that the concentration of clavulanic acid reduced in two batches and were out of the limit (82%-86%). Whereas the results of assay for local brand (clavimox) was within the limit (99%-121%) for amoxicillin and clavulanic acid (95.6%-120%) along the period was recommended in company leaflet.

KEYWORDS: co-amoxiclav, degradation, reconstitution, stability, suspension.

INTRODUCTION
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.[1] 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.[2]

Suspensions of Co-amoxiclav (amoxicillin-clavulanate) are available for children and must be refrigerated at 2-8 ^{O}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.[3]

Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating period.[4] It determines the drug substance or product's degradation as a result of exposure to a variety of conditions, such as temperature, humidity, light and packaging materials over an extended time frame. Stability is an essential factor of quality, safety and efficacy of a drug product.[5, 6] Stability testing also provides information about the degradation mechanisms, potential degradation products, possible degradation pathways of drug as well as interaction between the drug and the excepients in drug product.[7, 8]

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.[9, 10, 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 (2-8^{O}C) and if stored at room temperature its stability may be reduced to a week or less.[12]

MATERIALS AND METHOD

Materials

Amoxicillin tri-hydrate working stander powder (KDL laboratory, India); and clavulanic acid potassium (Zhuhai, China) were obtained from local pharmaceutical manufacturing company. Sodium di-hydrogen phosphate and methanol (Merck, India). Sodium hydroxide and phosphoric acid (Scharlau, Spanish). Also HPLC '(PU-2089'; Jasco, Jaban) are used in this study.

Method

1. Sample collection

Samples were collected from pharmacies in Thamar City, Yemen; the number of samples were taken is sufficient for the intended analysis and has the same batches and preferably from the same location[4], three bottles of each batch and three batches of each company were collected from Thamar City. Three companies were coded (O=Augmentin, Y=Clavimox and S=Augmenta).

2. 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 Co-amoxiclav (312.5mg/5ml) oral suspension after reconstitution and storage between 2-8˚C, according to the following period intervals 0 day, 3rd day, 7th day and 10th day. The analysis was carried out using calibrated HPLC (PU-2089'; Jasco, Jaban) instrument and the concentration of amoxicillin and clavulanic acid elevated after reconstituted and storage on 1st, 3rd, 7th and 10th days.[13]

3. Reconstitution of suspension powder

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

4. The project of study

The different Co-amoxiclav (312.5mg/5ml) brands which used in this study was shown below in table (1), these batches used for study in refrigerator (2-8ºC).

Table (1) illustrates the different brands of Co-amoxiclav.

NO	Name of drug	Batch No.	Manufacturing date	Expiry date
1	Clavimox (local)	1104152	04/2011	04/2014
		1108266	08/2011	08/2014
		1108267	08/2011	08/2014
2	Augmenta (imported)	34602	12/2011	12/2014
		34603	12/2011	12/2014
		32907	04/2011	04/2014
3	Augmentin (original)	518918	04/2011	04/2014
		518919	04/2011	04/2014
		528924	08/2011	08/2014

All three different batches for each brand were evaluated according to the pharmacopeias USP and BP[15, 17], then the results were analyzed statically.

5. 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.[13]

Physical tests

(a) Organoleptic and appearance inspection

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

(b) 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.[14]

(c) Water content
Determined using moisture analyzer at 80°C.

(d) Specific gravity
Clean and dry pycnometer was weighed and cleaned, then filled it with the sample at 25℃ 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.[15]

Chemical tests
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.[13, 15]

Preparation of sample
An accurately measured portion of amoxicillin-clavulanate for 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 complete dissolution.[13, 15]

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.

Calculations
Assay percentage of amoxicillin and clavulanic acid were calculated as the following:

$$\%Assay = \frac{AUC\ of\ sample}{AUC\ of\ standerd} X \frac{conc.of\ standerd}{conc.of\ sample} X\ assay\ of\ standerd$$

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 figure (1).

Table (4) 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*

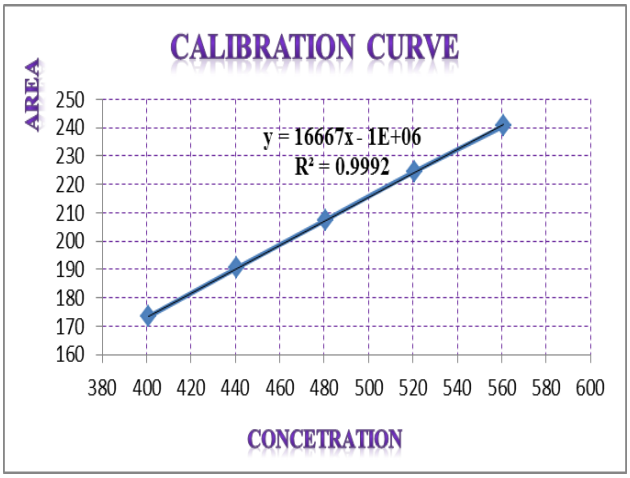

Figure (1) illustrates the linearity of calibration curve of amoxicillin.

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 figure (2).

Table (5) 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*

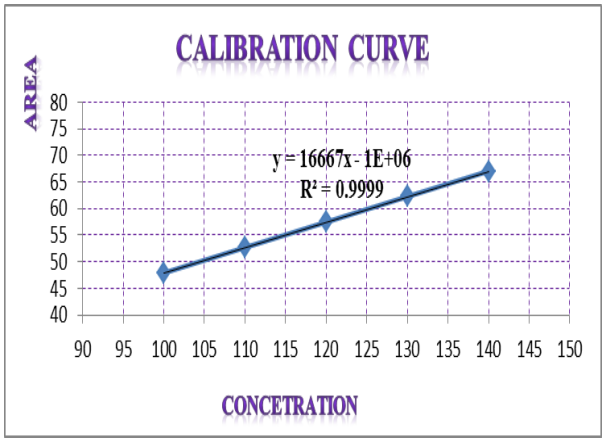

Figure (2) illustrates the linearity of calibration curve of clavulanic acid.

Results of quality control tests for Co-amoxiclav products

Result of physical tests

(a). Organoleptic and appearance inspection

The Co-amoxiclave for oral suspension was white free flowing powder. The reconstitution give 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 (6).

(b). pH measurements

The results of pH for the brands are within acceptance limit (3.8-6.6) according to USP 30, at initial time point and throughout the period as illustrate in table (6).

Table (6) shows physical tests for products after reconstitution and refrigeration (2-8°C).

Conditions	**In the refrigerator (2-8^{0}C)**									
Stored times		**(O) (B.N=18)**	**(S) (B.N=02)**	**(Y) (B.N=52)**	**(O) (B.N=19)**	**(S) (B.N=03)**	**(Y) (B.N=66)**	**(O) (B.N=24)**	**(S) (B.N=07)**	**(Y) (B.N=67)**
0 day	pH	4.23	4.69	4.26	4.2	4.64	4.43	4.22	4.65	4.53
	Color	Pale-milky	Off-white	Off-white	Pale-milky	Off-white	Milky-yellowish	Pale-milky	Creamy	Pale-Milky
	Taste	Sweet	Sweet	sweet	Sweet	sweet	Sweet	Sweet	Sweet	sweet
	Odor	Fruit	Orange	Mixed fruit	Fruit	orange	Mixed fruit	Fruit	Orange	Mixed fruit
3rd day	pH	4.66	4.84	4.97	4.94	4.85	4.76	4.67	4.88	4.94
	Color	Pale-milky	Dark-white	Yellowish-white	Pale-milky	Dark-white	Yellowish-white	Pale-milky	Dark-creamy	Yellowish-white
	Taste	Sweet	Sweet with very slight bitterness	Sweet	Sweet	Sweet with very Slight bitterness	Sweet	Sweet	Sweet with some bitterness	Sweet
	Odor	Fruit	Orange	Mixed fruit	Fruit	orange	Mixed fruit	Fruit	orange	Mixed fruit
7th day	pH	5.17	5.28	5.47	5.26	5.21	5.33	5.2	5.22	5.4
	Color	Pale-milky	Dark-white	Pale-yellow	Pale-milky	Dark-white	Pale-yellow	Pale-milky	Milky-yellowish	Yellowish-white
	Taste	Sweet	Sweet with slightly bitterness	Sweet with slightly bitterness	Sweet	Sweet with Slight bitterness	Sweet with Slight bitterness	Sweet with slight bitterness	Sweet with slight bitterness	Sweet
	Odor	Little fruit	Little orange	Mixed fruit	Little fruit	Little orange	little fruit	Little fruit	Little orange	Mixed-fruit
10th day	pH	5.49	5.53	5.78	5.72	5.54	5.56	5.55	5.6	5.58
	Color	Pale-milky	yellow	Milky-yellowish	Pale-milky	Pale-yellow	Yellowish-brown	Pale-milky	dark-yellow	Milky-yellowish
	Taste	Sweet with slightly bitterness	bitter	low bitterness	Sweet with slightly bitterness	bitter	bitter	Sweet with slightly bitterness	bitterness	Very bitterness
	Odor	Little fruit with yeast odor	Non-odor	Little fruit with yeast odor	Fruit with yeast odor	Non-odor	yeast odor with little fruit	Non-odor		Fruit with yeast odor

(c). Water content and specific gravity

The results of water content of three products O, Y and S were found within acceptance limit (not more than 7.5%) USP 30 as shown in table (7) below, but the results of two products of clavimox were in the upper limit and one product was out of the limit more than 7.5%.

The results of specific gravity for the three brands O, Y and S were found within acceptance limit (0.9-1.2) USP 30 as shown in table (7).

Table (7) shows the results of water content and specific gravity for three brand of Co-amoxiclav products.

Augmentin	**Batch No.**	(518918)	(518919)	(528924)
	Water content	6.01	5.91	5.98
	Specific gravity	1.03848	1.02299	1.02766
Clavimox	**Batch No.**	(1104152)	(1108266)	(1108267)
	Water content	7.5	7.8	7.19
	Specific gravity	1.0386	1.03789	1.04342
Augmenta	**Batch No.**	(34602)	(34603)	(32907)
	Water content	5.85	5.96	5.25
	Specific gravity	1.10858	1.10655	1.11124

Result of chemical test

a) Assay test

The results of assay test for three different brands of Co-amoxiclav (312mg/5ml) and three batches for each brand, after reconstitution during 10 days stored at (2-8^{o}C) are illustrated in table (8). The result of this study is similar to the work done by Naidoo which show that only amoxicillin suspension stored between 2^{o}C and 8^{o}C for 7th days show the lowest level of degradation.[16]

The result of assay test for amoxicillin (250)after reconstitution for three different brands during 10th days are shown in table (8) Co-amoxiclav oral suspension contains not less than 90%and not more than 120% of labeled amount of amoxicillin (USP 30). The results of assay test for amoxicillin in table (8) show that all three different batches (O=Augmentin, Y= Clavimox, and S= Augmenta) during first 7th day of studies were within the limit (90-120%) (USP 30).

Table (8) illustrates the results of assay test for amoxicillin in different Co-amoxiclav brands.

Day	Sample (O)						Sample (Y)						Sample (S)					
	Batch no (518918)		Batch no (418919)		Batch no (528924)		Batch no. (1104152)		Batch no. (1108266)		Batch no. (1108267)		Batch no (34602)		Batch no (34603)		Batch no. (32907)	
	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD
(0) day	105.8±.72	0.31	111.3 ±.15	0.06	109.4 ±.17	0.07	109.4±.72	0.29	99.0±.12	0.05	103.0±.35	0.15	104.7 ±.30	0.13	101.5 ±.15	0.07	107.8 ±.10	0.04
3rd day	104.9 ±.26	0.31	108.1 ±.49	0.20	107.3 ±.26	0.11	109.2±.46	0.19	99.6±.40	0.18	100.3±.88	0.39	103.7 ±.81	0.35	99.8 ±.20	0.09	107.6 ±.17	0.07
7th day	100.4± .69	0.11	104.7 ±1	0.86	104.5 ±.20	0.28	105.5±.23	0.10	99.7±.35	0.16	100.6±.98	0.44	99.5 ±.26	0.21	102.7 ±.15	0.07	106.6 ±.89	0.38
10th day	94.9±. 76	0.37	108.9 ±.35	0.50	102.6 ±1	0.48	121.3±.98	0.37	99.5±.42	0.19	103.9±2	0.92	96.9 ±1	0.61	103.9 ±.67	0.29	105.8 ±.36	0.15

A. The results of assay test for three different batches of each brand were within the limits are illustrate in table (8). the results of assay test for three different batches of the same brand (Clavimox) (Y= 1104152, Y= 1108267, Y= 1108267) of amoxicillin (250mg/5ml) after reconstitution during 10 days stored at (2-8^{o}C) which indicate that two batches have good result of assay during 10 days and within

the USP limit but the third batch have good result for the first 7 days and after that the result is out the USP limit. The clavimox product show an excess to the limit in the 10th days (121%) and sedimentation have been showed in the last days and it has been noted formation of flocculating in the suspension bottle in which amoxicillin is concentrated in the bottom of the bottle. But the percentage of amoxicllin in local product (Clavimox) show no degradation during study period.

B. The result of assay test for clavulanic acid (62.5mg) after reconstitution for three different brands during 10days are shown below in table (9). Co-amoxiclav oral suspension contains not less than 90% and not more than 125% of labeled amount of clavulanic acid.[15]

Table (9) illustrate the results of assay test of clavulanic acid for different brands.

Day	Sample (O)						Sample (Y)						Sample (S)					
	Batch no. (518918)		Batch no. (518919)		Batch no. (528924)		Batch no. (1104152)		Batch no. (1108266)		Batch no. (1108267)		Batch no. (34602)		Batch no. (34603)		Batch no. (32907)	
	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD	Mean ±SD	RSD
(0) day	108.2±.21	0.26	111.2±.06	0.07	110.0±.10	0.12	120.2 ±.15	0.17	113.6±. 31	0.37	114.1 ±.23	0.27	95.6±.44	0.61	93.7±.21	0.30	103.0±.10	0.13
3rd day	99.9±.15	0.21	106.8 ±.81	1.04	103.5±.20	0.26	107.5 ±.30	0.37	103.7±. 15	0.20	106.5 ±.12	0.15	82.7±.40	0.66	86.5±.60	0.95	98.6±.26	0.36
7thday	95.4±.17	0.24	99.2±.55	0.76	97.7±.36	0.16	103.2±.45	0.61	100.6±.50	0.68	99.6±1	1.73	78.7±46	0.90	83.2±.10	0.16	92.6±.29	0.39
10th day	90.4±.62	0.95	96.9 ±.72	0.30	97.7±.35	0.48	102.8±.40	0.53	95.6±1	1.62	99.1±.40	0.57	75.1±.35	0.63	77.7±.40	0.69	84.4±.12	0.18

The results of assay test for clavulanic acid in table (9) show that all different batches (O= Augmentin, Y= Clavimox, and S= Augmenta) during first day of study are within the limit (90-125% USP30). After that from the period (3rd day-10th day) the result of assay for the batches (O and Y) are within the limit (90-125%) (USP 30) but the brand (S) is out of the limit. The result of assay test for three different batches of the same brand (Augmentin) (O= 518918, O= 518919, O= 528924) of clavulanic acid (250mg/5ml) after reconstitution during 10 days stored at (2-8°C) indicate that all batches have a good results for assay during 10 days and within the USP limit as shown in table (9). Also the results of assay test for three different batches of the same brand (Clavimox) (Y= 1104152, Y= 1108266, Y= 1108267) of clavulanic acid (62.5mg/5ml) after reconstitution during 10 days stored at (2-8°C) were good throughout all study period and within the USP limit. Finally the results of assay test for the three batches of the (Augmenta) brand (S= 34602, S= 34603, S= 32907) for clavulanic acid (62.5/5ml) after reconstitution during 10 days stored at (2-8ºC) the results during 10 days in the first two days all the three batches within the limit but after the 3rd day to 10th day the result out of the limit for two batches and only one batch remained within the limit until 7th days, so this product is unacceptable because the three batches were not within the limit until the 10th day when stored at recommended conditions.

CONCLUSION

Amoxicillin and clavulanic acid remain stable in some batches when oral powder for pediatric suspension is reconstituted with distilled water and stored under a standard storage conditions of 2-8ºC over a period of ten days. The main results of original brand (Augmentin) was within the limits. The imported brand (Augmenta) was within the limit for amoxicillin along the recommended period and the clavulanic acid for two days only was stable (within the limit) after that the amount of clavulanic acid reduced in two batches and were out of the limit. Whereas the results of assay for local brand (clavimox) was within the limit for amoxicillin and clavulanic acid along the recommended period.

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