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STABILITY OF AMOXICILLIN TRIHYDRATE ORAL SUSPENSION IN CLEAR PLASTIC UNIT DOSE SYRINGES

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ABSTRACT

The stability of amoxicillin trihydrate oral suspension stored in clear plastic oral syringes was studied.

Commercially available amoxicillin trihydrate powder for oral suspension was reconstituted according to manufacturer's instructions and drawn into 5-mL clear polypropylene plastic oral syringes. The syringes were divided into groups and stored at 25, 40, 60 or 80°C. Powder from two additional lots was similarly reconstituted, packaged and stored at 80°C only to assess interlot variability. Immediately after reconstitution and at specified times during storage, three syringes at each storage temperature were removed and their contents analyzed for amoxicillin trihydrate concentration by a spectrophotometric assay.

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Samples stored at room temperature retained at least 90% of the initial amoxicillin concentration for at least 78 days. Samples stored at heated temperatures (40, 60, and 80°C) exhibited a first-order degradation process, with the concentration of amoxicillin decreasing to less than 90% of the initial concentration within 240, 7 and 1.5 hours, respectively.

Reconstituted amoxicillin trihydrate powder for oral suspension is stable for 75 days when stored at room, refrigerated, or frozen temperature in the clear plastic oral syringes studied. The expiration dates recommended by the manufacturer for amoxicillin trihydrate suspension stored in its original container can also be used for reconstituted suspension stored in these clear plastic syringes.

INTRODUCTION

Results published within the past few years have shown that the repackaging of drugs such as gentamicin,[1] insulin,[2] nitroglycerin,[3] and dicloxacillin,[4] can actually have an adverse effect on their stability, and that pharmacists should be made aware of such problems. Factors such as container composition, temperature, pH, drug concentration, humidity, and light exposure must be evaluated when considering the repackaging of a drug.

One general class of drugs often repackaged for unit-dose usage has been the oral liquid antibiotics. Despite their widespread use, few controlled studies exist characterizing their stability once removed from the manufacturer's container. Only

recently have studies appeared describing the stability characteristics of the penicillins after repackaging into unit-dose containers.[5,6,7,8,9] Plastic oral syringes are currently being promoted by several manufacturers for the distribution of liquid antibiotics to hospital pharmacists. These syringes provide an inexpensive disposable, yet safe and convenient means of delivering accurate antibiotic doses to pediatric, elderly and other compromised patients.

The purpose of this investigation was to study the effects of storing a commercially available oral suspension of amoxicillin in clear plastic unit-dose oral syringes at selected temperatures for specific lengths of time, and to determine the loss of potency in the syringes as compared to the loss of potency in the original container, stored concomitantly under similar conditions.

METHODS

Commercial amoxicillin trihydrate powder for oral administration[a] was reconstituted with deionized, distilled water in accordance with the manufacturer's label instructions to a theoretical concentration of 125mg/5mL. Once reconstituted, the bottle was shaken vigorously and the cap replaced by a plastic syringe-filling adapter. Through this adapter, aliquots (5-mL) of the resulting suspension were drawn into 5-mL clear polypropylene unit-dose oral syringes[b] by complete inversion of the bottle. The loaded syringes were capped, coded, weighed, and

divided into six groups for storage at each of four temperatures: 25, 40, 60, and 80 (±1)°C. Commercial amoxicillin trihydrate powder for oral administration was utilized throughout this study. One single lot (lot 2102-03311) of drug was obtained for use in all trials; also, two additional lots (lots 2011-05090 and 2014-05140) were compared at 80°C only to assess interlot variability.

At designated times, three syringes at each storage temperature were removed from storage, allowed to equilibrate to ambient temperature, and assayed for amoxicillin concentration. For syringes stored at 25°C, samples were obtained at 0, 4, 6, 16, 68, 78, and 90 days; and for syringes stored at 40°C, samples were obtained at 0, 1, 4, 10, 12, 18, 22, 29, and 35 days. For syringes stored at 60°C, samples were obtained at 0, 2, 4, 7, 8, 10, 12, 14, 16, 19, 21, 23, 25, and 27 hours and for syringes stored at 80°C, samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours. Whenever a sample was withdrawn from the constant temperature environment, the three syringes as well as the original containers were removed and allowed to equilibrate to the ambient temperature.

The syringes were weighed both before and after exposure to the constant temperature environment to detect potential losses of water. Such losses would affect the concentration of amoxicillin remaining within the syringe. After recording the weights throughout the 80°C and the 60°C trials no appreciable

weight loss was observed; therefore, the weighing procedure was discontinued in subsequent trials.

After the samples had equilibrated to room temperature, they were agitated for approximately 10 seconds using a micromixer. The entire contents of each syringe was then transferred to a 20-mL blood collection tube (with stopper removed) and agitated for an additional 10 seconds. Three 1-mL samples were removed from each tube and diluted 1:100 with distilled water. The resulting solutions were further diluted 1:10 with distilled water before being assayed.

Amoxicillin trihydrate concentrations were determined utilizing a spectrophotometric technique developed by Bundgaard and Ilver[10] which is specific for the intact beta-lactam ring. It was found that imidazole in a neutral aqueous solution containing mercuric chloride reacted with several of the semi-synthetic penicillins to yield the mercuric mercaptides of the corresponding pencillenic acids. However, it was later discovered that ampicillin differs from other penicillins in that it formed an unstable reaction product when exposed to the imidazole-mercuric chloride solution, and that this product also carried a different spectrophotometric absorption maximum.[11] Further study has now shown that by initially acetylating the side-chain amino group, ampicillin (and amoxicillin) can then be assayed by the originally described method of Bundgaard and Ilver.[10] It is this acetylation-modified technique that has been utilized throughout this study.

Specifically, the amoxicillin molecule is initially acetylated with 0.2M Acetic Anhydride within a borate buffer solution at pH = 9. Following this, a solution of 1.2M Imidazole containing 0.003M Mercuric Chloride is added, yielding a penicillenic acid-mercuric mercaptide reaction product. It is the quantitative yield of this specific reaction product that is measured at the absorption maximum of 325 nm[10] against an imidazole/water "blank". All spectrophotometric measurements were performed at a maximum absorbance of 325 nm with a double-beam spectrophotometer[c] using a deuterium lamp. All reagents were of analytic or reagent grade.

A five point standard curve was generated by the serial dilution of a standard stock solution of 100 mcg/ml of pure amoxicillin trihydrate[d]. From this stock solution aliquots were taken and appropriately diluted with deionized, distilled water to obtain working standard solutions of known concentrations ranging from 5 to 40 mcg/ml. The standard curve had a correlation coefficient (r) of 0.99.

RESULTS AND DISCUSSION

The percentage of the initial concentration of amoxicillin trihydrate remaining at various times in samples of suspensions stored at various temperatures is presented in Tables I and II. These data indicate that amoxicillin trihydrate oral suspension can be repackaged in clear plastic oral syringes with no adverse effect on the stability of the reconstituted drug. The

TABLE I

STABILITY OF AMOXICILLIN TRIHYDRATE SUSPENSION STORED IN THE PLASTIC SYRINGES AND ORIGINAL CONTAINERS AT 25°C AND 40°C

TIME (DAY)	% INITIAL CONCENTRATION IN SYRINGES REMAINING IN SAMPLES FROM INDICATED LOT[a] 2011-03311		% INITIAL CONCENTRATION IN ORIGINAL CONTAINERS REMAINING IN SAMPLES FROM INDICATED LOT[a] 2011-03311	
	25°C	40°C	25°C	40°C
0	100.0[b]	100.0[b]	100.0[b]	100.0[b]
1	----[c]	97.0	----	95.4
4	98.5	95.6	95.7	95.4
6	95.5	----	91.3	----
8	----	----	----	----
10	----	67.9	----	59.0
12	----	59.7	----	54.5
16	94.0	----	91.3	----
18	----	33.6	----	20.4
22	----	18.3	----	16.0
25	----	----	----	----
29	----	15.0	----	10.2
35	----	11.0	----	9.3
38	----	----	----	----
43	----	----	----	----
58	----	----	----	----
63	----	----	----	----
66	----	----	----	----
68	91.0	----	87.0	----
78	91.0	----	----	----
81	----	----	----	----
90	74.6	----	69.6	----
91	----	----	----	----
100	----	----	----	----

a Reported as mean ± SD of three determinations
b Actual mean initial concentration was 114.50±2.08/5mL
c Not determined at this sampling time

TABLE II

STABILITY OF AMOXICILLIN TRIHYDRATE SUSPENSION STORED IN PLASTIC SYRINGES AND ORIGINAL CONTAINERS AT 80°C AND 60°C

	80°C						60°C	
	% INITIAL CONCENTRATION IN SYRINGES REMAINING IN SAMPLES FROM INDICATED LOT[a]			% INITIAL CONCENTRATION IN ORIGINAL CONTAINERS REMAINING IN SAMPLES FROM INDICATED LOT[a]			% INITIAL CONCENTRATION IN SYRINGES REMAINING IN SAMPLES FROM INDICATED LOT[a]	% INITIAL CONCENTRATION IN ORIGINAL CONTAINERS REMAINING IN SAMPLES FROM INDICATED LOT[a]
TIME (HOUR)	2102-03311	2011-05090	2014-05140	2102-03311	2011-05090	2014-05146	2102-03311	2102-03311
0	100.0[b]	100.0[c]	100.0[d]	100.0[b]	100.0[c]	100.0[d]	100.0[b]	100.0[b]
0.5	---[e]	90.6	---	---	91.2	96.3	---	---
1.0	---	77.3	98.8	91.3	87.7	92.6	---	---
1.5	---	---	80.4	---	---	70.4	---	---
2.0	92.5	68.0	75.7	87.0	66.7	68.1	93.7	---
2.5	---	66.7	50.1	---	66.7	63.0	---	---
3.0	72.7	44.6	48.0	58.7	66.7	52.8	---	---
4.0	52.2	31.0	36.4	50.0	45.6	50.0	92.6	87.1
5.0	43.8	30.3	32.8	41.3	41.3	40.8	---	---
6.0	39.2	---	---	28.3	---	---	---	---
7.0	---	---	---	---	---	---	77.4	72.6
8.0	---	---	---	---	---	---	58.4	62.9
10.0	---	---	---	---	---	---	55.3	59.7
12.0	---	---	---	---	---	---	51.1	58.1
14.0	---	---	---	---	---	---	50.5	53.2
16.0	---	---	---	---	---	---	50.5	50.0
19.0	---	---	---	---	---	---	41.3	46.0
21.0	---	---	---	---	---	---	36.9	46.0
23.0	---	---	---	---	---	---	31.3	35.5
25.0	---	---	---	---	---	---	25.3	30.7
27.0	---	---	---	---	---	---	21.6	29.0

a Reported as mean ± SD of three determinations
b Actual mean initial concentration was 114.50 ± 2.08 mg/5mL
c Actual mean initial concentration was 128.00 ± 2.37 mg/5mL
d Actual mean initial concentration was 121.05 ± 2.29 mg/5mL
e Not determined at this sampling time

concentration of amoxicillin trihydrate in samples of suspension stored at room temperature remained within 90% of the initial concentration for approximately 78 days. Thus, the expiration dates recommended for reconstituted amoxicillin trihydrate suspension stored in its original container (7 days after reconstitution if stored at room temperature) could be recommended for amoxicillin trihydrate suspension repackaged in at least the clear plastic oral syringes that we studied.

Data from suspension samples stored at 40°C, 60°C, and 80°C indicated a first-order degradation process, with the concentration of amoxicillin decreasing to less than 90% of initial concentration within 240, 7 and 1.5 hours, respectively (Figure 1); whereas the ambient temperature showed no appreciable degradation for approximately 78 days.

The lot-to-lot comparison was performed on both original containers and the syringes. Accelerated stability studies at 80°C failed to show a difference among lots when comparisons were made among original containers and among syringes; additionally, there were no interlot differences in stability when original containers were compared with the repackaged syringes. Furthermore, accelerated stability studies at 60°C and 40°C failed to show any differences in stability when original containers were compared with the repackaged syringes. The stability study at 25°C, also failed to show any differences in stability when original containers were compared with the repackaged syringes.

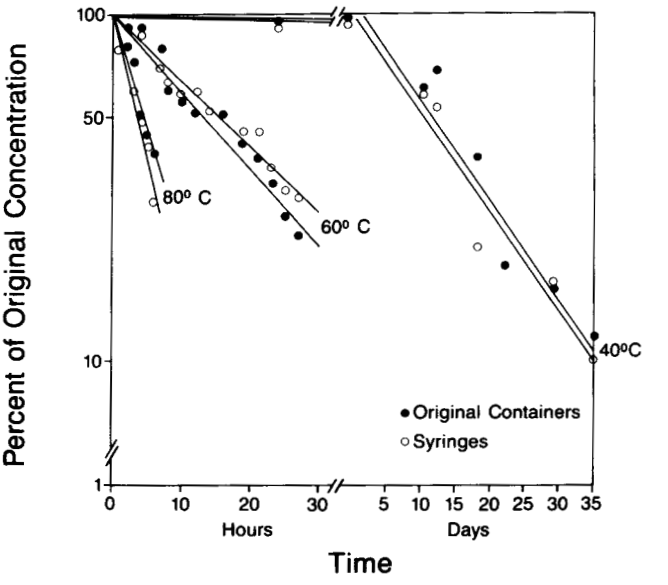

FIGURE 1. First-order degradation profile of reconstituted amoxicillin trihydrate (lot 2011-03311) for oral suspension under high temperature conditions. Regression equations for determining the percentage of drug remaining in the original containers or syringes are as follows. At 80°C, percent drug remaining = (original container) $112.3e^{-0.211t}$, r=-0.97; (syringes) $115.8e^{-0.181t}$, r=-0.97. At 60°C, percent drug remaining = (original container) $101.5e^{-0.045t}$, r=-0.98 (syringes) $104.9e^{-0.054t}$, r=-0.98. At 40°C, percent drug remaining = (original container) $106.3e^{-0.075t}$, r=-0.95; (syringes) $113.7e^{-0.069t}$, r=-0.98.

CONCLUSION

Amoxicillin suspension is stable for a minimum of two months at ambient temperature. In addition, the suspension is equally stable when stored in either plastic oral syringes or the original container.

No statistically significant inter-lot variability was demonstrated at the 80°C accelerated study and no statistically significant difference was noted at all temperatures studied between original containers and clear plastic oral syringes.

The reconstitution and repackaging of amoxicillin suspension into clear plastic oral syringes was not deleterious to its stability when compared to the original containers of amoxicillin suspension stored under similar conditions.

This study showed that the manufacturers recommended expiration date for reconstituted amoxicillin suspension can be applied to the reconstituted and repackaged product.

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FOOTNOTES

a Larotid®, 125mg/5ml, Roche, Division of Hoffman-LaRoche, Inc. Nutley, NJ 07110

b Exacta-Med Liquid Dispenser, Baxa Corporation, Denver, CO 80209

c Model 356, Perkin-Elmer Corporation, Norwalk, CT 06856

d Amoxicillin Trihydrate Reference Standard, Lot L9M96, Bristol Laboratories, Inc. Syracuse, NY 13201

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