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EFFECT OF STORAGE CONDITIONS ON THE STABILITY OF ALBENDAZOLE AND OXYTETRACYCLINE VETERINARY PRODUCTS MARKETED IN SUDAN

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The effect of storage conditions on the stability of albendazole and oxytetracycline veterinary products marketed in Sudan was evaluated.

Stability of Albendazole suspension and Oxytetracycline injectable solution has been investigated under two different storage conditions, according to the ICH guidelines for the drug stability testing.

The change in colour (using visual inspection), pH value (using pH meter) and the degradation process by an HPLC method, were monitored at different time points. Investigated drugs were stored in two different stores. The first one (A) is equipped with controlled temperature and humidity control systems. The second one (B) was a veterinary pharmacy selected randomly from East Nile locality. The temperature and humidity in the stores A and B were monitored and recorded daily using hygrometer for I year.

At the beginning of the study all products were proved to be compatible with the recommendations of the manufacturers. There was no change in the colour of albendazole during the nine months at both stores. The pH values in the first store expressed noticeable reduction, although it is still within the recommended range. Following nine months storage the drug content of albendazole was reduced below the recommended level. In the second store (B), there was no change in the colour of both albendazole products tested. There was considerable change in pH value during the nine month storage, but still it is within the recommended level. The active pharmaceutical ingredient concentration (assay %), of albendazole fell below the recommended level (USP) following storage for nine months.

In the first store (A), the two oxytetracycline products expressed no change in colour, and there was slight reduction in pH level (but still within the recommended level) within the six months storage period. The experiment was terminated just after six months due to the reduction of the active ingredient concentration (assay %) below the recommended level. In the second store (B), there is only change in the colour in one of the products following six months storage. pH level also here expressed moderate reduction, but still in the recommended range. The concentration (assay %), of oxytetracycline expressed prominent reduction following storage for six months.

The obtained results are of interest for stability studies and/or quality control purposes of Albendazole and Oxytetracycline commercial products. Here we could conclude that, the two veterinary drugs evaluated in this study (albendazole and oxytetracycline) proved to be unstable under environmental conditions in veterinary pharmacies in Khartoum state, Sudan.

INTRODUCTION

United States Pharmacopeia (USP) defined stability of pharmaceutical products as the point at which a product stays in the same properties and characteristics that it possessed at the time of its manufacture, within known time, and throughout its period of storage and

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use (i.e. its shelf life). The shelf life of medicinal product kept in its closed container under specified conditions is commonly defined as the time from manufacture up to expiry date[1].

The purpose of the on-going stability programme is to monitor the product stability over its shelf life and to determine whether the product remains, within specifications under the labelled storage conditions[2].-

For real time stability studies, frequency of testing should be enough to establish the stability profile of the drug substance. For drug substances with a proposed retest period of at least one year, the frequency of testing at the real time stability studies condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period[3&4].

Benzimidazole drugs were found to be sensitive to light, with behaviour common to all compounds of the class[5&6]. Accordingly, a close monitoring of these drugs, as such or in pharmaceutical formulations, constitutes a noteworthy analytical problem in regions presenting tropical climate.

Oxytetracycline is stable in air but exposure to strong sun light causes it to darken. Oxytetracycline deteriorates in solution with pH below 2 and is rapidly destroyed by alkali hydroxide[7]. Under abnormal conditions (heat, pH, and humidity), tetracyclines undergo reversible epimerization at positions C-4 and C-6 to form a mixture of degradation products. These degradation products or contaminants have very low antibiotic activity; in addition, some of them could be toxic[8].

If a significant change occurs to the product during the stability study it is considered as unstable after analysis of pharmaceutical product. In general, "significant change" for a pharmaceutical product is defined as[4]:

1. A 5% change in content from its initial point.
2. Any degradation in the product exceeding its acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., colour, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., Like colour or volume or softening of suppositories, melting of creams, partial loss of adhesion for transversal Products) may be expected under accelerated conditions; and, as appropriate for the dosage form.
4. Failure to meet the acceptance criterion for pH; or
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

The objective of this study was to determine the stability of two veterinary medicinal products viz: Albendazole drench formulation and Oxytetracycline HCl 5% injectable formulation; stored at two different storage conditions.

MATERIALS AND METHODS

Site of study

Experimental drugs were stored at two different stores located at East Nile locality, Khartoum state, Sudan.

Storage conditions

Drugs under investigation were incubated at two different storage conditions as follows:

Store A: the store was equipped with cooling and ventilation facility, that allow to maintain stable temperature (25°C) and humidity (40%), conditions.

Store B: Mimic storage condition available in veterinary pharmacies in Sudan. There was no cooling system and with poor ventilation.

Weather records: The temperature (°C) and humidity (RH) using calibrated hygrometers were recorded daily for the two stores from the first day up to the end of the experiments.

Experimental drugs

1. Oxytetracycline HCl 5% - 100 ml injection (Oxyko® 5%, Gingko-China).
2. Oxytetracycline HCl 5% - 100 ml injection (Oxtra® Italy).
3. Albendazole oral suspension 2.5% - 1000 ml (Albenko®, Gingko-China).
4. Albendazole oral suspension 2.5% - 1000 ml (Albendazole, pharma swede medicine, Egypt).

From each of the above mentioned preparations we did choose two different batches and from each batch 20 vials or bottles were selected (the total were 40). The total quantity of samples was 80 vials Oxytetracycline HCl 5% and 80 bottles Albendazole Oral Suspension.

Working standards and reagents

Albendazole working standard powder 99.07% was obtained from Changzhou yabang-qg pharmachem co, ltd, China. Oxytetracycline HCl working standard powder 95.5%, was purchased from Shandong jinyang pharmaceutical Co, ltd, China. Tetrabutylammonium hydrogen sulphate for HPLC 99.9% was purchased from Lopachemie, India. Disodium edetate powder for HPLC (99%), monobasic sodium phosphate, for HPLC, (99%), and dibasic potassium phosphate, for HPLC (99%), were purchased from Ttechno pharmacheme. India. Tertiary butyl alcohol, for HPLC (99.1%), Methanol for HPLC (99.8%), and HCL 35% - 38%, were obtained from Lobachemie, India. Buffer solution pH 4.00, (Scharlab, Spain). Buffer solution pH 10.01 (HANA 211. Romania).

Stability study

The study time points

1. Point zero: on first day of experiment, just from store A, we did choose one sample from each batch (8 samples from the store A).
2. Point one: (after 6 months) 8 samples were selected from each store so 16 samples were collected and the data was compared with zero point.
3. Point 2: (after 9 months) we did choose 8 samples from each store. We had 16 samples. Data obtained compared with zero point.

We compared all these points with the zero point. According to the guidelines of WHO, ICH and VICH, if we found any change in the: chemical properties, e.g. pH, (out the acceptance pharmacopeia criteria), 5% change in assay from the initial point to all the batches. Or any change in the physical properties (colour). This would indicate that the medicine or batch was not stable[3,4&9].

Parameters tested

pH: The pH of each drug was measured using pH meter (HANA 211, Romania).

Colour: The evaluation of the colour by visual test; because the methods used in international pharmacopoeia is not applicable because the reagents are not available, so we used digital camera and make photos for each sample at the predetermined time points, after that we compared between the photos using computer colour techniques.

% content of active ingredients[1]

HPLC methods for the determination of oxytetracycline (injection) and albendazole (suspension), were applied using CECILL 110 HPLC series, England, connected with UV detection (210-380 nm) high performance variable wave length monitor, with pump, injector, column, computer, and degasser device, all from CECILL company.

Albendazole solvent: a mixture of methanol and HCl 0.1 M (99:1) was used for the preparation of samples and standard solution and a mobile phase was prepared by dissolving 11.0 g of monobasic sodium phosphate analytical grade in 800 ml of distilled water, and 1200 ml of methanol HPLC grade was added and the volume was completed to 2000 ml with water.

Albendazole standard preparation: 0.05 g of working standard of albendazole was accurately weighed and transferred to 50 ml volumetric flask the volume was completed by the solvent to 50; 5 ml of this solution was transferred to 50 ml volumetric flask, and the volume was completed by the mobile phase.

Albendazole sample preparation: 2 ml of albendazole suspension was accurately measured and transferred to 50 ml volumetric flask, the volume was completed by the solvent. 5 ml of this solution was transferred to 50 ml volumetric flask and the volume was completed by the mobile phase.

Oxytetracycline solvent preparation: a mixture of distilled water and HCl 0.1 M (90:10) was prepared.

Oxytetracycline mobile phase: a mixture of acetonitril, 0.25M -tetrabutylammonium hydrogen sulphate pH 7.5, 0.25 M-EDTA pH 7.5 and H_2O (115:360:160:365, v/v/v/v) was prepared.

Oxytetracycline standard preparation: 0.05 g of working standard of oxytetracycline was accurately weighed into 100 ml volumetric flask and the volume was completed by the solvent, 5 ml of this standard solution was transferred to 50 ml volumetric flask, and was completed to the volume by the solvent.

Oxytetracycline sample preparation: 1 ml of oxytetracycline HCl injection was accurately measured and transferred to 100 ml volumetric flask, and the volume was completed by the solvent, 5 ml from this sample solution was accurately measured and transferred to 50 ml volumetric flask and the volume was completed by the solvent.

C18 Column was used and maintained at room temperature at a flow rate of 1 ml per minute; UV detector was used at wave length 380 nm (Albendazole) and at wave length 280 nm (Oxytetracycline) was used.

RESULTS

Temperature and humidity monitoring: The temperature and humidity in the two stores (A and B), were monitored and recorded daily using hygrometer for a whole year the results were shown in table 1. In the second store (B) during the cold months (November-February) the range of temperature was 30-33°C. While in hot months (March-June) the range was 33-38°C. In the rainy season (July-October) the range was 34-38°C. For humidity in the second store (B) the range was 13-46 relative humidity for the whole year.

Albendazole oral suspension: At the beginning of the study all samples were compatible with the manufacturers' recommendations. In both stores (A and B); there was no change in the colour of albendazole during the nine months of the study. The pH values in the two stores expressed noticeable reduction, although it is still within the acceptance criteria (Table 2). Following nine months storage the % content of active ingredients of albendazole showed reduction below the acceptance criteria, in both stores (Table 3).

Oxytetracycline HCl 5% injectable solution: The two products utilized in this study were within the manufacturer's acceptance criteria at the start of the experiment.

In the first store the two products expressed no change in colour, while in the second store (B), there is only change in the colour in one of the products following six months storage (Table 4). There was slight reduction in pH level (but still within the acceptance criteria) within the six months storage period for the products in the two stores (Table 5). The experiment was terminated just after six months due to the reduction of the active ingredient concentration (assay %) below the acceptance criteria for products in both stores, just after six months as shown in table 6.

DISCUSSION

The temperature records at the second store (B) were above the recommendations of the WHO in which Sudan was classified in Zone IVb and IVa for Port Sudan, for the whole year the temperature values were equal to or above 30°C. This may also support our hypothesis that veterinary medicinal products exhibit harsh environment conditions during storage in veterinary pharmacies. Normally drug dealers tend to purchase large quantities of veterinary medicines during summer months to sell them during rainy season, where animal owners tend to purchase large quantities of medicine to keep them with animals in the pasture.

In Sudan, as in other tropical and subtropical countries, worm infestations continue to represent a serious health hazard. The most common drugs used as anthelmintics belong to the benzimidazole series. Albendazole, Fenbendazole (FEN) and Mebendazole (MEB)[10-12], are among the most commercialized benzimdazole in the world. Albendazole is a potent anthehelminthic benzimidazole, widely used in the human helminthiasis treatment due to its efficiency against all helminth classes which usually infest animals[10,13&14].

Table 1: Temperature and Humidity record of stores A and B.

Months	Temperatures		Relative Humidity	
	Store A (Avg. ± SD)	store B (Avg. ± SD)	store A (Avg. ± SD)	store B (Avg. ± SD)
January	22.36 ± 1.41	33.15 ± 5.52	36.80 ± 2.82	26.88 ± 3.86
February	24.65 ± 3.93	31.80 ± 1.23	27.78 ± 4.49	23.04 ± 2.57
March	24.48 ± 3.82	33.12 ± 2.73	26.60 ± 4.34	13.29 ± 1.73
April	26.19 ± 2.20	38.33 ± 1.49	19.04 ± 3.08	28.69 ± 3.72
May	25.66 ± 2.11	37.19 ± 2.19	22.17 ± 7.49	21.95 ± 14.50
June	28.33 ± 1.00	37.54 ± 1.22	35.75 ± 5.49	24.19 ± 7.86
July	28.37 ± 1.83	36.08 ± 2.28	42.41 ± 5.19	36.79 ± 8.74
August	28.58 ± 1.74	34.67 ± 1.85	51.66 ± 3.19	46.03 ± 8.29
September	28.20 ± 1.10	34.31 ± 1.91	49.04 ± 3.65	40.63 ± 6.30
October	28.41 ± 0.92	38.26 ± 1.42	42.83 ± 2.68	32.65 ± 2.91
November	26.03 ± 1.83	33.18 ± 2.10	38.91 ± 3.00	35.40 ± 3.60
December	26.41 ± 3.20	30.00 ± 6.41	41.37 ± 3.78	33.15 ± 5.52

Table 2: pH values of Albendazole suspension samples in store A and B.

Stores	Store A (pH value)			Store B (pH value)		
Sample	Day zero	Six months	Nine months	Day zero	Six months	Nine months
Albendazole 1	4.87	4.66	4.60	4.87	4.67	4.58
Albendazole 2	4.90	4.71	4.68	4.90	4.69	4.60
Albendazole 3	4.81	4.69	4.65	4.81	4.69	4.60
Albendazole 4	5.00	4.87	4.84	5.00	4.90	4.81

Table 3: % content (w/v) of Albendazole suspension samples in store A and B.

Stores	Store A (% content)			Store B (% content)		
Samples	Day zero	Six months	Nine month	Day zero	Six months	Nine months
Albendazole 1	94.0	93.3	85.8	94.0	93.9	85.8
Albendazole 2	95.6	96.2	83.3	95.6	91.0	83.3
Albendazole 3	95.6	92.8	88.2	95.6	92.5	88.2
Albendazole 4	95.6	92.4	85.3	95.6	91.8	85.3

Table 4: The colour of oxytetracycline HCl 5% injection following storage for 6 months in store A and B.

Stores	Store A		Store B	
Samples	Day zero	Six months	Day zero	Six months
Oxytetracycline 1	An amber clear liquid	An amber clear liquid	An amber clear liquid	An amber black lighter liquid
Oxytetracycline 2	An amber clear liquid	An amber clear liquid	An amber clear liquid	An amber black lighter liquid
Oxytetracycline 3	An amber clear liquid	An amber clear liquid	An amber clear liquid	An amber clear liquid
Oxytetracycline 4	An amber clear liquid	An amber clear liquid	An amber clear liquid	An amber clear liquid

Table 5: pH values of oxytetracycline HCl 5% injection following storage for six months in store A and B.

Stores	Store A (pH value)		Store B (pH value)	
Samples	Day zero	Six months	Day zero	Six months
Oxytetracycline 1	8.50	8.33	8.50	8.30
Oxytetracycline 2	8.20	8.43	8.20	8.39
Oxytetracycline 3	8.60	8.59	8.60	8.53
Oxytetracycline 4	8.40	8.63	8.40	8.62

Table 6: % content (w/v) of oxytetracycline injectable following storage for six months in store A and B.

Stores	Store A (% content)		Store B (% content)	
Samples	Day zero	Six months	Day zero	Six months
Oxytetracycline 1	99.0	84.0	99.0	81.2
Oxytetracycline 2	99.9	83.4	99.9	75.2
Oxytetracycline 3	100.5	78.0	100.5	76.7
Oxytetracycline 4	96.2	75.3	96.2	75.4

For Albendazole (Fig. 1), at the beginning of the study all compounds were within the acceptance criteria of the manufacturers.

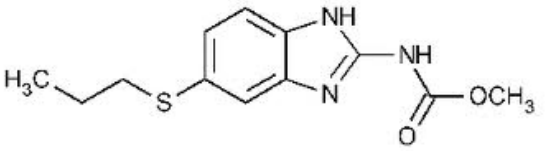

Fig. 1: Albendazole structure.

There was no change in the colour of albendazole during the nine months following storage of albendazole in ideal storage conditions (store A) as we could observe in table 2. The pH values in the store (A) expressed noticeable reduction, although it is still within the acceptance range (Table 3). Following nine months storage the % content of albendazole showed significant reduction ranging from 7.2% to 12.3%.

In the second store (B), there was no change of the colour of both albendazole products. There was considerable change in pH level during the nine month storage, but still it is within the recommended level. Following nine months of storage; there was reduction in the active ingredient concentration (assay %) of albendazole to fall below the recommended level, here the change is ranging from 7.4% to 12.3%.

Here we could partially attribute the degradation observed in the active material to the high temperature in the second store (B).

Due to their chemical features, all the benzimidazole drugs are sensitive to light, with behaviour common to all members of this class of compounds[4&5]. The amine derivative from hydrolysis of the carbamic group has been reported to be the main photo-degradation product, indicated also by metabolism studies as the major metabolite of the drugs[4]. Accordingly, a close monitoring of these drugs, as such or in pharmaceutical formulations, constitutes a noteworthy analytical problem in regions presenting tropical climate.

For oxytetracycline (Fig. 2), the two products utilized in this study were within the manufacturer's acceptance criteria at the start of the experiment.

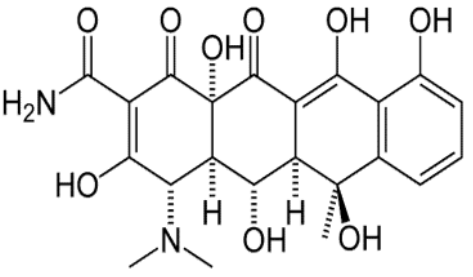

Fig. 2: Oxytetracycline hydrochloride structure.

Under ideal storage conditions the two products remained stable in colour, although there was slight reduction in pH level (but still within the recommended level) within the six months storage period. It is noteworthy to mention here the experiment was terminated just after six months due to the significant change of the active ingredient concentration (assay %) between 22.5% and 15.0% in some samples which exceed the acceptance limit (not more than 5%).

When the drugs stored in the selected pharmacy (store B) they were exposed to atmosphere stressing temperature in the range of 30-38°C. One of the products showed a change in colour following six months storage. pH level also expressed moderate reduction, but remain within acceptance range. The active ingredient concentration of oxytetracycline expressed prominent reduction following storage for six months.

Tetracycline antibiotics were known to undergo rapid decomposition in aqueous solutions, which was reported to be pH-dependent[15-19]. So here we could attribute the change in the active ingredient concentration and the change in the pH value due to decomposition caused by air.

The degradation of tetracyclines is complex and the drugs are subject to decomposition in both acidic and alkaline media[20]. Oxytetracycline (OTC) decomposition followed first-order kinetics at any given pH and from pH 3.5 to 10; the degradation rate was practically independent of pH[21]. In contrast, kinetic studies of OTC revealed that from pH 2.0 to 6.0, first-order kinetics were not found, but rather an initial equilibration occurred which was followed by a much slower rate of degradation[22].

Conclusion

It is to be concluded that, regular close monitoring of veterinary medicinal products should be conducted regularly by authorities. Both products tested for real time stability in this study showed minor to moderate degradation in some of the stability parameters tested. This could be of value in quality control purposes of Albendazole and Oxytetracycline commercial products. Improvement of storage conditions in veterinary pharmacies should be maintained.

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نشرة العلوم الصيدلية
جامعة أسيوط

أثر ظروف التخزين علي ثبات أثنين من الادوية البيطرية المسوقة في السودان: البندازول و أوكسي تتراسايكلين

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تم فحص ثبات الالبندازول (معلق) والاوكسي تتراسايكلين (محلول للحقن) تحت ظل ظروف مختلفة للتخزين اعتمادا علي دليل فحص ثبات الادوية المعد من قبل (ICH).

عملية تحلل (تفكك أو تخلخل) الدواء، اذا وجدت، تمت مراقبتها بواسطة جهاز الكروماتوغرافيا السائلة عالية الاداء. التغير في اللون تمت مراقبته باستخدام الفحص البصري وقيمة الاس الهيدروجيني باستخدام جهاز قياس الاس الهيدروجيني. تم تخزين الادوية محل الاختبار في مخزنين مختلفين المخزن الاول (A) معد بالاجهزه التي تحافظ على درجتي الحرارة والرطوبة بنسبة ثابته اما المخزن الثاني (B) فكان عباره عن صيدلية بيطرية تم اختيارها عشوائيا بمحلية شرق النيل. معدل درجة الحراره والرطوبه في كلا المخزنين الاول والثاني تم مراقبته وتسجيل القراءات من خلال استخدام أجهزة مراقبة قياسية لمدة سنه كاملة حتى انقضاء فترة الدراسة. في بداية هذه التجربه تم أخذ القراءات المبدئية للادوية محل الاختبار ومقارنتها مع دساتير الادوية حيث اثبتت أنها متوافقة مع القراءات الموصي بها.

في المخزن الاول لم يطرأ اي تغيير في اللون خلال فترة التسع اشهر لعقار الالبندازول، اما معدل الاس الهيدروجيني فقد اظهر تغيير طفيف لم يخرج من المدي الموصى به من قبل المصنع ودستور الادوية الامريكي، قياس تركيز المادة الفاعلة اظهرت تغيير كبير بعد التسعة اشهر اقل من الموصى به لدساتير الادويه والمصنع. اما في المخزن الثاني لم يظهر اي تغيير في اللون لكلا المنتجين للالبندازول لطوال فترة التسع اشهر، ايضا هنالك تغيير في الاس الهيدروجيني لم يخرج من المدي الموصي به ، كانت الملاحظه في التغييير الكبير في تركيز المادة الفاعلة التي انخفضت بنسبة كبيرة جعلت من المنتج غير مطابق للمواصفات التي اوصي بها الصانعين ومتطلبات دستور الادوية الامريكي.

عقار الاوكسي تتراسايكلين في المخزن الاول لم يظهر اي تغيير في اللون طوال فترة الست اشهر للدراسه لكلا المنتجيين، وهنالك تغيير طفيف في معدل الاس الهيدروجيني لم يخرجه من المعدل الموصى به لكلا العقارين طوال فترة الدراسة، اما تركيز المادة الفاعلة فقد انخفض بعد سته اشهر بمعدل اقل من الموصى به مما يجعله غير ثابت. اما في المخزن الثاني فهنالك تغيير في اللون بعد مضي سته اشهر لاحد المنتجين، معدل الاس الهيدروجيني به تغيير طفيف لم يخرجه من المعدل الموصى به لكلا العقاريين، اما الملاحظ فهو الانخفاض الملحوظ لتركيز المادة الفاعلة لكلا المنتجين مما يجعلهما غير مطابقين لمواصفات المصنع ودستور الادوية الامريكي.

النتائج التي تم الحصول عليها ذات اهمية في دراسة الثبات الدوائي أو ضبط الجودة لكل من عقاري البندازول والاوكسي تتراسايكلين. عليه فاننا نخلص بناء على هذه الدراسة بان عقاري الالبندازول والاوكسي تتراسايكلين غير ثابتين تحت ظروف التخزين الموجودة بالصيدليات البيطرية الموجودة بولاية الخرطوم.