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Microbiological and Analytical Evaluation of Semi-Solid Formulations of Doxycycline Hyclate under Accelerated Stability Conditions

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Abstract

Doxycycline Hyclate (DOX) is a broad-spectrum antibiotic that belongs to the tetracycline family. It has been widely used in the treatment of several inflammatory diseases, and is considered the first-line therapy in the management of moderate to severe cases of acne. In this research, Doxycycline was formulated in four semi-solid formulations (F1and F2 as Gels, F3 and F4 as ointments), then these formulations were subjected to accelerated stability conditions for three months. The formulations were evaluated using microbiological and analytical methods after one and three months. Agar well diffusion method was used as a microbiological method to screen the antibacterial activity of semi-solid formulations against two types of bacteria, Staphylococcus Aureus and Pseudomonas Aeruginosa. HPLC was used as an analytical method for the quantitative and qualitative determination of these formulations. A comparison between a microbiological assay and analytical assay was achieved to evaluate the activity. The results showed that the ointment formulations were more stable than gel formulations since the percentages of drug were 91%, 93% at 25 ˚C after one month for formulations (F3, F4) against 90%,65% for formulations (F1, F2) respectively. Antibacterial activity results showed that formulation F4 had the highest zone of inhibition, which is 31mm for S.aurues and 26 mm for P. aeruginosa after storing it for three months at 25C°. The formulations were still effective despite the chemical degradation of doxycycline, this effectiveness returns to the fact that degradation products could still have active structural parts responsible for the antibacterial activity.

Keywords: Accelerated stability study, Antibacterial activity, Doxycycline Hyclate, HPLC, Semi-solid formulation.

Introduction

Doxycycline (DOX) is a broad-spectrum bacteriostatic antibiotic, that belongs to the second-generation tetracyclines family[1] Fig. 1. Doxycycline hyclate is reversibly bound to the 30S ribosomal subunit inhibiting the protein synthesis[2]. DOX is more effective than other tetracyclines against a wide variety of microorganisms including the enterococci and various anaerobes, plasmodium

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and protozoa[3]. It also has antibacterial properties against *P. aeruginosa* and *S.aureus* which are considered the most common bacteria causing chronic wound and soft tissue infections, with inhibition zone between 13.66±1.69 mm to 32.00 mm against *S. aureus* and 4.00± 1.63 to 12.33±0.94 mm for *P. aeruginosa* [4]. According to the American Academy of Dermatology, oral tetracyclines (doxycycline and minocycline) are considered the first-line therapy for the treatment of moderate-to-severe acne vulgaris [5].

At present, doxycycline is administered orally but it is associated with systemic side effects such as oesophageal ulceration, photosensitivity and systemic allergic reactions [6, 7]. Systemic side effects might be circumvented by topical preparations which have the advantage of delivering the active ingredient more directly to the site of action avoiding the first- pass metabolism and selectively targeting microorganisms in the affected area [8, 9].

Stability testing may provide evidence to assess the quality of a drug substance, the product variations over time and the influence of environmental factors such as temperature and humidity[10, 11]. DOX has a poor stability profile and could be degraded by hydrolysis and epimerization, producing several degradation products[12]. Keto-enol tautomerism has also been described in the degradation of DOX[13]. It has been reported that these derivative degradation products of Doxycycline might be more active and/or toxic than their parents[14]. In the literature, the stability of doxycycline and other tetracyclines has been studied in water, in a non-aqueous solvent [13], in a variety of formulations including suspensions, slow release systems, tablets and capsules [10], while stability studies in topical formulations were rare. There were many attempts to develop stable topical formulations of tetracycline. (Gupta et al. …2021) developed and formulated doxycycline hydrochloride hydrogels employing various polymers for wound healing applications and investigated their stability[15]. In another work, (Soni et al. …2021) prepared and evaluated bigel of doxycycline hyclate for the effective treatment of acne using Carbopol 940 to prepare hydrogel phase whereas span-60 and olive oil for the oleogel phase[16]. In addition, a gel of doxycycline (Atridox®) has been developed to treat the chronic adult periodontitis, the product is composed of a two syringe mixing system. Syringe A contains the delivery system (flowable polymeric formulation PLA), while syringe B contains doxycycline. Upon contact with the crevicular fluid, the liquid product solidifies leading to control of the drug release for 7 days[17].

The aim of this study was to prepare and evaluate the stability of doxycycline in different topical formulations. In addition, a comparison was performed between the amount of doxycycline measured chemically by the HPLC method, and the antibacterial activity of doxycycline carried out microbiologically by the Agar well diffusion method after the exposure of the formulations to accelerated stability conditions.

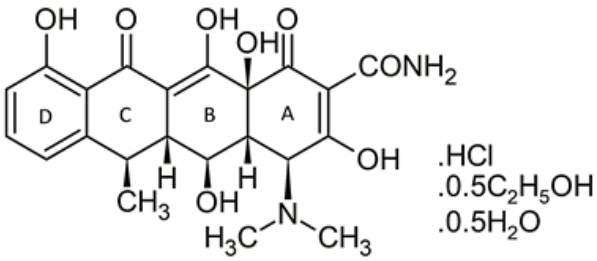

Figure 1. The structural formula of Doxycycline Hyclate [1].

Materials and Methods

Doxycycline Hyclate (DOX)(purity≥97) was obtained from (Hebei Dongfeng, China). Carbopol 940 was purchased from (Speciality, UAE). HPMC E6 was purchased from (Shan-dong, China). Propyl paraben and methyl paraben were purchased from (Salicylate, India). Propylene glycol and Vaseline were purchased from (Noor orchid, India). TEA (Tri Ethanol Amine) was purchased from (Merck, USA). Vit E and BHT (butylated hydroxyl toluene) were purchased from (BASF, USA). And lastly Ethanol 96% was purchased from (Sari- Syria).

Preparation of semi-solid Formulations

Four semi-solid formulations with different physicochemical properties were prepared (hydrogel

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F1, organo gel F2, hydrophobic ointment F3, and hydrophobic ointment with additive antioxidant F4). Table 1 illustrates the compositions of the four formulations and the percentage of each component. Hydrogels were prepared by dispersing carbopol and HPMC E6 in water (F1)/water and alcohol (F2) with stirring and heating to 60°C. Doxycycline, methyl paraben and propyl paraben were dissolved in glycerine and propylene glycol, then were added to the carbopol gel. pH was adjusted to 5-7 using triethanolamine (TEA). The ointment formulations were prepared by melting vaseline, paraffin oil and BHT at 70°C. After cooling the previous mixture, doxycycline was suspended and mixed with Vit E(F4) using a colloid mill.

Table 1. Composition of formulations and the percentage of each component (%).

Component	F1 Hydrogel W/W%	F2 Organogel W/W%	F3 Hydrophobic Ointment W/W%	F4 Hydrophobic ointment W/W%
Doxycycline Hyclate	0.1	0.1	0.1	0.1
Carbopol 940	0.5	1.25	--	--
HPMC E_6	0.7	0.7	--	--
Methyl paraben	0.2	0.2	--	--
Propyl paraben	0.5	0.5	--	--
Glycerin	15	2.5	--	--
Propylene glycol	15	7.5	--	--
Ethanol 96%	--	67.3	--	--
Distilled water	67.35	19.5	--	--
TEA	0.65	0.45	--	--
Vit E	--	--	--	0.9
BHT	--	--	0.01	0.1
Vaseline	--	--	96.89	95.9
Paraffin oil	--	--	3	3

Accelerated stability study

After filling the formulation in aluminum containers, a number of prepared formulations were incubated under three different conditions: In the first chamber, the incubation was carried out at 25°C and 40% RH, in the second chamber (30°C, 60% RH), and in the third chamber, (40°C, 75%RH). The formulations were evaluated at three time periods, immediately at the beginning of the procedure, after one and three months, in terms of color, appearance, determination of the content and antibacterial activity.

Chemical assay

High performance liquid chromatography analysis was carried out for the determination of drug content using Shimadzu HPLC equipped with a UV detector, at 40°C using a 250×4.6 mm, 5 mm particle size reversed phase C18 column, Hypersil ODS. The mobile phase employed was a mixture of buffer (5 ml of TEA was taken and dissolved in 500 ml volumetric flask containing distilled water and adjusted the pH to 3.5 using phosphoric acid) and methanol at a volume ratio of (20:80) at a flow rate of 1.3 ml/min. 2g of each formulation F1 and F2 were dissolved in 100 ml of HCl 0.1N (the concentration is 20 µg/ml). For F3 and F4, 2g of ointment was mixed with30 ml Hexane and diluted with HCl 0.1N to 100 ml in a separation funnel, then the acidic part was extracted (with a concentration of 20 µg/ml). The HPLC method was developed and validated in-house. The percentage of drug was calculated by the following Eq. 1:

Percentage of DOX in formulation %= (The area under the curve of sample solution during stability study /the area under the curve of sample solution at t=0) * 100 …..1

Antibacterial assay

The Agar well diffusion method was used to screen the antibacterial activity of semi-solid formulations against two types of bacteria, which are Gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*Pseudomonas Aeruginosa*) [18, 19]. Bacterial suspensions were pre-cultured in Mueller Hinton broth (MHB) overnight in a rotary shaker at 37°C. Afterward, each strain was adjusted at a

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concentration of 1.5×10^8 colony-forming unit (CFU)/mL using 0.5 McFarland standard. Tripton Soya Agar (TSA) medium was prepared and autoclaved at 121° C for 20 minutes. Four Petri plates containing TSA medium were cultured with 100 µL of *S. aureus* bacterial suspension while the other four plates were cultured with 100 µL of *P.aeruginosa* bacterial suspension. In order to prepare a solution of formulation at a concentration of 100 µg/ml, 5g of each formulation F1 and F2 were dissolved in 50 ml of HCl 0.1N. For F3 and F4, 5g of each ointment was mixed with 25 ml Hexane and 25 ml HCl 0.1N in a separation funnel and the acidic extract was taken. Each Petri plate containing TSA medium was cultured with S. aureus. Five wells with a diameter of 7 mm were punched in each plate with a sterile cork borer. The first well was for F1 solution, the second for F2 solution, the third for F3 solution, the fourth well for F4 solution, and the last well for the Doxycycline solution (100 µg/ml) was placed as a control. The same procedures were repeated in the plates cultured with *P. aeruginosa*, this test was carried out for all the samples which were incubated in the stability conditions mentioned previously. Later, all plates were incubated in the incubator at 37 °C for 24 hrs. The anti-bacterial activity of formulations was determined by measuring the diameter of the inhibition zone and calculated as a percentage according to the following Eq. 2**:**

The percentage of inhibition zone = [The diameter of the inhibition zone of formulation (cm) during stability stability/ the diameter of the inhibition zone of control (cm)] * 100 ….2

Results and discussion

Characteristics of formulations during accelerated stability study

The physiochemical properties of the prepared formulations should be evaluated to obtain a good formulation that meets the requirements. The organoleptic tests are considered crucial parameters of the quality and stability of the product, so failure of these tests can result in rejection of the preparation. The results showed that the ointment formulations F3, F4 are the most acceptable, they have a greasy feel, an oily smell and a yellow color which returns to the original color of doxycycline. Severe color changes were observed in formulations F1, F2 as it returned from yellow to dark-yellow and brown Fig. 2, while the color change was less remarked in formulation F4, that might be explained by its content of vitamin E as an additive antioxidant Table 1. Color change in F1 and F2 could be attributed to the negative effect of high temperature in addition to the presence of aqueous medium in these formulations, that induce the oxidation of phenolic groups into colored quinones compounds [20, 21]. No change was observed in the consistency of the prepared formulations during the stability period.

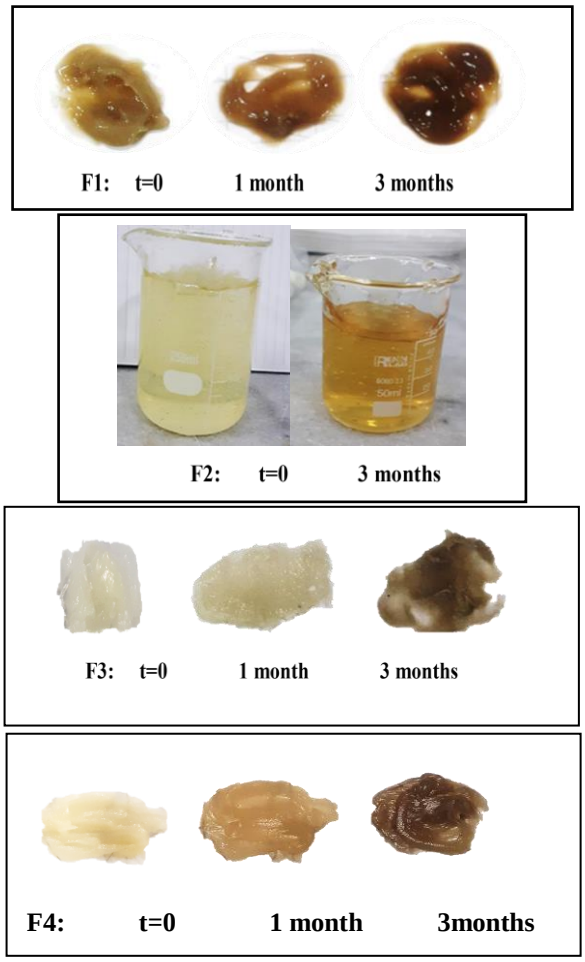

Figure 2. color change during stability period (3 months, 25°C), for F1, F2, F3 and F4.

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Chemical assay

The percentage of drug content during the stability study was determined for the four topical formulations Table 2. The results showed a decrease in the percentage of DOX in all prepared formulations during the stability studies. Although the ICH recommends studying the accelerated stability for 6 months, in our research, it was conducted for only 3 months because the amount of Dox was reduced to less than 55%.

The ointment formulations (F3, F4) were more stable than gel formulations (F1, F2). The percentages of drug were 91% and 93% at 25ºC after one month for ointment formulations (F3, F4) against 90% and ,65% for gel formulations (F1, F2) respectively. This could be interpreted by that F1 and F2 have aqueous medium that is preferable for epimerization, hydrolysis, deamidation and decarbonylation reactions. This has been recently reported by Bin yang et al. [22], who found that DOX in aqueous medium and high temperature tends to degrade and is subjected to different degradation pathways Fig. 3. In comparison between the ointment formulations F3 and F4, the result revealed that F4 is more stable than F3 formulation, this is likely related to the positive effect of the combination of two antioxidants (vitamin E and BHT) which could enhance the stability and reduce the oxidation processes of doxycycline. However, the alcoholic formulation F2 was the least stable among the other formulations although it contained small amount of water, the percentage of DOX reached 35.5% after one month of incubation at 40Cº. The reason for this is not clear but it might be related to the low viscosity of alcoholic formulation F2 which could be affected by three factors: the effect of decreased pH on the rheology of Carbopol during stability study and led to a weak gel matrix [23], in addition to the low viscosity of Ethanol itself, and the low percentage of glycerin and propylene glycol, so these factors effect on the viscosity of formulation F2 and led to an increase in the chemical reactivity of Doxycycline [24]. Fig. 4 shows the chromatograms of two formulations; F2 and F4. The F2 chromatogram showed peaks that might return to the degradation products, with a decrease in the DOX content after one month, thus making the F2 formulation the least stable formulation. Whereas the F4 chromatogram showed fewer degradation product peaks especially after 1 month without a significant decrease in DOX content and this made it considered the most stable formulation.

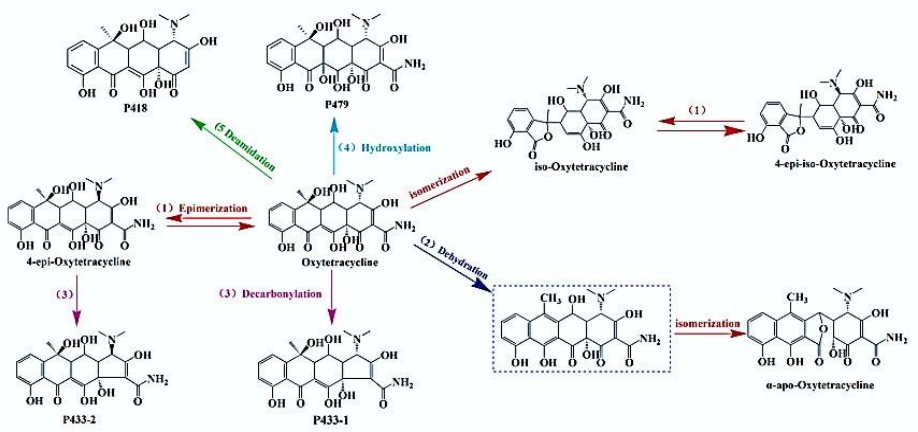
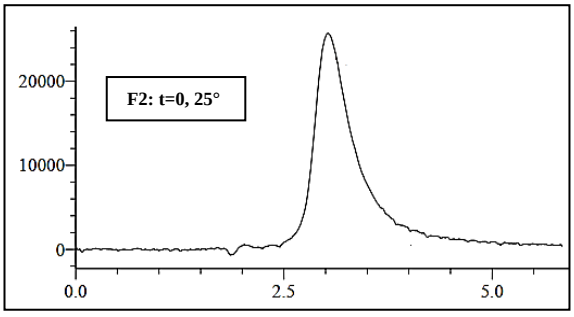


Figure 3. Proposed transformation pathways of doxycycline hydrolysis [22].

Table 2. Percentage of DOX in formulations during accelerated stability study.

	T=0	After one month		After three months
Temperature	**25°C**	**25°C**	**40°C**	**25°C**	**40°C**
F1	99	90	71	71	23
F2	94.4	65	35.5	40	20
F3	94.6	91	75	77	40
F4	95	93	77	80	55



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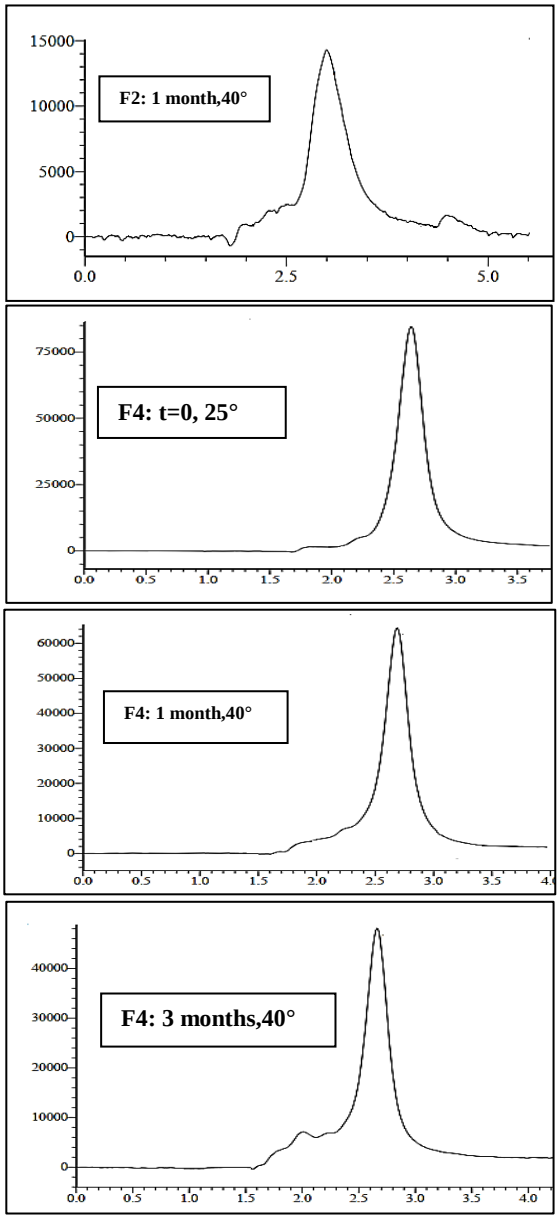

Figure 4. Chromatograms of the formulations; F2 and F4 at different conditions of time and temperature

Antibacterial activity

The antibacterial activity of the drug was determined by measuring the diameter of inhibition zone. The results in Table 3, Fig. 5 showed that the formulation F4 had the highest zone of inhibition with 31 mm and 26 mm diameters for *S.aurues* and *P.aeruginosa* respectively, after storing the formulations for three months at 25C°. This result also accords with earlier study [4] which found that DOX is more sensitive to *S.aurues* than *P.aeruginosa*. It's interesting to note that this result was in the t=0, but during stability study, the formulations were more sensitive against *P.aeruginosa* than *S.aurues*. This might be related to the antibacterial activity of degradation products formed during stability study. However, all formulations have the diameter of inhibition zone larger than 80% for both types of bacteria after stability study at 40C° for 1 month except F2 formulation which has inhibition zone diameter of about 65% for *S.aurues*. On the other hand, the diameter of inhibition zone under the same conditions after 3 months was larger than 55% for both types of bacteria except F2 which was still active for about 40%. As a result, we could confirm that the formulation F2 has the smallest diameter of inhibition zone towards both types of bacteria, and the formulation F4 has the largest diameter. The comparison between the inhibition zone as a percentage and the concentration of doxycycline was shown in Table 4. This comparison revealed that despite of decrease in concentration of DOX with time, all formulations were still microbiologically effective. Chemically, the ointment formulation F4 was the most stable formulation as it kept about 55% of DOX after storing at 40°C for three months. But biologically, this decrease in concentration was not accompanied by the same decrease in the antibacterial activity, as it was estimated to be about 85%. The same issue also occurred in gel formulations F1, F2, the remaining concentration of the active substance was 23% and 20% respectively, while these formulations remained biologically effective at about 75%, 65% against (*P.aeruginosa*) and 56%, 40% against (*S.aurues*). We can attribute this decrease in the microbiological activity and the difference in percentage between the two types of bacteria to the effect of degradation on the active structural site responsible for antibacterial activity. According to Zhong SF et al[22], the possibility of isomerization occurrence at C12 led to dissociate the B ring, and influence on the sequence of naphthacin rings which play an important role in antibacterial activity. Furthermore, the possibility of deamidation occurrence at C2 site leds to a decrease in biological activity. The potential of epimerization at C4 site affects the antibacterial efficacy, especially toward Gram-negative bacteria**.** Also the presence of enol-keton group at the C11-C12 site contributes to enhancing the therapeutic efficacy, when hydroxylation occurs, the enol group will be lost. So the degradation will occur at one of previous active sites could give degradation products with different antibacterial properties. Moreover, the result of chemical analysis will give a decrease in the

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concentration values as a result of the degradation in the structure of doxycycline. Therefore, the antibacterial activity of the formulation was still effective despite the degradation of doxycycline and the physical degradation of formulation, this effectiveness is due to the degradation products which still have the active structural parts responsible for antibacterial activity.

Table 3. Percentage of inhibition zone of formulations (%).

S.aurues							
	Initial	**1 month**			**3 months**		
	25°C	**25°C**	**30°C**	**40°C**	**25°C**	**30°C**	**40°C**
F1	96	92	92	88	90	72	56
F2	97	96	88	65	80	50	40
F3	92	88	85	81	86	80	70
F4	96	94	93	90	92	84	85
P. aeruginosa							
	Initial	**1 month**			**3 months**		
	25°C	**25°C**	**30°C**	**40°C**	**25°C**	**30°C**	**40°C**
F1	96	92	90	89	85	80	75
F2	100	93	86	80	75	70	65
F3	100	98	95	90	92	92	80
F4	98	96	95	92	92	92	85

Table 4. Comparison between the chemical assay (HPLC) and the percentage of inhibition zone during stability study.

Antibacterial Activity (%)			**HPLC Assay (%)**
	P. aeruginosa	**S.aurues**	
	3months/40°C	**3months/40°C**	**3months/40°C**
F1	75	56	23
F2	65	40	20
F3	80	70	40
F4	85	85	55

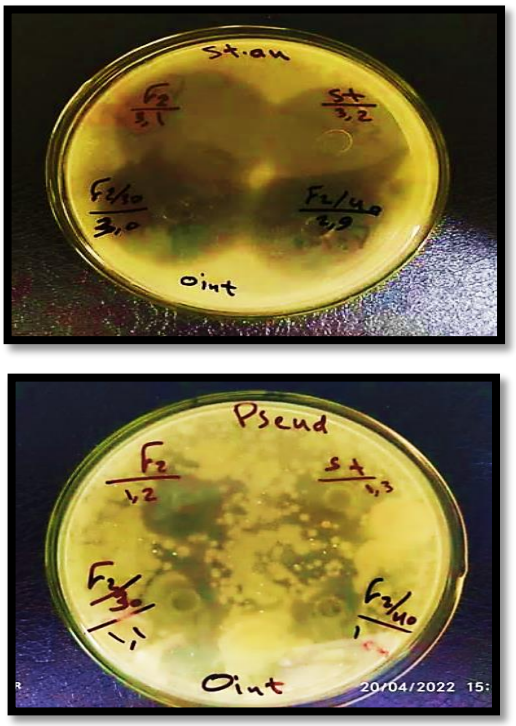

Figure 5. Inhibition zone of F4 formulation against S. aureus and P. aeuroginosa at different stability conditions

Conclusion

As a result of the accelerated stability study of Doxycycline semi-solid formulations, ointment formulations are better than gel formulations in terms of color, appearance, drug content and antibacterial activity. The concentration of doxycycline was decreased with time by increasing the temperature, while antibacterial activity was relatively conserved against *Staphylococcus aureous and Pseudomonas aeruginosa*. The chemical degradation does not necessarily reflect the antibacterial activity due to the similarity in structure of the degradation products to the parent compound, in addition to having antibacterial properties even though the formulations are physically destroyed.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Al-Baath.

Authors' Contribution Statement

O.A., Y.A., M.B and A.S contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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التقييم التحليلي والميكروبيولوجي لتحضيرات صيدلانيًة نصف صلبة من الدوكسيسيكلين هايكلات تحت شروط الثبات المسرَّع

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الخلاصة

الدوكسيسكلين هايكلات هو مضاد حيوي واسع الطيف ينتمي لعائلة التتراسيكلينات، يستخدم بشكل واسع في معالجة العديد من الأمراض الالتهابيًة، ويعتبر الخط العلاجي الأوَّل في تدبير الحالات المتوسطة إلى الشديدة من حب الشَّباب. تم في هذا البحث صياغة أربع صيغ نصف صلبة للدوكسيسيكلين (F2,F1 كصيغ هلاميًة، F3,F4 كصيغ مرهميًة)، ثم عُرّضت الصيغ السابقة إلى شروط ثبات مسرَّعة في حاضنات الثبات لمدة ثلاثة أشهر. تم تقييم الصيغ المحضرة باستخدام طرق ميكروبيولوجيًة وتحليلية وذلك خلال شهر وثلاثة أشهر. استخدمت طريقة الانتشار على الآغار لتقييم الفعاليًة المضادة للجراثيم وذلك على نوعين من الجراثيم، العنقوديات المذهَّبة والزائفة الزنجاريًة. بينما استخدم HPLC كطريقة تحليل كمية وكيفية لمقايسة الصيغ. أجريت مقارنة بين نتائج المقايسة الميكروبيولوجيًة والمقايسة التحليلية لتقييم الفعاليًة. أظهرت النتائج أن الصيغ المرهميّة F3,F4 أكثر ثباتاً من الصيغ الهلاميّة F1,F2، حيث بلغت النسبة المئوية للدوكسيسيكلين 93% و91% للصيغة F3,F4 على التوالي وذلك عند الحفظ بدرجة حرارة الغرفة بعد شهر واحد. بينما بلغت النسبة90% و65% للصيغ الهلاميّةF2,F1 عند الحفظ في نفس الشروط السابقة. أظهرت نتائج قياس الفعاليًة المضادة للجراثيم أن الصيغة المرهميًة F4 امتلكت أكبر قطر تثبيط جرثومي ويقدر بحوالي 31 ملم للعنقوديات المذهبة و26 ملم للزوائف الزنجارية وذلك بعد حفظ الصيغة لمدة ثلاثة أشهر عند درجة الحرارة 25°م. وبالتالي حافظت الصيغ على فعاليتها على الرغم من التخرّب الكيميائي البنيوي للحاصل للدوكسيسيكلين. تعود هذه الفعالية إلى حقيقة أن نواتج التخرب لا تزال محافظة على الموقع البنيوي الفعّال والمسؤول عن إعطاء الفعاليًة المضادة للجراثيم.

الكلمات المفتاحية: دراسة ثبات مسرعة، الفعالية المضادة للجراثيم، دوكسيسيكلين هايكلات، الكروماتوغرافيا السائلة عالية الأداء، صيغ صيدلانية نصف صلبة.