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TAUTOMERIC TRANSITIONS WITH PHOTO-INDUCED EFFECTS USING LASER BEAM OBSERVED IN ANTIBIOTIC ERYTHROMYCIN - ESTOLATE

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ABSTRACT:The photo transitions of Erythromycin 2-propionate dodecyl sulphate (C40H71NO14, C12H26O4S) using Nitrogen Laser beam have been studied at different periods of time. Different techniques have been used to analyze and identify final products.

The results showed that photo transitions of Erythromycin - Estolate which measured by conductivity initially increased and then decreased with time especially at high pulse rate. While pH showed a different behavior and initially there was reduction in pH values by increasing the pulse rate. The kinetic study indicated that the rate of reaction is of the second-order type . The qualitative identification showed that the final products were;

- **First: 6-(4-Dimethylamino-3-O-propionyl –6-methyl- tetrahydro-pyran-2-yloxy)-14-ethyl-4-(5-hydroxy-4-methoxy-4,6-dimethy-tetrahydro-pyran-2-yloxy)-3,5,7,9,11,13-hexamethyl-oxacyclotetradeca-2,10-dione-7,12,13-propaniol dodecyl sulphate.**
- **Second: 6-(4-Dimethylamino-3-O-propionyl –6-methyl- tetrahydro-pyran-2-yloxy)-14-ethyl-4-(5-hydroxy-4-methoxy-4,6-dimethy-tetrahydro-pyran-2-yloxy)-3,5,7,9,11,13-hexamethyl-oxacyclotetradeca-2,9-diene-2,7,10,12,13-pentaol dodecyl sulphate.**

The final products showed an existaence of enol group through a tautomerism reaction of keto enol.

Keywords: Tautomeric transitions, Erythromycin, Estolate, Laser

Introduction

Macrolides are a group of closely related compounds characterized by a macrocyclic lactone ring (usually containing 14 or 16 atoms) to which deoxy sugars are attached(1). These compounds are weak bases, highly molecular weight, slightly soluble in water and low toxic (2). Biogenesis is a major path for macrolides synthesis, which is done by consecutive additions of Methyl Malonyl – SCOA to Propionyl – SCOA (3). One of the most important compound in macrolides is Erythromycin which consists of three groups named as A, B and C (4).

Erythromycin is very soluble compound in alcohol, chloroform and acetone with half life of two hours (5). Erythromycin is using as antibiotic for many diseases such as respiratory infections, pneumonia infections, pertussis, diphteria, meningitis, acne, gas gangrene, …….etc.(6-10). At the same times, Erythromycin could causing some toxicity such as gastrointestinal side-effects, hepa toxicity, skin rashes, oto toxicity, cardiac toxicity and miscellaneous side-effects (11-14). However, Erythromycin is produced as a pellets or capsules due to inhibition by gastric acid (15,16). Meanwhile, the mechanism of Erythromycin is mainly related to protein synthesis in ribosome (17), which causing inhibition of tRNA translocation (18) and is catalyzed by Translocase enzyme (19).

Many attempts and investigations showed how to use and apply the irradiation techniques in the reactions of organic compounds (20), such as methyl sulphanilyl carbomate in the presence of TiO_2 (21), 2,3- Dichloro propion amide (22), Tetra chlorovinphos (23), Phenyl triflouro-methyl keton (24) and 4- chloro phenol (25). The photochemical processes for most antibiotic compounds are concern as tuatomerism and causing a prototropy phenomena (26). These processes including high rate transformations from Keto to Enol such as ethyl 2- keto butanoate and Nitro methane (27).

This research is conducted to establish the effect of irradiation techniques of Laser source on the transition and decomposition processes of the most wide use antibiotic compounds in the world. Meanwhile, the toxicity of final products is also concern.

Experimental Part:

Five mls of Erythromycin Estolate were irradiated by three different pulse rates of 1,3 and 6 pulse/second for periods of 5,10,15,20 and 30 minutes and wavelength of 337.1 nm using a Nitrogen Laser, Model UV 24 supplied from Molectron Company. The pH and conductivity of Erythromycin Estolate solutions were estimated by regular methods. The final products of Erythromycin decomposition were identify by using UV-visible and FT-IR. Chemical – identification of Enol group (28) and ester ions (29) were also used to confirm the final products. The calculations of reaction rate and reaction order were done for the transition and decomposition process.

Results and Discussion:

The changes in pH and conductivity of Erythromycin Estolate solutions irradiated for different periods of time were shown in tables 1 to 3 . The conductivity values for decomposition processes were approach a maximum of 0.13, 0.43 and 0.48 m S. cm^{-1}.at 10 min for 1, 3 and 6 pulse/sec respectively. There was a reduction in conductivity values with time due to formation of new compounds in solution. However, this increase is more clearly at 6 pulse/second compared to that of other rates (30). Meanwhile, there was dramatic decrease in pH values at 10 min irradiation time especially for 6 pulse/sec due to the formation of ions in solution by keto- enol tautomerism (27).

The results of reaction rate for pulse rates showed that a second-order is matching very well with the transition and decomposition processes (Fig. 1, 2 and 3) . However, the rate constant of these processes showed a value of 1.1X10-3 S^{-1} by using a light of 1 Pulse/ sec and a value of for a rate of 3 Pulse/ sec . While a value of 6 $\times 10^{-3}$ min^{-1} was obtained with light of 6 Pulse/ sec which focus up the importance of this rate.

Identification techniques showed a good match between final products of Erythromycin Estolate decomposition and suggested structure formula (Table 4). The UV-spectrum of decomposition products for two wavelengths showed that electronic transition band of n ΠΠ* of carbonyl group in ester is dominated at 204-206 nm (31). Meanwhile, there is an appearance of very weak symmetry forbidden band at 273-282 nm. This band is belong to the transision of n--- ΠΠ* which is related to keton group and formed by excitation by unpaird electrons on oxygen atoms (32) as pointed out in table (5). The UV spectrum of the products of irradiated Erythromycin Estolate showed different absorbtion sites compared to that of standard solution of Erythromycin Estolate. The results pointed out that two absorbance bands of 204 nm which is related to ester-carbonyl and that of 281 nm are dispersed, while a new absorbance band appeared at 216-218 nm (Figs. 4-8 and Table 5). These changes emphases the occurrence of red-shift due to the formation of (HO-C=C) group which contains C=C chromphore with absorption band at 190 nm, while the HO group is auxochrom (33).

IR- spectrum of standard Erythromycin Estolate solution noted a broad absorption band at 3200-3450 cm^{-1} which

belongs to stretching vibration of (O-H) band that is connected with hydrogen bond (Fig. 9 and Table 6). At the same times appearance of 2860-2970 cm^{-1} bands were occurred which are represent stretching vibration of saturated (C-H) bond while bands of (C-H) bond were existed at 1380-1460 cm^{-1}. Other bands of (1280 and 1340), (1050 and 1090), 1820 and 1650 cm^{-1} were related to stretching of (C-O) ester bond, (C-O) ether bond, of (C=O) ester bond and (C=O) keton bond (34,35,36).

IR- spectrum of decomposition products of irradiated Erythromycin Estolate showed appearance of absorbance bands at (2840-2930) cm^{-1} for stretching of (C-H) bond while absorbance bands of (1380-1450) cm^{-1} for binding of (C-H) bond. However, absorbance bands of (3200-3380) cm^{-1} band were remain unchanged through decomposition processes which emphases the existence of (O-H) bond. Meanwhile, there was a disappearance of absorbance band of ester carbonyl group at 1820 cm^{-1} and a new absorbance bands of enol group was exist at 1690 cm^{-1} (Table 6 and Figs. 10-13). Disappearance of carbonyl group was due to a red-shift according to electronic density prior to the resonance (31). The appearance bands of (C-O) ester group is occurred at 1270 $cm^{-1}$and 1340, while another band occurred at 1050 $cm^{-1}$and 1090 $cm^{-1}$are belong to a group of ether (32). All these appearances of the groups emphasized decomposition processes to final products of enol group through keto enol tautomerism reaction.

Conclusions

1. **More compounds were produced by photo degradation.**
2. **The pulse rate of 6 pulse/second is the most effective rate for Erythromycin Estolate application.**
3. **More careful should be taken with application and storage of Erythromycin Estolate.**
4. **Final products of Erythromycin Estolate decomposition are almost enol compounds.**

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Table 1: Conductivity and pH values for standard and irradiated Erythromycin Estolate at 1 pulse/second.

Period , h	Cond mS.cm^{-1}	pH
0	0.10	5.87
5	0.10	5.32
10	0.13	4.81
15	0.12	4.89
20	0.12	5.30

Table 2: Conductivity and pH values for standard and irradiated Erythromycin Estolate at 3 pulse/second.

Period , h	Cond mS.cm^{-1}	pH
0	0.10	5.87
5	0.40	4.65
10	0.43	4.60
15	0.39	4.95
20	0.30	4.98
30	0.27	5.10

Table 3: Conductivity and pH values for standard and irradiated Erythromycin Estolate at 6 pulse/second.

Period , h	Cond mS.Cm^{-1}	pH
0	0.10	5.87
5	0.45	4.28
10	0.48	2.26
15	0.33	4.70
20	0.29	5.32

Table 4 : Name and structure for products of irradiated Erythromycin Estolate .

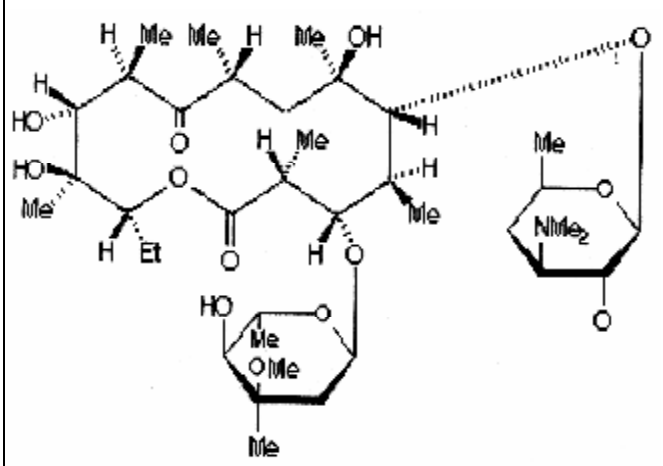
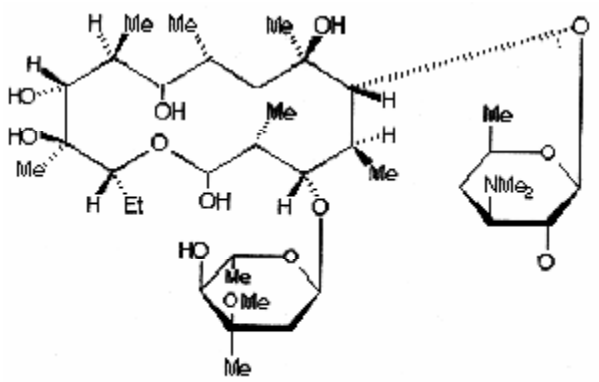
compound	Structure	Name
1		**6-(4-Dimethylamino-3-O-propionyl –6-methyl- tetrahydro-pyran-2-yloxy)-14-ethyl-4-(5-hydroxy-4-methoxy-4,6-dimethy-tetrahydro-pyran-2-yloxy)-3,5,7,9,11,13-hexamethyl-oxacyclotetradeca-2,10-dione-7,12,13-propaniol dodecyl sulphate.**
2		**6-(4-Dimethylamino-3-O-propionyl –6-methyl- tetrahydro-pyran-2-yloxy)-14-ethyl-4-(5-hydroxy-4-methoxy-4,6-dimethy-tetrahydro-pyran-2-yloxy)-3,5,7,9,11,13-hexamethyl-oxacyclotetradeca-2,9-diene-2,7,10,12,13-pentaol dodecyl sulphate.**

Table 5 : Absorption of UV bands for standard and irradiated Erythromycin Estolate

l max (nm)	Absorbance(A)	Time(h)	Irradiation pulse sec^{-1}
204.5,281.5	**0.863,0.017**	**0**	**Standard**
219	**1.78**	**5**	**3**
218	**1.02**	**30**	**3**
220	**1.90**	**5**	**6**
221	**1.90**	**20**	**6**

Table 6 : Absorption of IR bands for standard and irradiated Erythromycin Estolate

n(O-H)	n(C-H) streching	n(C=O) Ester	n(C=O) Keton	n(C-H) bending	n(C-O) Ester	n(C-O-C) Ether	OH n(-C=C-) Enol	t(h)	Irradiation pulse sec^{-1}
3200-3450(s)	2860-2970(s)	1850(s)	1650(m)	1380 (s) 1435 (s) 1450 (s)	1270(w) 1340(w)	1050(s) 1090(s)	-	0	Standard
3220-3450(s)	2860-2950(s)	1850(s)	1650(m)	1380 (s) 1435 (s) 1450 (s)	1270(w) 1340(w)	1050(s) 1090(s)	-	5	3
3300-3450(s)	2860-2960(s)	1850(w)	-	1380 (s) 1435 (s) 1450 (s)	1270(w) 1340(w)	1050(s) 1090(s)	1690(w)	30	3
3250-3460(s)	2860-2960(s)	1850(w)	-	1380 (s) 1435 (s) 1450 (s)	1270(w) 1340(w)	1050(s) 1090(s)	1690(m)	5	6
3300-3450(s)	2850-2960(s)	-	-	1380 (s) 1435 (s) 1450 (s)	1270(w) 1340(w)	1050(s) 1090(s)	1690(w)	20	6

S= strong m = medium w= weak

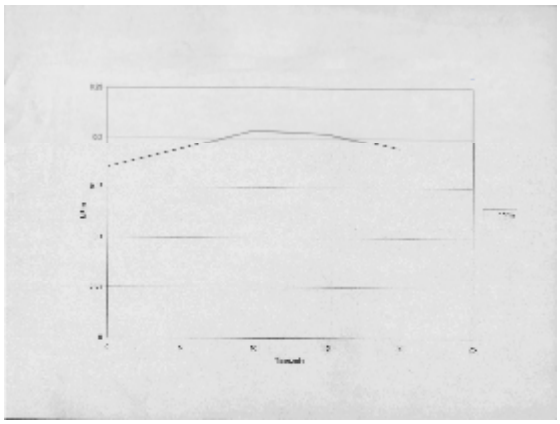


Fig. 1: Decomposition rate for irradiated of Erythromycin Estolate at (1Pulse /Sec)

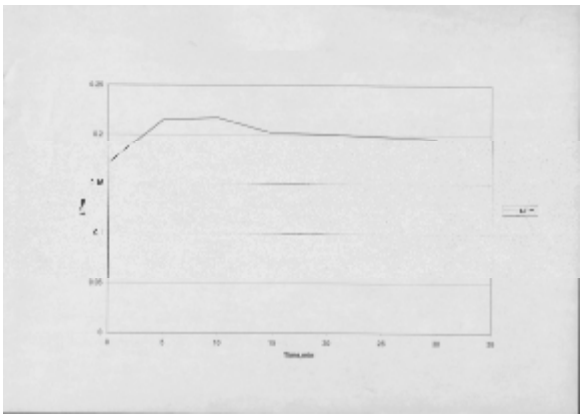


Fig. 2: Decomposition rate for irradiated of Erythromycin Estolate at (3 Pulse /Sec)

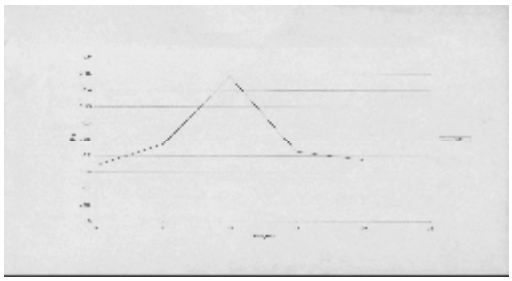


Fig. 3: Decomposition rate for irradiated of Erythromycin Estolate at (6 Pulse /Sec)

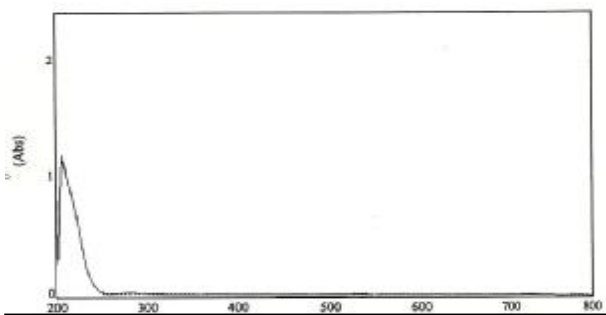


Fig. 4: UV-spectrum for standard solution of Erythromycin Estolate

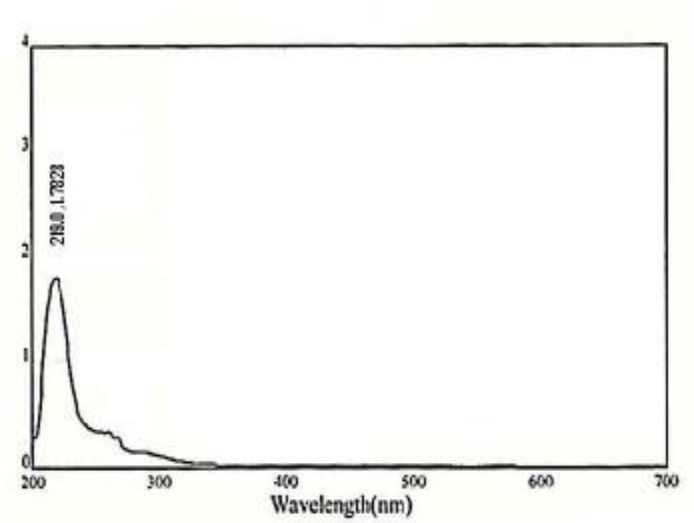


Fig. 5: UV-spectrum for irradiated of Erythromycin Estolate at (3 Pulse /Sec) for 5 Minute.

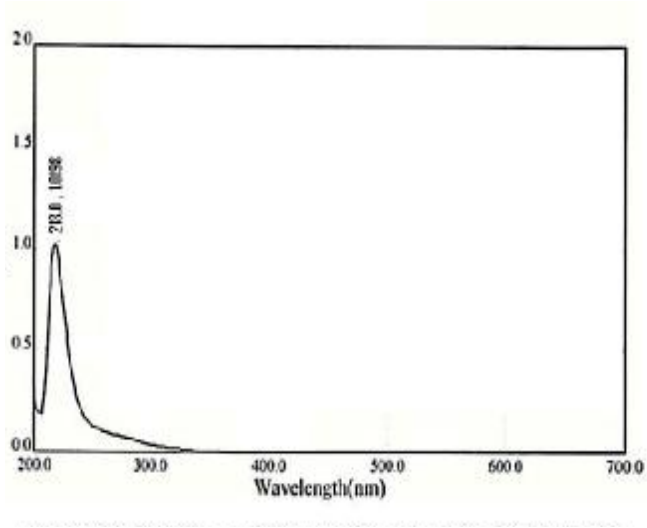


Fig. 6: UV-spectrum for irradiated of Erythromycin Estolate at (3 Pulse /Sec) for 30 Minute.

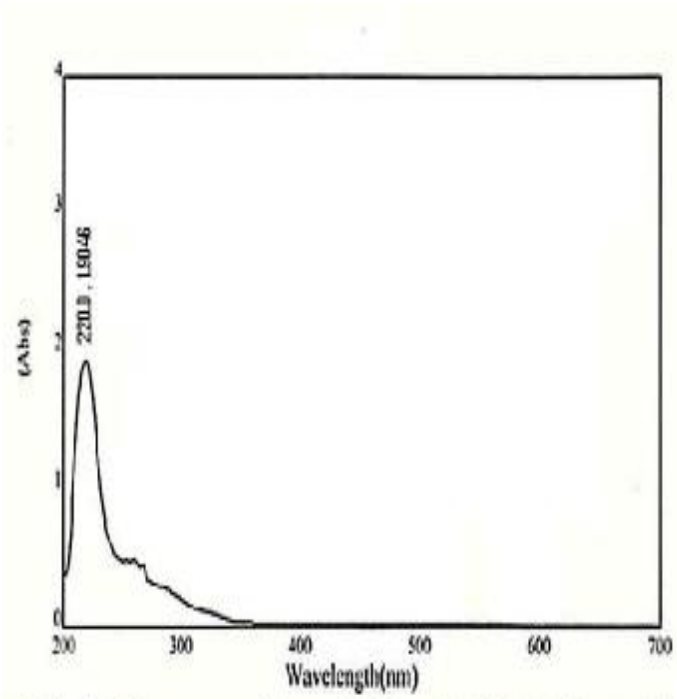


Fig.7: UV-spectrum for irradiated of Erythromycin Estolate at (6 Pulse /Sec) for 5

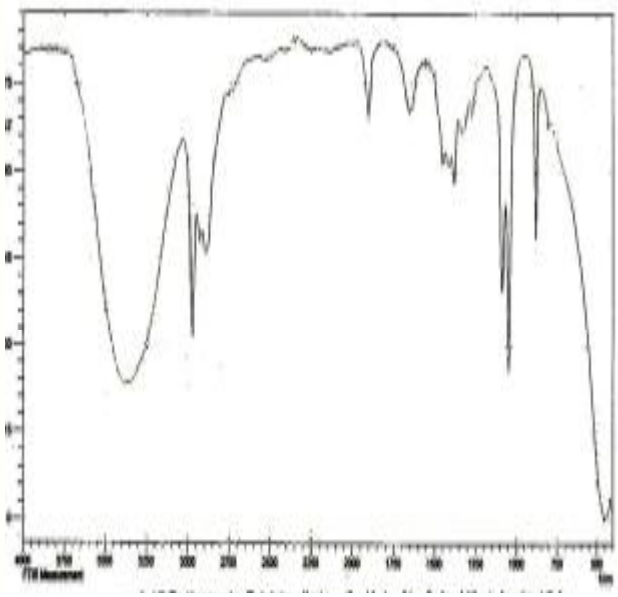


Fig.8: UV-spectrum for irradiated of Erythromycin Estolate at (6 Pulse /Sec) for 20Minute.

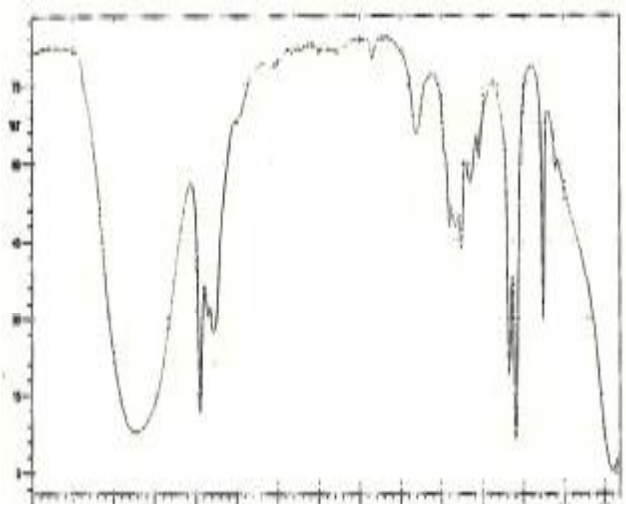


Fig. 9: IR-spectrum for standard solution Erythromycin Estolate .

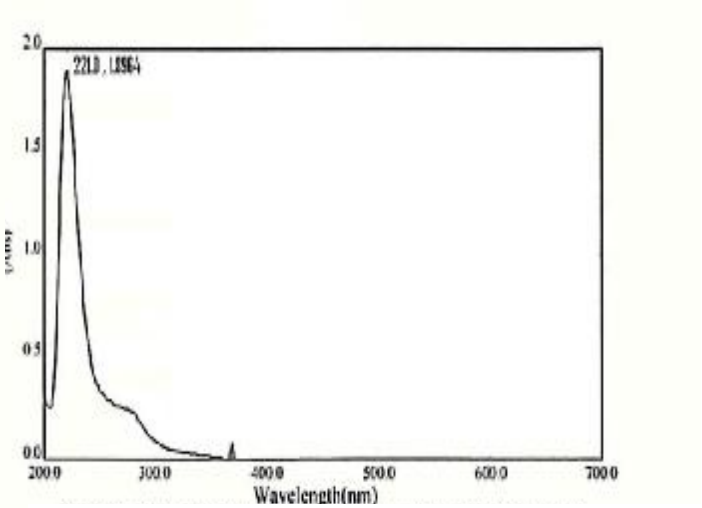


Fig. 10: IR-spectrum for irradiated of Erythromycin Estolate at (3 Pulse /Sec) for 5 Minute.

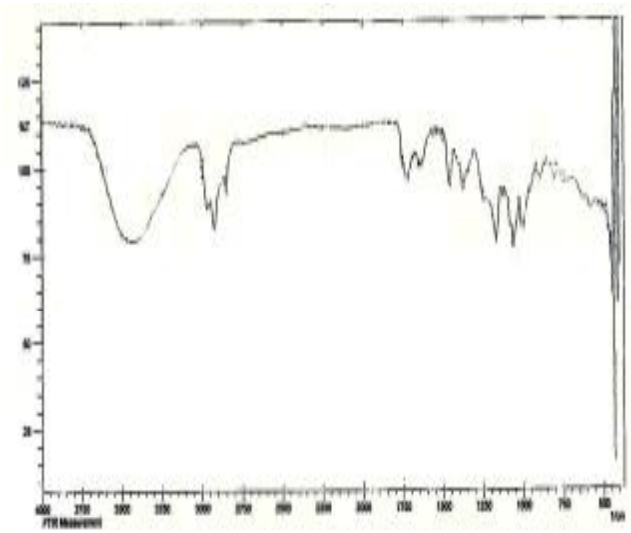


Fig. 11: IR-spectrum for irradiated of Erythromycin Estolate at (3 Pulse /Sec) for 30 Minute.

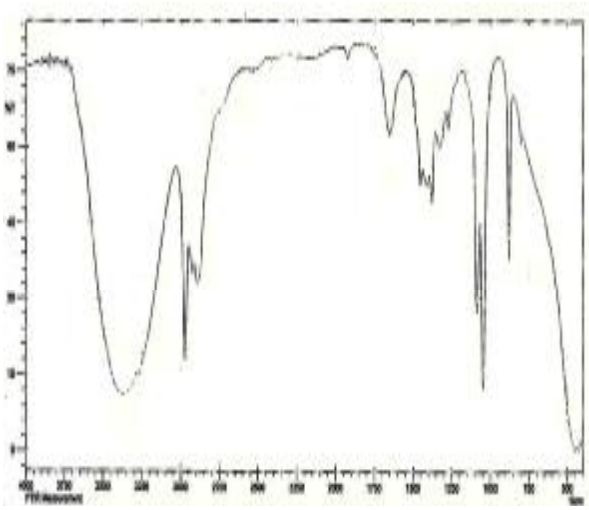


Fig12 : IR-spectrum for irradiated of Erythromycin Estolate at (6 Pulse /Sec) for 5 Minute.

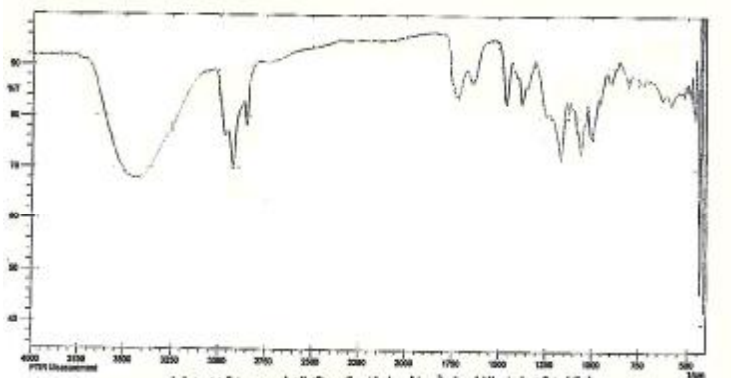


Fig.13 : IR-spectrum for irradiated of Erythromycin Estolate at (6 Pulse /Sec) for 20 Minute.

الانتقالات التوتمرية المصاحبة للتأثيرات الضوئية لشعاع الليزر في المضاد الحيوي ارثرومايسين - اوستليت

إسماعيل خليل الخطيب يسرى محمود العبيدي حسين علي

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الخلاصة

تم دراسة الانتقالات الضوئية للمضاد الحيوي الارثرومايسن - اوستليت **Erythromycin 2-propionate dodecyl sulphate (C40H71NO14, C12H26O4S)** بأستخدام شعاع الليزر النتروجيني بمعدل سرع نبضات مختلفة من الشعاع، كما وتم استخدام تقنيات مختلفة لتحليل وتشخيص النواتج النهائية.

توضح نتائج الانتقالات الضوئية للمضاد الحيوي الارثرومايسن - اوستليت والمعبر عنها بالتوصيلية بأن قيم التوصيلية تزداد في بداية التشعيع ثم تبدأ بالنخفاض مع الزمن وخاصة عند المعدل العالي لنبضات شعاع الليزر. بينما تعطي قيم الاس الهيدروجيني سلوكا مختلفا حيث تبدأ بالانخفاض عند بداية التفاعل مع الزيادة في سرعة نبضات شعاع الليزر. في حين تشير الدراسة الحركية الى ان معدل سرعة التحول للمركب المدروس يكون من الرتبة الثانية.

يوضح التشخيص النوعي بأن النواتج النهائية تكون كما يلي:

First: 6-(4-Dimethylamino-3-O-propionyl –6-methyl- tetrahydro-pyran-2-yloxy)-14-ethyl-4-(5-hydroxy-4-methoxy-4,6-dimethy-tetrahydro-pyran-2-yloxy)-3,5,7,9,11,13-hexamethyl-oxacyclotetradeca-2,10-dione-7,12,13-propaniol dodecyl sulphate.

Second: 6-(4-Dimethylamino-3-O-propionyl –6-methyl- tetrahydro-pyran-2-yloxy)-14-ethyl-4-(5-hydroxy-4-methoxy-4,6-dimethy-tetrahydro-pyran-2-yloxy)-3,5,7,9,11,13-hexamethyl-oxacyclotetradeca-2,9-diene-2,7,10,12,13-pentaol dodecyl sulphate.

وتشير هذه النواتج الى وجود مجموعة الاينول خلال التفاعل التوتمري لمركب الكيتو - اينول.