FORMULATION OF ECONAZOLE NITRATE AS A TOPICAL SOLUTION

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ABSTRACT :

Econazole nitrate (EN) is considered as the most effective agent for the treatment of all forms of dermatomycosis caused by dermatophytes. This study was carried out to formulate a stable Econazole nitrate solution for a topical use through preparation of different formulas and selected the most suitable one. The results indicated that the use of propylene glycol and ethanol as a vehicle for EN which is very slightly soluble in water gave amore stable formula as EN topical solution, with a shelf life of about 3.15 years .The data also indicated that the light accelerated the degradation of EN, while the type of container (glass or plastic) had no effect on the rate of drug. The overall results of this study suggest that the selected formula could be used as a topical solution for EN.

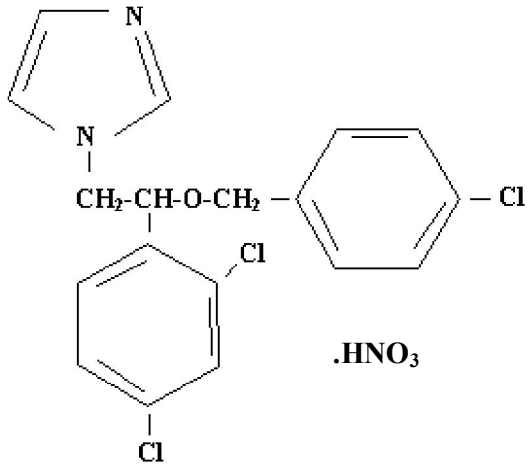
الخلاصة:

أن محلول (نترات الايكانازول) يعتبر الأكثر فعاله لاستخدام هذا الدواء في علاج جميع أشكال الفطريات الجلدية الناتجة عن العوامل المسببة لتلك الالتهابات الفطرية. كان هدف الدراسة أيجاد صيغه تركيبيه مستقره (لنترات الايكانازول) على شكل محلول، من خلال تحضير عدد من الصيغ التركيبية واختيار الصيغة الأكثر فعاليه .

النتائج أثبتت أن استعمال (بروبلين كلايكول)و(الكحول الاثيلي) كمادة ناقله (لنترات الايكانازول) والذي يكون قليل الذوبان في الماء أعطى صيغه تركيبيه اكثر استقرارا لهذا المحلول وعمر صلاحية 3,15 سنه .أشارت النتائج أيضا إلى أن الضوء ساعد في تسريع عمليه تحلل (نترات الايكانازول)، بينما نوع الحاوية (بلاستك أو زجاج) ليس له تأثير على استقرارية (نترات الايكانازول). أن حصيلة نتائج هذه الدراسة أظهرت أن الصيغة التركيبية المختارة يمكن استعمالها لتحضير (نترات الايكانازول)على شكل محلول.

INTRODUCTION:

Econazole nitrate is (RS)-1-[2,4-dichloro-B (p-chorobezyl- oxy) phenethyl] imidazole nitrate[1].



It is a white or almost white crystalline powder.m.ρ. About 164C°, with decomposition. Very slightly soluble in water and ether: soluble 1 in 125 of ethanol (96%) 1in 60 of chloroform and l in 25 of methanol [1, 2].

Econazole nitrate is used for the topical treatment of all forms of dermatomycosis caused by Dermatophytes like trichophyton rubum, trichophyton mentagrophytes, trichophyton tonsusrans which cause tinea pedis, tinea cruris, and tinea corporis respectively[3].

It is used for dermatomycosis caused by yeasts like candida albicans and candida guilliermordi[4].

Econazole nitrate is available in a variety of dosage form such as skin cream (alone or in combination with triamcinolone), skin solution, skin lotion and spray solution [3].

It has been proven to be effective in the presence of mixed infection. The antibacterial effect of the preparation offers an additional outstanding advantage.

The purpose of this work is to formulate a stable Econazole nitrate solution for topical application using different types of vehicles like propylene glycol, polyethylene glycol (PEG), Glycerol and ethyl alcohol which they are inert nontoxic and maintain the solubility of drug.

Furthermore, the effects of container type and light on the stability of the prepared formula are studied as well as its shelf life.

MATERIALS, INSTRUMENTS AND METHODS

Materials

Econazole nitric powder (Alesmalia company-Iraq), methanol, polyethylene glycol, glycerol, ethanol (BDH, Chemicals, Ltd, Pool, England), hydrochloric aid (Riled DE Haen AG Seelze, Hanover, Germany). Standard
buffer (pH 4 and 7) . Propylene glycol (MERK Germany) .

INSTRUMENTS

Spectrophotometer (Pye-Unicom SP-8-100 England Model 292 MK2 England) Sartorius balance (Werke-GMBH, Type 2842, Germany – GMBH,Type 1265 NIP,W.G Autoclave (Vebstatex Jimenau , Type SD505) PH-meter(Schott-Geate,Type CG820,W.Germany.

METHOD

Assay of Econozole nitrate topical solution:

A simple and fast procedure for the determination of (EN) based on the UV spectrophotometry[5], was applied as follows.

Test solution: 5ml was measured and diluted with pure methanol to 100ml.
Reference solution: 50mg of pure (EN) was exactly weighted and transferred into 100ml volumetric flask. About 50 ml of pure methanol was added, shacked well until it was dissolved, completed the volume to 100ml with methanol and mixed.

The UV absorbency was then recorded in 1cm quartz cell for the reference and test solutions against pure methanol.

The quantity of Econazole nitrate in topical solution was calculated using the following equation.

% Econazole nitrate = (A_{corr} sample X mg standard) / (A_{corr} standard Xmg sample X 10)
(A_{corr}= $A_{271.5}$ _ $A_{278.5}$)

Formulation of Econazole nitrate as a topical solution.

Different formulas of Econazole nitrate for topical solution (1%w/v) were prepared as shown in Table-1.

Formula	Econazole nitrate (gm)	Propylen glycol (ml)	Polyethylere glycol (ml)	Glycerol (ml)	Ethanol a.s.to (ml)
A	1	----	75	----	100
B	1	----	35	40	100
C	1	50	12	13	100
D	1	50	25	----	100
E	1	75	----	----	100

Table-1 Schedule of Different formulations of Econazole Nitrate as a topical Solution

All formulas (A,B,C, Dand E) were composed of Econazole nitrate (1%) and completed to 100 ml volume with ethanol(95%).

Stability Study

Stability of (EN) in a normal and accelerated conditions was carried out by incubating samples of formula E in ovens at 40,45 and 50^{o} C for 120 days.

Samples were taken and assayed for their drug content at suitable time intervals (2 weeks) using spectrophotometry method.

Effect of light

This factor was studied by placing formula E in a clear glass container and subjected to light at room temperature for 2 months [6, 7]. Samples were taken every two weeks and analyzed for their drug content.

Effect of containers

The functions of container are to maintain the quality, safety and stability of its content [8, 9]. Various samples of formulaE were stored at different conditions (room temperature, 40^{o}C) in glass bottles and plastic bags for 120 days.

Samples were taken and assayed for their drug content every one month using spectro photometric method.

Quality control

The concept of total quality control refers to the process of striving to produce perfect product by a series of measurements. The quality control tests that were done, included density, pH, drug content and appearance of solution

RESULTS AND DISCUSSION

Method of Assay

In this study the ultraviolet spectrophotometry was used for the quantification of (EN) as a topical solution, the data indicated that the method gave acceptable results since a good standard curve with a correlation of 0.996 was obtained as seen in fig.1.

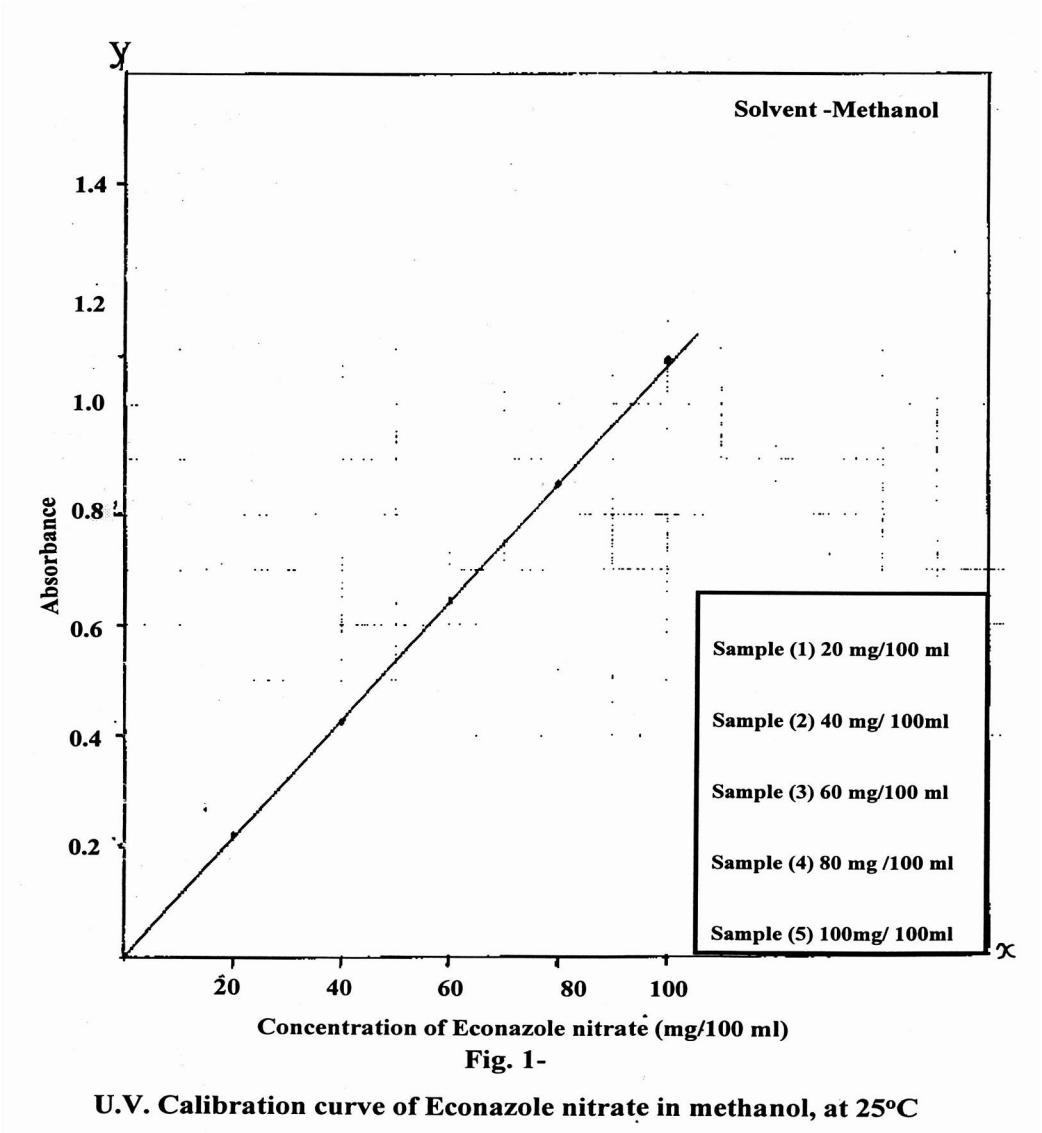


Fig. 1-

U.V. Calibration curve of Econazole nitrate in methanol, at 25°C

The U.V. spectrum of (EN) is shown in Fig.2. The profile indicates that, the drug has maximum absorbance at 271.5 nm and minimum absorbance at 278.5nm in methanol as it has been reported.

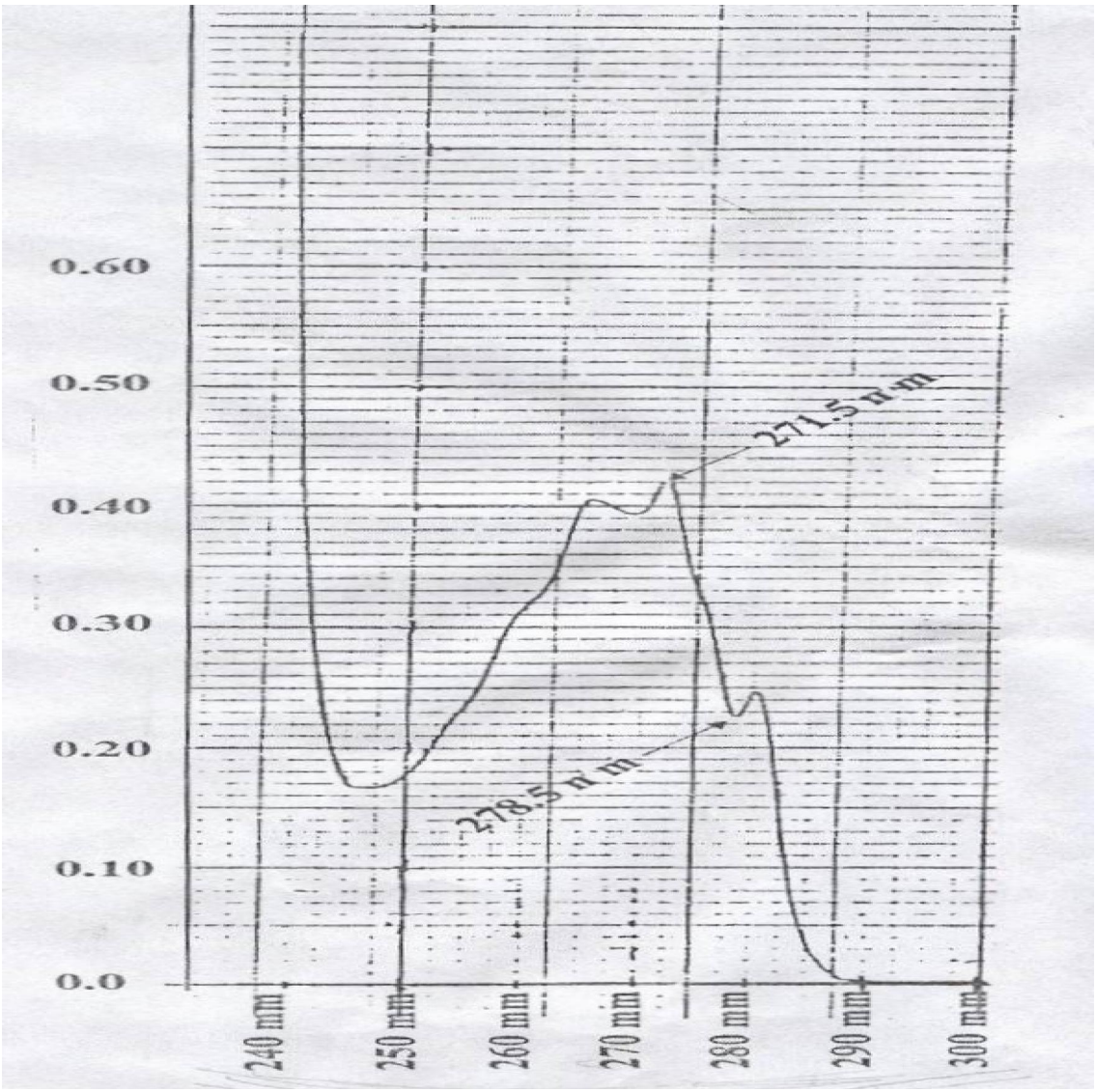


Fig 2
UV spectrum of Econazole Nitrate in solvent Methanol at 25 °C

Formulation of Econazole nitrate

Table –2 shows the percent remaining after 4 months and rate of hydrolysis of the five formulas calculated from the slope of first-order kinetic plots in order to select the most stable one.

Formula	Method of Assay	Remaining (90-110)%	$K40\mathring{C}$ $(X10^{-3})day^{-1}$
A	UV	90.3	0.81
B	UV	85	1. 3
C	UV	83	1. 5
D	UV	94.9	0.41
E	UV	98.6	0.16

Table-2 The Percent Remaining after 4 months and Degredation Rate Constant (K) Of Econazole nitrate in Formulas A, B, C, D and E at 40°C

The data indicate that minimum rate of hydrolysis of (EN) was achieved using 75% propylene glycol as a solvent (formula E) since it has the lowest rate constant ($0.16x0^{-3}day^{-1}$).

This may suggest that propylene glycol is the most suitable vehicle for the formulation of (EN) topical solution. It acts as a solvent for many dermatological drug and ensure homogenous dispersion of drugs used in low concentration [10].

Stability study

Stability Study in normal and accelerated conditions was carried out [11]. Table-3- shows the percent remaining of (EN) at room temperature for formula E after storage.

Formula E Storage time	Appearance	Method of Assay	% Remaining (90-110)%
Zero time	Clear liquid	UV	100.1
2 months	=	UV	100
4 months	=	UV	100.1
6 months	=	UV	99.0

Table-3 The percent Remaining of Econazole Nitrate (Formula E) At Room Temperature after 4 months.

The effect of temperature on the rate of hydrolysis of (EN) was also studied using different accelerated temperatures (40,45and 50°C) for 120 days.

The degradation of (EN) in formula (E) follows a first-order kinetics, since straight lines were obtained when the logarithm of percent remaining of (EN) was plotted versus time as shown in fig.3.

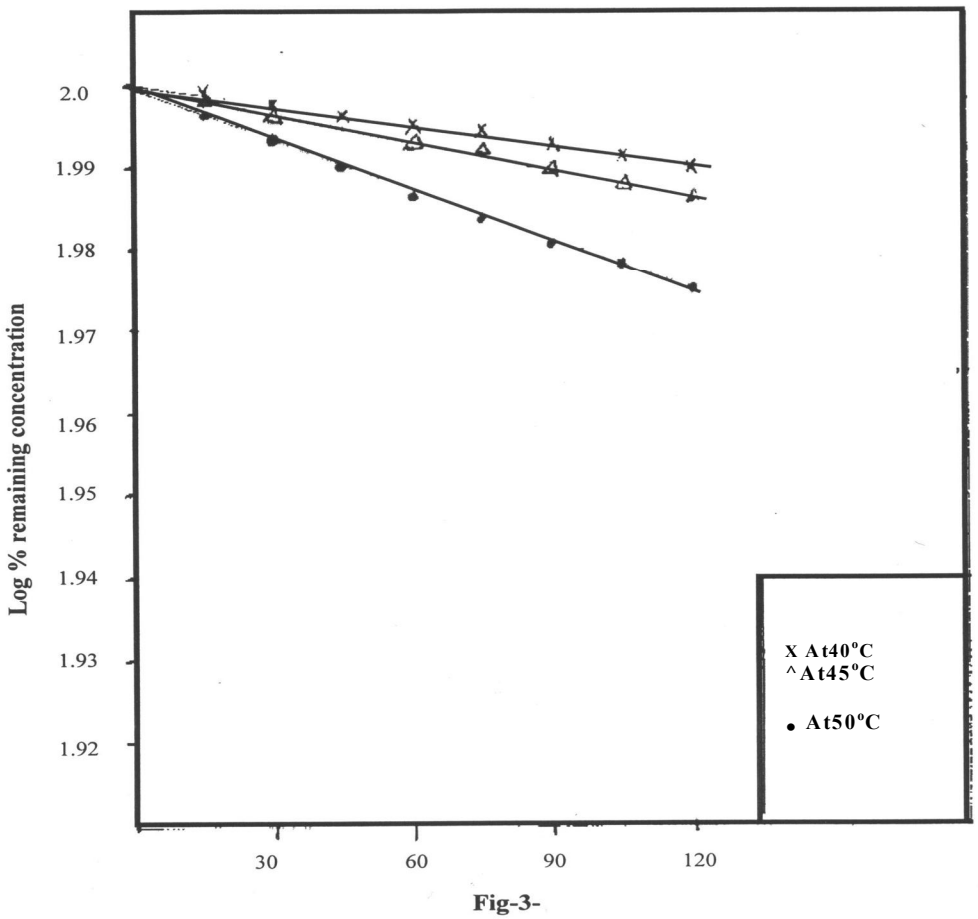


Fig-3-

Degradation curve of Econozole nitrate at different temperatures (formula E)

The degradation rate constants (K). at (40, 45 and 50°C) were calculated from the slopes of lines as illustrated in table 4.

Temp	K $X10^{-3}$ day^{-1}
40°c	0.200
45°c	0.268
50°c	0.420
25°c	0.9

Table-4 Degradation Rate Constants (K) of Econazole Nitrate in Formula E at Different temperatures

To determine the expiration date (t10%) at 25°C, Arrhenius plot [12] was constructed to predict the degradation rate constant at 25°C (k_{25}) for formula E as shown in Fig.4.

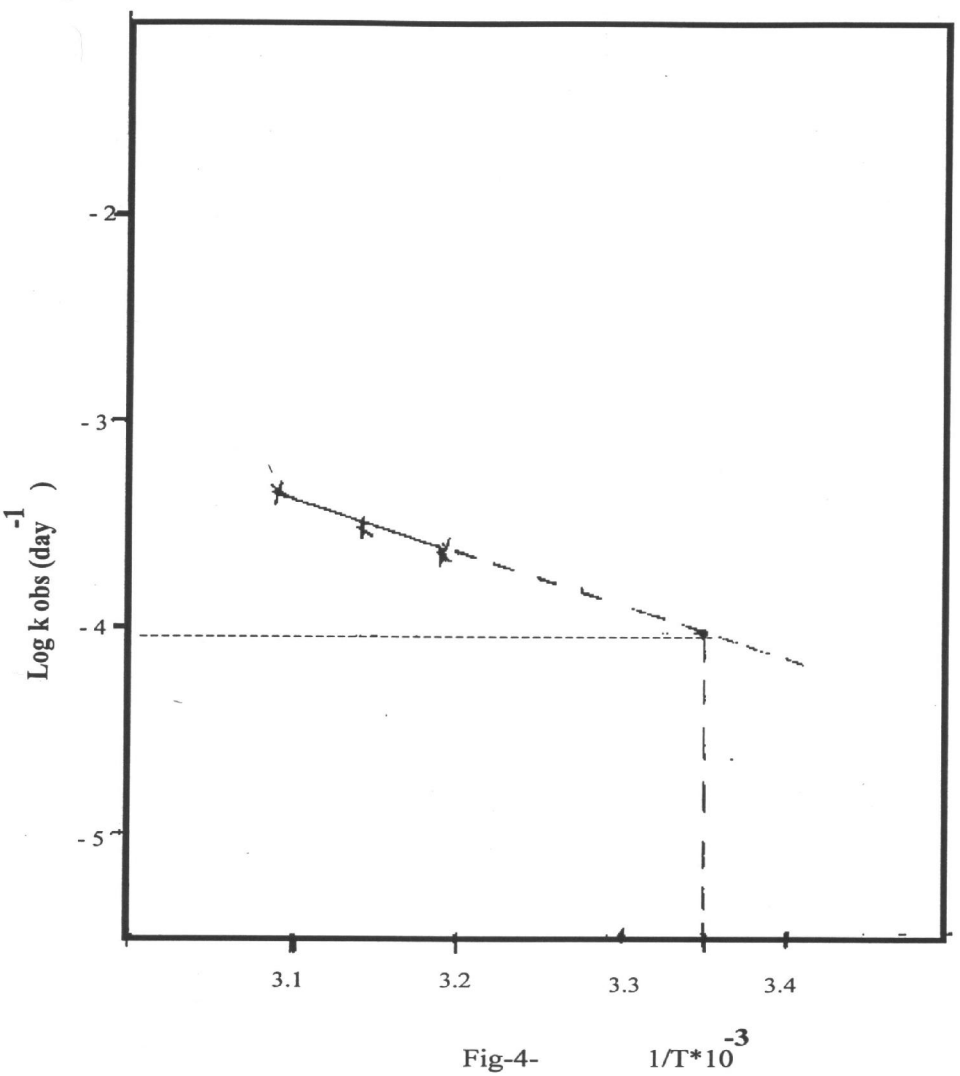


Fig-4- Arrhenius plot for estimation of the expiration date (t 10%) of Econozole nitrate at 25c (formula E)

Since the degradation of drug follows first-order kinetics, therefore, the expiration date can be calculated using the following equation.

$t_{10\%}= 0.104/ K_{25}$

It appears from the results that the drug in formula E. (Selected formula) has a $t_{10\%}$ value of about 3.15 years.

Effect of light:

The effect of light on hydrolysis of Econazole nitrate was studied by placing the selected formula (formula E) in clear and dark containers at room temperature for 2 months.

As shown in figure 5, there is a linear relation ship for logarithmic plot of the percent remaining of Econazole nitrate versus time when the drug was stored in clear and dark containers, indicating that the degradation of drug follows first order kinetics figure5.

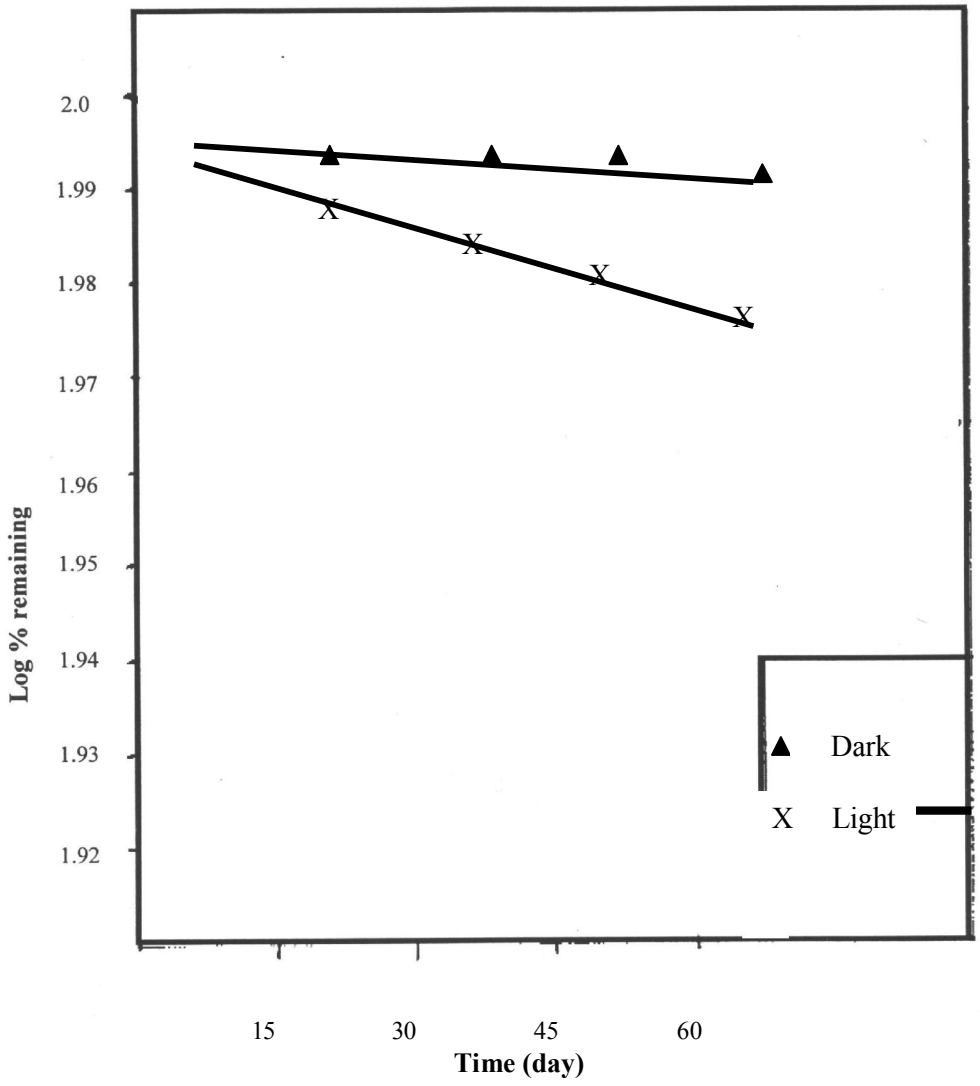


Fig- 5-
The effect of light on the rate of hydrolysis of Econazole Nitrate in formula E at room temperature.

The results indicate that the percent remaining of drug was 95.91% when exposed to light at room temperature after 2 months. This is in consistent with the reference which state that EN is known to be affected by light and should be stored in a well closed container protected from light[13].

On the other hand, the samples which were stored in dark containers showed no detectable change in the percent remaining when exposed to the same condition

Effect of container

Table 5 shows the percent remaining of EN when placed in glass and plastic container at different conditions (room temperature, 40°C) ,for 4 months. The result showed that no detectable change in percent remaining especially when stored at room temperature.

Formula E	%Remaining	K 40°C ($X10^{-3}$)day^{-1}
Glass container	97.7	0.20
Plastic container	97.8	0.20

Table-5 The effect of containers on the stability of Econazole nitrate at 40°C after 4 months .

Quality control

The selected formula (formula E) was subjected to many types of product control test for topical solution

these tests include appearance of solution , drug content ,pH, and density. The prepared product passed all these tests successfully as shown in table 6.

Type of Test	Results	
	Formula E	Requirement
Drug content	100.1%	90 –110 %
PH	3.5 – 4.5	-----
Clarity of Solution	Clear colorless Solution	Clear colorless solution
Density(20 ºC)	0.975 – 0.995 g/ml	0.995 g/ml

Table-6 Results of the Quality Control Test for the selected Formula (formula E) of Econazole Nitrate

This indicates that the method of preparation is efficient and effective.

CONCLUSIONS

(EN) is a novel antimycotic preparation for topical use. After conducting this investigation on Econazole nitrate as a solution dosage form for topical application, one can conclude the followings:

1. formula E consider the most stable formula since log percent remaining for this formula was 1.995(99%) after incubation in 40ºc for 4 months

2. propylene glycol is an excellent vehicles used to increase the solubility of medicament, it also act as a solvent for EN to ensure homogeneous dispersal of drug used in low concentration[10,14].
3. It was noticed that there was a significant effect of light on degradation of Econazole nitrate

4. Econazole nitrate show a good linearity of UV response which is simple and fast procedure for determination of Econazole nitrate in the drug substance based on UV.

5. The use of plastic or glass container for Econazole nitrate drug had no effect since the same percent remaining were seen when drug solution was stored the drug at different temperature.

6. The product passed all the quality control tests successfully which indicate the efficiency of the method of preparation.

7. The expiration date of EN drug was found to be 3.15 years.

8. Further study will be done to formulate Econazole nitrate as a topical cream with triamcenolone

REFERENCES:

1- British Pharmacopoeia, P.245, 1998.
2- Clark's, isolation and identification of drug, 2th. Ed, the pharmaceutical press, London; P.579, 1986.
3- Physician Desk References 1999.
4- Scholar-M; Prediel-H; Korting –HC, Light and Electron Microscopic finding in amodel of Human Coetaneous Candidacies, Journal of Drug Targeting, 1999; 6(5) 361 – 372.
5- Sastry, B.S; Rao, J.V, spectrophotometric method for determining of Econazole nitrate, Indian Drug, 1992; 29 (Mar) ,277,280.
6- The Arab Good Manufacturing Practice guilders "GMP" 1995 by the Arab Union of the Manufacturers of pharmaceutical and Medical Appliances (AUPAM).
7- Guidance for industry (Q.B photo stability testing of new drug substances and products).November 1999.
8- Marcie, K.N., "Utilization of Nicotinamide as a complexing agent in the formulation of diazepam oral solution," PhD. Thesies Baghdad University, college of pharmacy, 1996.
9- Remingtin's pharmaceutical science 7th. Ed. Mark publishing company, Easton, Pennsylvania. chap.80,87, 1985.
10- Carter, S.J, the ointment, pastes and jellies, chap.13 in "dispensing for pharmaceutical students "12th ed. Churchill Livingstone 1987.
11- Wolfgang Grim, Extension of the International Conference on Harmonization Tripartite Guideline for Stability Testing of New Drug Substance and Product to Countries of Climatic, Zones III and IV. Drug development and industrial pharmacy, 1998; 24(4), 313 – 325.
12- Lachman, L., liberman, H.A. and. Change J.L., "the theory and practice of industrial pharmacy" 3rd ,er., Lea and Febiger Publishing Company, Philadelphia (1986).
13- The United States Pharmacopoeia, VOL 32,p.1189.
14- Ford, J.L., parenteral product, chap. 21in" pharmaceutics, the science of dosage form design, by Alton ,N.E, Churchill Livingstore, 1988.