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Formulation and evaluation of itraconazole via liquid crystal for topical delivery system

Demiana I. Nesseem *

National Organization for Drug Control & Research, 51 Wezaret El Zeraa St., Agouza, Cairo, Egypt

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Abstract

Liquid crystal systems are used to tailor drug delivery from topical delivery system. Ternary polyoxyethylene [21] stearyl ether/ oil and water form liquid crystalline system cream, which has a potential as dosage form for 1% itraconazole as topical dermal drug delivery. Evaluation of the suggested formula was performed for the best physical performance, the compatibility of the components of lyotropic liquid crystal with itraconazole was conducted through polarized light microscopy, differential scanning calorimeter, thermogravimetric analysis and viscosity measurements. Fourier transform infrared spectroscopy has been studied. Furthermore, *in vitro* antimycotic inhibitory activity of 1% itraconazole from liquid crystal, was conducted using agar-cup method and *Candida albicans* as a test organism. The pH value of the cream was found to be 7.1, while when the drug was incorporated in the cream, the pH value was 6.7. The formula was examined under polarized microscope at $20\times$ magnification and the birefringence that is characteristic of concentric lamellar liquid crystal was observed around the oil globules. Differential scanning calorimeter of itraconazole cream showed higher transition peak temperature at 120°C for the hydrophilic gel phases. Fourier transform infrared spectroscopy revealed that there was no complex or any interaction between the surfactant and the drug. The microbial studies revealed that our formula had the highest zone of inhibition. The average $\pm$ SD inhibition zone values of the test, control I and control II are 30.4 ± 1.14, 19.6 ± 1.14 and 14.8 ± 0.83 mm, respectively. It was found that the test was significantly different from control I and control II, $P = 5.33 \times 10^{-6}$, 8.92×10^{-5}, respectively, so it may be concluded that incorporation of the drug in liquid crystal increased its antimicotic activity against *Candida albicans*.

Keywords: Itraconazole; Liquid crystals topical DSC TGA

1. Introduction

The design of new forms that increases the effectiveness of existing drugs is one of new trends observed in pharmaceutical technology in recent years [1]. In this context, liquid crystals (L.C.) have aroused great interest as novel dosage forms,

* Tel.: + 20-202-7603897; fax: + 20-202-7603897.
E-mail address: demiananesseem@hotmail.com (D.I. Nesseem).

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due to their considerable solubilizing capability for both oil and water soluble compounds [2].The total therapeutic effect of percutaneous preparations depends not only on the action of the drug itself, but also on other factors related to the structure of the vehicle [3,4]. Liquid crystal systems L.C. are used to tailor drug delivery from topical delivery system. They have been found to be a part of the microstructure of a variety of preparations suitable for topical use. Lameller L.C. have been proposed as semisolid vehicles for topical administration of drugs [5]. Liquid crystalline structures cover a wide range from lameller to hexagonal to cubic [6]. They exhibit birefringence under polarized light and the flow properties of viscous liquids [7,8]. Kislalioglu and Friberg reported that the liquid crystalline phase was formed toward the oil phase, where the spontaneuos emulsification took place toward the aqueous phase [9]. The liquid crystalline phase surrounding the droplets is highly viscous, and has an ordered structure and a low interfacial tension. These phases have also a tendency to form a semisolid network extending through the continuous phase of the dispersion. The network slows the movement of the droplets and exhibits a viscoelastic behavior [10]. Today, liquid crystals incorporated in microcapsules made of gelatin which rupture on topical application are available. Lyotropic liquid crystals are also incorporated in a special dermatological formulations that exhibit hydrating properties. Most of all, liquid crystals are used as excipients to protect sensitive substances (vitamins, antioxidants, oils). They may enhance the stability of creams while creating a rheological barrier resulting in an increase in the viscosity and a decrease in a coalesence by modification of Van der Waals forces [11]. The present work is a trial to apply theory and practice of liquid-crystals in pharmaceutical topical delivery systems. So the aim of this work is to formulate and evaluate an antifungal agent with topical therapeutic activity in pharmaceutically acceptable nonionic surfactant system to enhance its cutaneous penetration. As a model drug, itraconazole [12] was chosen as antifungal agent. It has been effective in dermatophytoses [13] (tinea cruris, pedis, corporis). Ternary water/ nonionic surfactant/ oil formulation were used to formulate 1% itraconazole. Polyoxyethylene [21] stearyl ether was chosen as a surfactant. The oil selected was silicon oil which is commonly used in dermatological pharmaceutical formulations.

2. Experimental

2.1. Apparatus

1. pH meter CG 820 Schott- Gerate, W.Germany.
2. Electric water bath, Sartorius, Gottingen, W. Germany.
3. Polarized light microscope, Nikon FX-35 Japan.
4. Differential scanning calorimeter, Shimadzu, model DSC-50.
5. Thermogravimetric analyzer (TGA), Shimadzu, model TGA-50H.
6. FTIR 1650 Perkin Elmer Spectrophotometer.
7. Digital viscometer Brookfield LV-4, Brookfield Engineering Lab. Inc. USA.
8. Cone and plate viscometer, model DV-III Brookfield Engineering Lab. Inc. USA.

2.2. Materials

1. Itraconazole was generously supplied by Janssen pharmaceutica INC.
2. Cetostearyl alcohol, Henkel, Germany.
3. Polyoxyethylene (21) stearyl ether, ICI, Chemicals & Polymers, USA.
4. Hydroxyethyl cellulose gel, silicon oil and Liquid paraffin, Exxon, USA.
5. Cetyl alcohol, Henkel, Germany.
6. Glyceryl monostearate, ICI, USA.
7. Sabouraud dextrose agar, Oxoid;England.

2.3. Methods

2.3.1. Itraconazole liquid crystals preparation

2.3.1.1. Formula (a) (test). A liquid crystalline emollient cream was prepared containing polyoxyethylene [21] stearyl ether as surfactant, ce-

tostearyl alcohol as cosurfactant, silicon as an oil phase (A). The aqueous phase (B) contains propylene glycol, preservative and water. The oil phase (A) was melted at 70°C on water bath, 1% itraconazole was added and mixed well. The aqueous phase was heated to the same temperature. The oil phase was added dropwise to the aqueous phase while mixing at high speed using blender and then cooled to room temperature. The system was then stored for about 48 h until equilibrium was reached before subjected to evaluation.

2.3.1.2. Formula (b) as control I (CI). One percent itraconazole was incorporated in hydroxyethyl cellulose gel.

2.3.1.3. Formula (c) as control II (CII). Containing glyceryl monostearate (GMS) cream. GMS cream was chosen as it contains propylene glycol as in formula (A), allowing valid comparison as moisturizer [14]. This cream was prepared, containing glycerylmonostearate, stearyl alcohol, cetyl alcohol and liquid paraffin as an oil phase (a). The aqueous phase (B) contains propylene glycol, preservative and water. This cream was prepared by heating the oil phase (A) containing 1% itraconazole and the aqueous phase (B) separately to 75°C. Then, the oil phase was added to the aqueous phase dropwise whilst blending until cool to room temperature.

2.3.2. Physical investigation

The prepared formulae were subjected to the following evaluations:

2.3.2.1. Organoleptic characteristics. Each cream was tested for color, odor, texture, phase separation or bleeding as well as the feel upon application (stiffness, grittness, greasiness and tackiness) once the preparation is on the skin and also after two minutes of application.

2.3.2.2. Homogeneity test. A small quantity of each cream is pressed between the thumb and the index finger and the consistency of the cream is noticed (whether homogeneous or not) and if there is any coarse particles appeared or detached on fingers. Also, the homogeneity can be detected when a small quantity of the cream is rubbed on the skin of the back of the hand.

2.3.2.3. Sensitivity test. A drop of diluted suspension of the tested cream (1:1) and another drop of saline (control) were put on two corresponding spots of the arms of three human volunteers. After ten minutes the patch was investigated for any erythema, wheel or any allergic reaction.

2.3.3. Determination of pH

The pH of cream was determined using a pH meter. On the other hand, a solution containing 1 g of the cream in 30 ml of the neutralized distilled water (pH 7) was prepared and the pH was measured.

2.3.4. Examination under polarized microscope

Investigation of the samples were done by examination under polarized light microscopy, in order to study the texture of the anisotropic phases. A small quantity of the sample was placed on a clean glass slide. The existence of birefringence was verified by observation under crossed polars employing magnification of $20\times$. Photomicrographs of these samples were taken.

2.3.5. Differential scanning calorimetry measurements

Differential scanning calorimetry (DSC) measurements were performed on the drug, as well as itraconazole cream using Shimadzu, DSC-50 with cell mode aluminum seal. The flow rate employed was 30 ml/min in the temperature range (0–200°C). The weight of the sample was 1–3 mg and the heating rate was 10°C/min.

2.3.6. Thermogravimetric analysis

Thermogravimetric analysis (TGA) of cream without drug, as well as 1% itraconazole cream was performed using Shimadzu TGA-50 H. The flow rate employed was 30 ml/min in the temperature range (0–150°C). The weight of the sample was about 4 mg and the heating rate was 5°C/min TGA of the samples were repeated by changing the heating rate to 2°C/min to achieve better resolution.

2.3.7. FTIR analysis

The IR spectra of the drug, cream without drug, the physical mixtures of the drug-cream (1:1), as well as 1% drug in cream were recorded using infrared spectrophotometer. The samples were prepared by elaborating compressed KBr disks. The IR analysis was performed with spectra measures over the frequency range 500–4 000 cm^{-1}.

2.3.8. Viscosity measurements

The performance of dermatological products depends to a great extent on their rheological behavior. Itraconazole creams being liquid crystals were thought to have an intermediate behavior between liquids and solids. Therefore, rheological study was performed on chosen samples by the conventional digital viscometer Brookfield LV-4, using concentric cylinder spindle 4, then reinvestigated using cone and plate viscometer, spindle 40, to elucidate its rheogram after 1 week of the preparation, 1 month and after 3 months.

2.3.9. In vitro antimycotic study

Agar-cup diffusion method was adopted [15]. These tests were carried out using cultures of *Candida albicans* ATCC 10231 (0.1%), USA in Sabouraud- dextrose agar, Oxoid, England. Fifteen milliliters of the media with 24 h-subculture *C.albicans* was distributed in each petri-dish (10 cm-diameter). On solidification, 1 cm holes were made and filled with an accurately weighed 0.25 mg cream. In each plate, three holes for the tested formula,1% itraconazole in liquid crystal cream (T), and compared it with two controls, one containing 1% drug in hydroxyethyl cellulose gel as control I (CI) and the other with 1% drug in GMS cream as control II (CII).

3. Results and discussions

3.1. Physical investigation

All formulae were examined 2 days after preparation for performance as regarding the physical characters. It appeared white, opaque, smooth, semifluid, homogeneous with no bleeding or phase separation. The cream was free from any gritty particles and it was neither greasy nor tacky and spread easily over the skin. After 2 min of application, the skin did not look greasy or tacky, and the cream was felt to penetrate the skin with soothing effect and it was washable with water. On the other hand GMS cream, as a reference, appeared white, thick, homogeneous cream. The cream was free from any gritty particles but it was difficult to spread over the skin and did not penetrate through easily. After 2 min of application, the cream was not easily washable with water. All tested creams were subjected to sensitivity test, and it was found that no erythema, pruritis or allergic reaction had occurred when applied to the skin in all cases. The pH value of cream was found to be 7.1, while when the drug was incorporated in the cream, the pH value was 6.7.

3.2. Examination under polarized microscope

Freshly prepared and stored samples of the cream containing 1% drug was investigated under polarized light microscopy. Fig. 1a. shows a typical polarized light micrograph of liquid crystals. The birefringence that is characteristic of concentric lamellar liquid crystal was observed around the oil globules. The oil is uniformly dispersed with a definitive cross similar to those described as Mathesian crosses [16], indicating a lamellar structure.This lamellar structure is not disappeared after storing the sample for 1 month, and condensed globules with variable shapes and sizes were visible as shown in Fig. 1b.

3.3. Differential scanning calorimetry measurements

Itraconazole creams with crystalline gel structure are supposed to contain lamellar gel phase entrapping water, in addition to the bulk water phase and dispersed oil phase. A dynamic equilibrium is maintained between the water interlamellarly inserted into the hydrophilic gel phase and bulk water phase. The latter is mainly fixed mechanically by the hydrophilic gel phase. A dif-

ferentiation between interlamellarly fixed water and bulk water is possible by means of a differential scanning calorimetry (DSC) as there is sufficient high difference in the free energy between the two types of water. The thermal analysis of the drug, as well as the lamellar structure of the drug incorporated in liquid crystal was performed using DSC. In Fig. 2a itraconazole shows a single sharp endothermic peak at 167.3°C with total enthalpy changes $\Delta H = 66.3$ mJ/mg. Fig. 2b where the calorimetric scan of 1% drug in liquid crystal, the main transition peaks temperature to be at 81.77, 103.48 and 119.13°C and the main transition enthalpy changes (ΔH) are 30.4, 180.0 and 9.6 J/gm respectively. At 81.77°C melting of solids cream was observed. Mainly the bulk water evaporates at 103°C. At 119.13°C the interlamellarly fixed water was released.

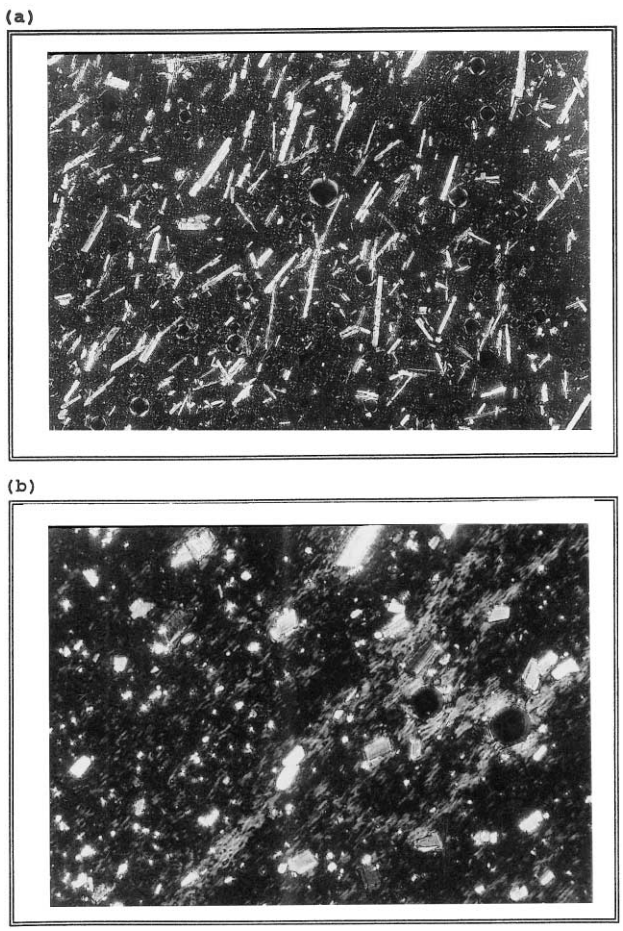

Fig. 1. A typical polarized light photomicrograph of itraconazole cream (a) 1 week after preparation and (b) after 1 month storage at room temperature.

3.4. Thermogravimetric analysis (TGA)

The TG curves represents the weight loss of the sample as a function of temperature [17]. The scale for percent weight loss is on the left side. The DTG curve represents the rate of evaporation of incorporated water. The scale of evaporation rate is on the right side. When the heating rate was 2°C /min in the temperature range (0–100°C), following the DTG-curve of cream without drug, the evaporation rate of the bulk water phase increases until 35.6°C is reached with 8.7 and 5% loss of the total weight of the cream, subsequently the water evaporation rate decreases Fig. 3a. At a temperature of 40°C the TG-curve shows a point of inflection corresponding to a minimum in the DTG-curve. The evaporation rate increases very strongly due to the melting of the hydrophilic gel till it reaches a plateau at 65°C with about 51.5% loss of the total weight of the cream, the total% weight loss was about 74.9%. Fig. 3b shows the TG curve of 1% drug in cream at temperature range 0–150°C with heating rate of 2°C/min. At a temperature below 50°C the bulk water was evaporated with about 16.5% loss of the total weight of the cream, and thereafter the water fixed between the lamellae begin to evaporate with about 36.5 and 37% loss of the total weight of the cream, the total percent weight loss about 74.7%. According to the thermogravemetric curves and their derivative curves of the cream without drug, When the heating rate was 5°C/min. and the temperature range was (0–120°C) Fig. 3c. The bulk water starts to evaporate below 50°C. At 57.7°C the cetostearyl alcohol melts. In the temperature range of 58–65.8°C, the evaporated bulk water is superceded by the evaporation of semihydrated water from cetostearyl alcohol and by the evaporation of water which is entrapped mechanically in the cetostearyl alcohol gel network. After melting of the hydrophilic gel phase at 65.8°C, the weight loss is governed by the evaporation of the interlamellary fixed water.

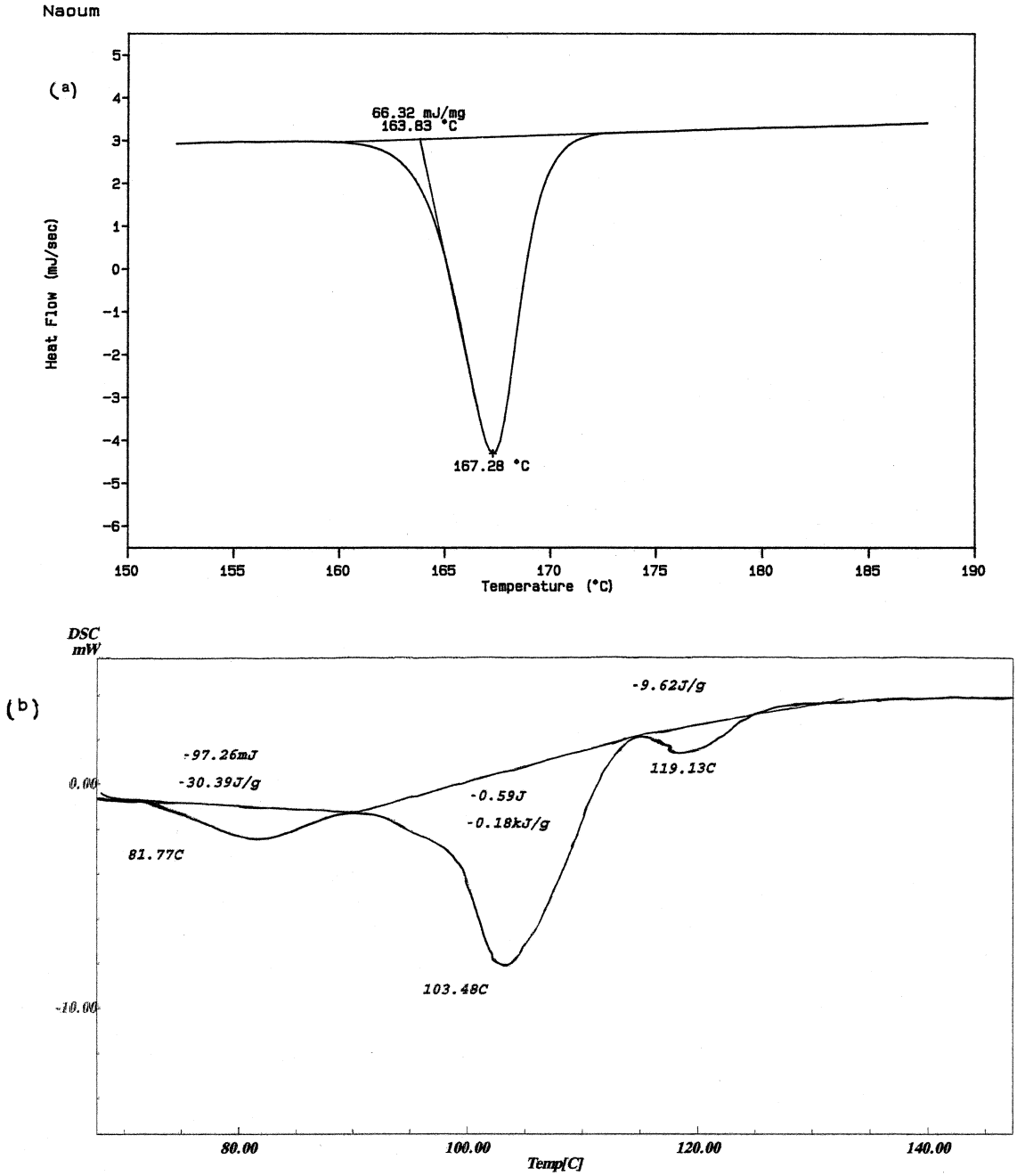

Fig. 2. Differential scanning calorimetry-heating curves of (a) itraconazole (b) 1% drug in liquid crystal.

In the temperature interval of 84–100°C the inter-lamellary fixed hydration water is released. Fig. 3d shows the TG curve of 1% drug in cream at temperature range 0–100°C with heating rate of 5°C/min. At a temperature below 50°C the bulk water was evaporated with about 31.8% loss of the total weight of the cream, and thereafter the water fixed between the lamellae begin to evapo-

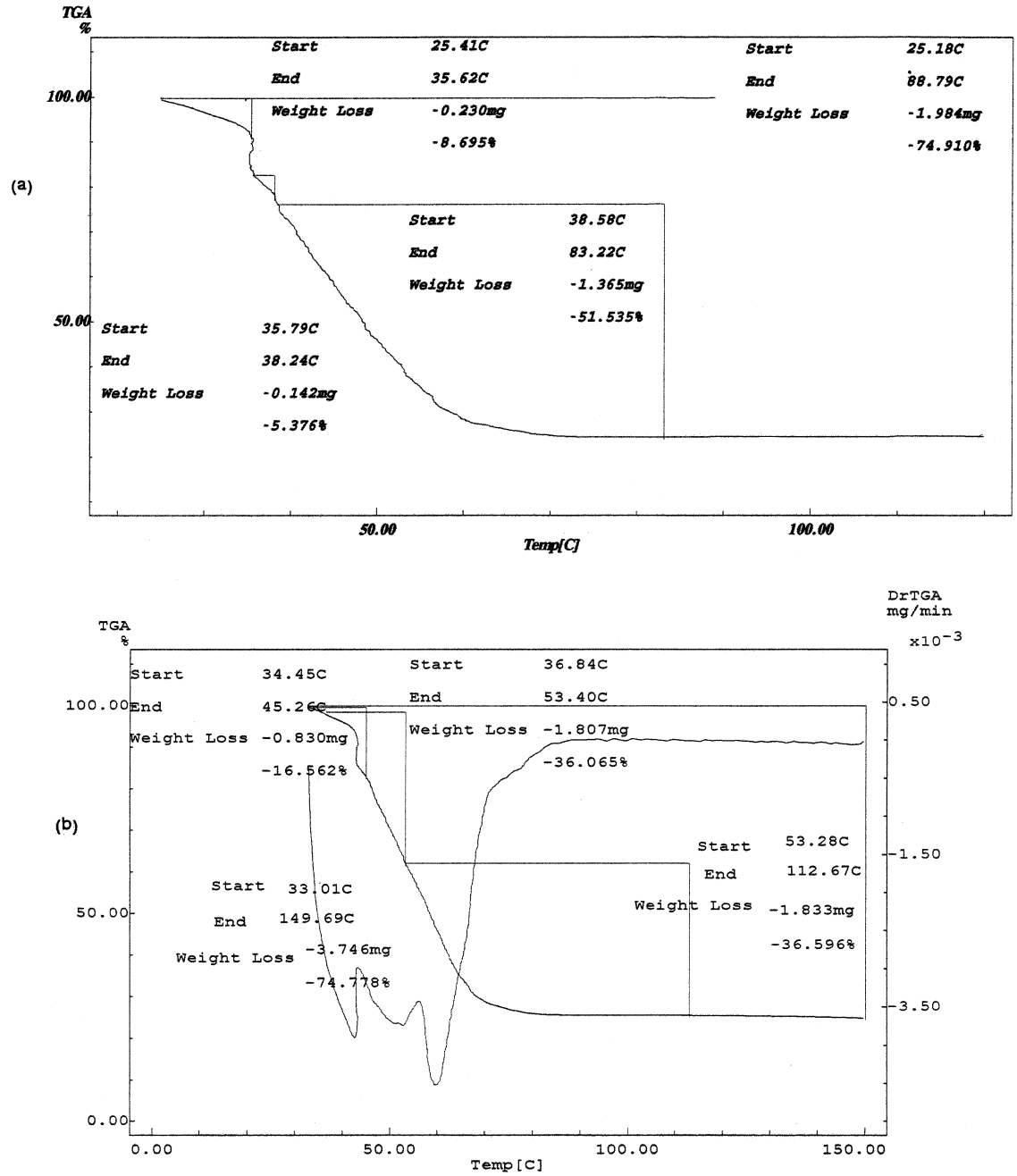

Fig. 3. Thermogravimetric curve measurements and their derivative curves corresponding to (a) Thermogravimetric curve of cream at heating rate 2°C/min. (b) Thermogravimetric curve of cream containing itraconazole at heating rate 2°C/min. (c) Thermogravimetric curve of cream at heating rate 5°C/min. (d) Thermogravimetric curve of cream containing 1% itraconazole at heating rate 5°C/min.

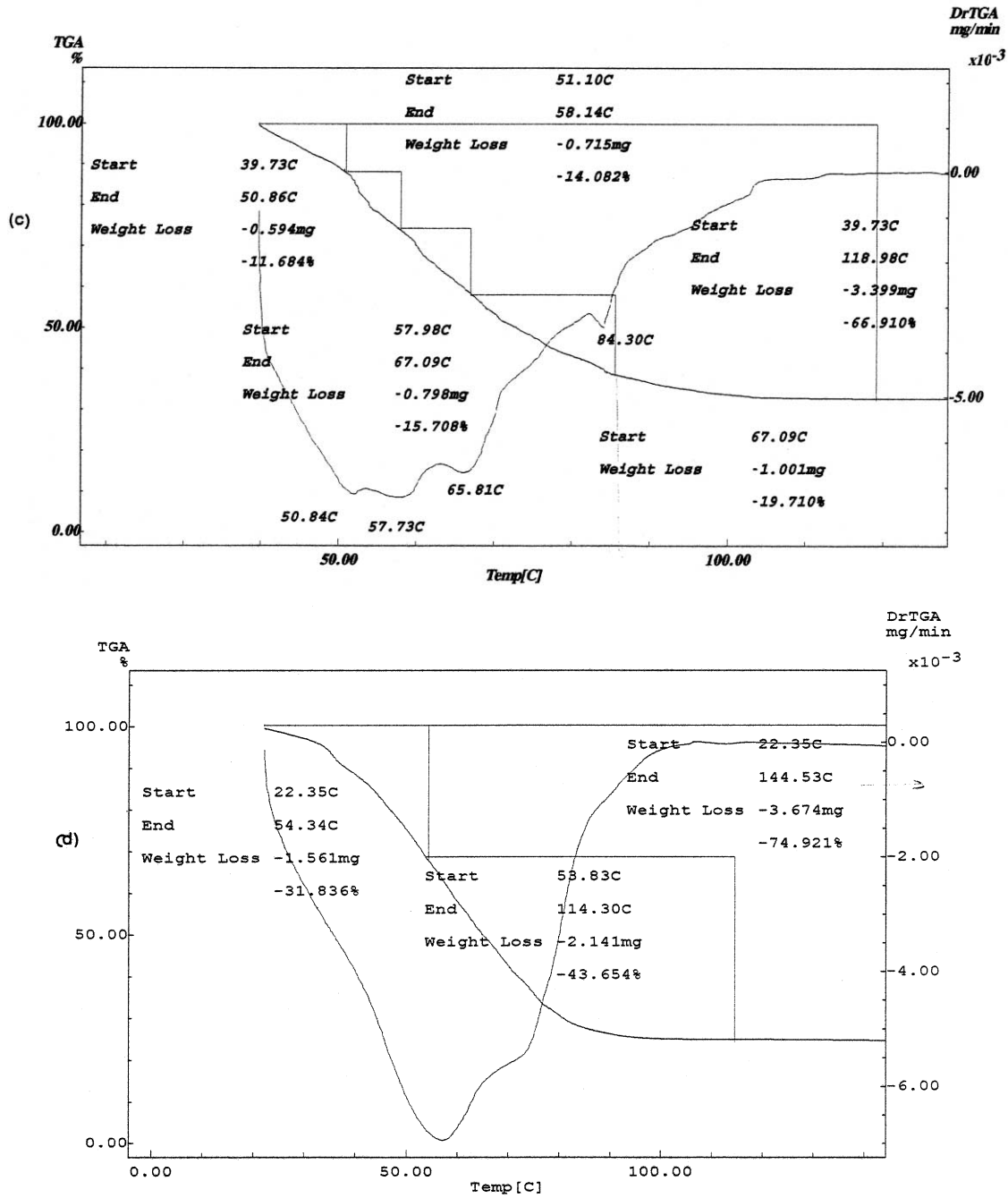

Fig. 3. (*Continued*)

rate with about 43.7% loss of the total weight of the cream and the total percent weight loss about 74.9. It can be inferred that the ratio of interlamellary fixed water and bulk water is an important criterion for the properties of such system.

3.5. FTIR analysis

Infrared spectroscopy have been studied to determine the suitability of the selected carriers for itraconazole as antifungal topical formulation. Fig. 4. shows the FTIR of the samples under study. The characteristic peaks of itraconazole occurred at 3381, 3126, 3069, 2962, 1697, 1510, 1450, and 418 cm^{-1} Fig. 4a. The absorption of the NH_2 groups, are located in the bands at 3381, 3126, 3069, cm^{-1}. The first band is assigned to be due to stretching vibrations of the free NH_2 group in the molecule of the pure drug. The rest of the bands at 3126, 3069 cm^{-1} are caused by the amino-group. The wave numbers observed at 1609 and 1425 may be assigned to the C = N and C-N bonds respectively and the sharp peak occurred at 1697 is due to C = O of the drug. As can be seen in the spectral pattern of the physical mixtures of the drug-cream (1:1), it corresponds simply to the position of the I.R. spectra of the two components as shown in Fig. 4b, that revealed no changes were observed as all the functional groups of the drug and cream still showed their bands in the spectra. It should be noted that the cream contain high percent of water, which is characterized by the band at 3423 cm^{-1} as shown in Fig. 4c. However in the 1% drug incorporated in the cream, it is appreciated the almost total smoothing of the band situated in its position Fig. 4d. Therefore, it is apparent that no interaction had been occurred, as all the functional groups still showed their bands in the spectra.

3.6. Viscosity measurements

The rheology of itraconazole cream was measured by concentric cylinder Brookfield viscometer where the viscosity and the yield value were calculated. The yield value is the minimum force per unit area required to initiate flow of the fluid

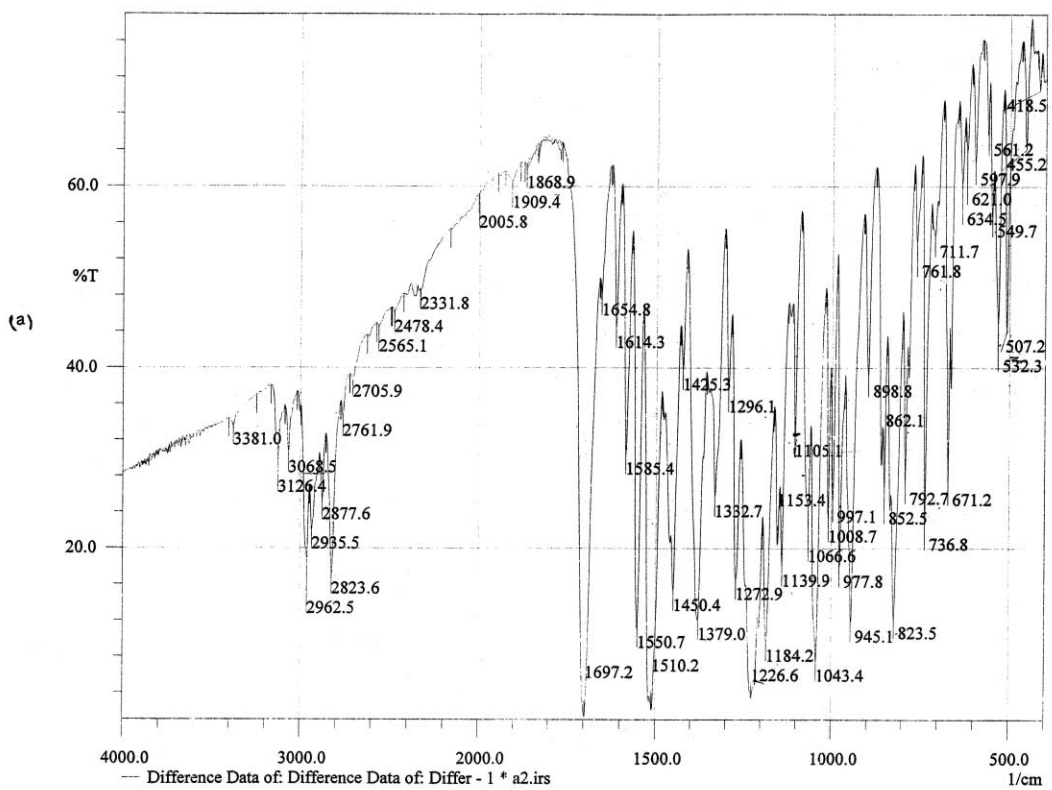

Fig. 4. FTIR spectra corresponding to (a) drug; (b) physical mixture 1:1 of drug and cream; (c) cream and (d) 1% drug in cream.

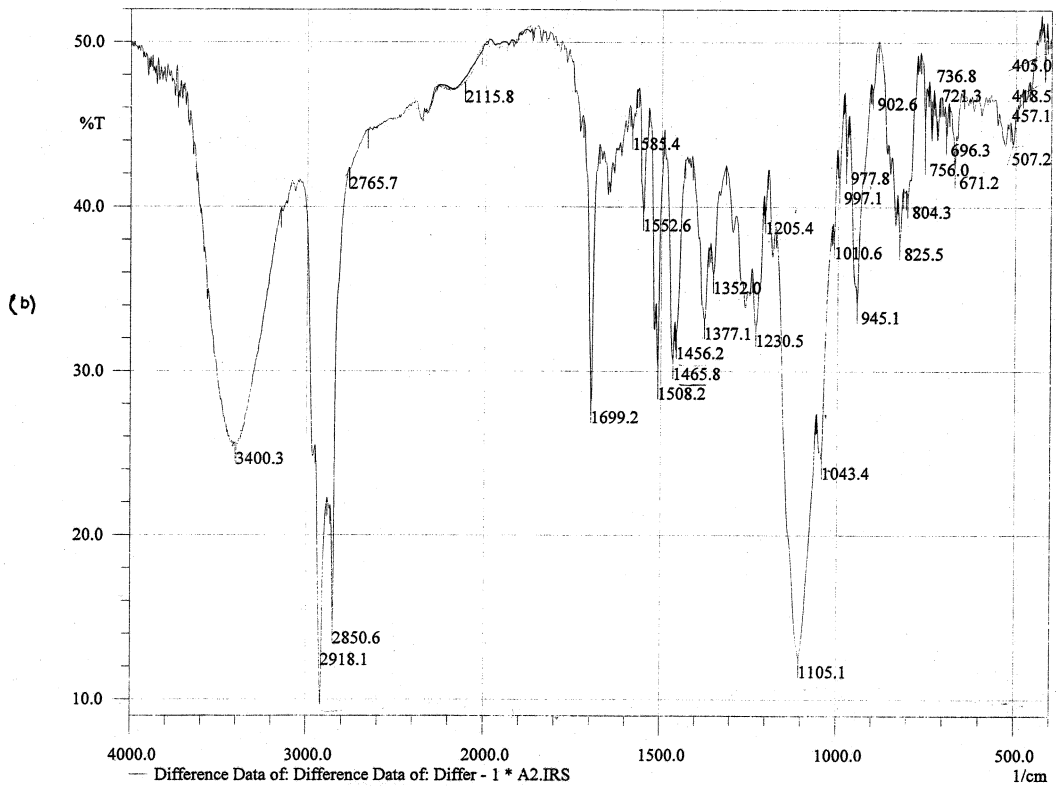

Fig. 4. (*Continued*)

and was calculated using the following formula [18]:

$$\text{Yield value (dynes/cm}^2) = 0.12\ (V_6 - V_{12})$$

Where V_6 and V_{12} are Brookfield viscosity at 6 and 12 r.p.m respectively. The effect of storage time on the viscosity of the cream was studied by storing the cream for variable periods of 1 week, 1 and 2 months under ambient conditions and the viscosity was determined. At 25°C, after 1 week of the preparation the viscosity of itraconazole cream was 62 000 Cp. at 0.3 r.p.m and the yield value was 0.44 dynes/cm^2. For sample that was stored for 1 month, it showed an increase in viscosity, which was 94 000 Cp. with yield value 0.66 dynes/cm^2. On the other hand, sample that stored for 2 months, the corresponding value showed an increased in the viscosity to 127 000 Cp. and developed a very high yield value 1.74 dynes/cm^2, as shown in Table 1. It can be concluded that the liquid crystalline system of the tested itraconazole cream requires long time to attain equilibrium between bulk and fixed water [19]. This can be attributed to the fact that the samples stored for 2 months has the highest yield value and only under high shearing stress it flows. To confirm such behavior, the rheogram of these creams were studied using cone and plate viscometer Fig. 5. The cream shows a plastic flow behavior, the up-curve does not coincide with the down-curve, indicating the presence of thixotropy, with a wide hysteresis loop [20].

3.7. In vitro antimycotic study

In vitro antimycotic inhibitory activity of 1% itraconazole from liquid crystal, hydroxyethyl cellulose gel as control I and GMS cream as control II were conducted using agar-cup method and *C. albicans* as a test organism. Inhibition zone values for the test and the two controls were presented

individually in Table 2 and Fig. 6. The average ± SD inhibition zone values of the test, control I and control II are 30.4 ± 1.14, 19.6 ± 1.14 and 14.8 ± 0.83 mm respectively. The inhibition zone values of the test were compared to control I and control II using two-tailed unpaired Student *t*-test. It was found that the test was significantly different from control I and control II, $P =$

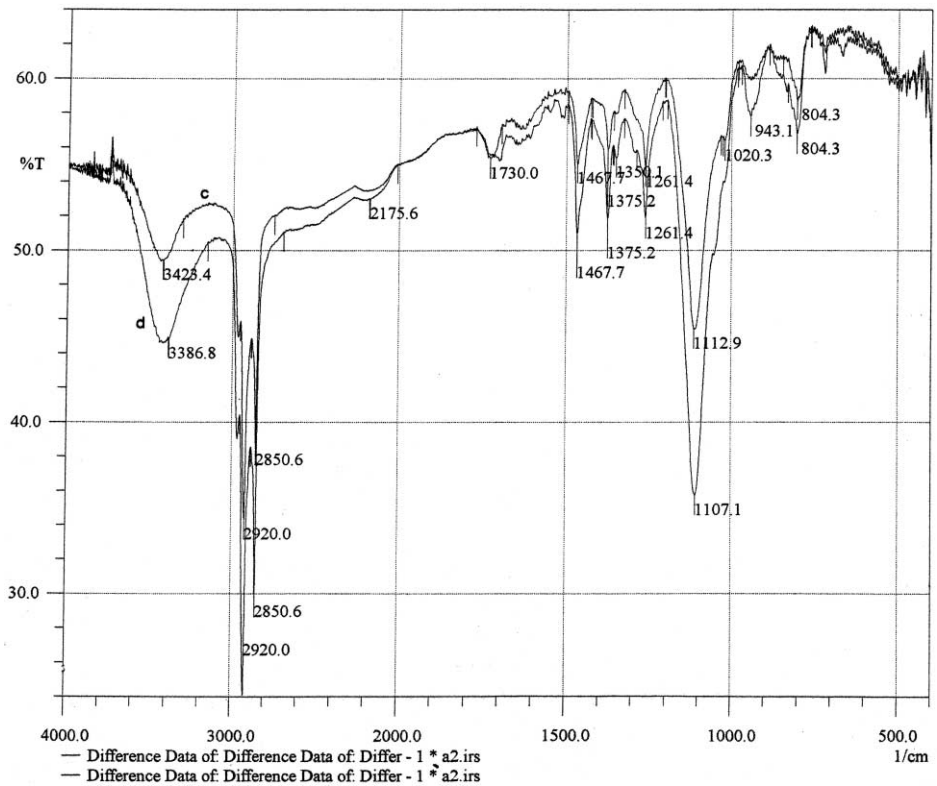

Fig. 4. (*Continued*)

Table 1
Determination of viscosity of itraconazole cream by concentric cylinder Brookfield viscometer (spindle)

RPM	(a) One week after preparation		(B) One month after preparation		(C) Two months after preparation	
	Viscosity upward (CP)	Viscosity downward (CP)	Viscosity upward (CP)	Viscosity downward (CP)	Viscosity upward (CP)	Viscosity downward (CP)
0.300	62.000	92.000	127.000	78.000	94.000	59.000
0.600	51.720	70.000	86.000	53.000	57.000	48.690
1.500	26.000	44.400	53.800	33.800	36.200	23.200
3.000	19.800	30.000	46.000	25.000	30.000	16.600
6.000	11.700	23.200	33.000	14.500	25.100	10.100
12.000	8.000	12.400	18.500	9.000	19.600	7.200
30.000	7.360	10.200	15.000	7.000	9.420	5.250
60.000	5.950	7.860	9.700	5.100	7.180	3.950

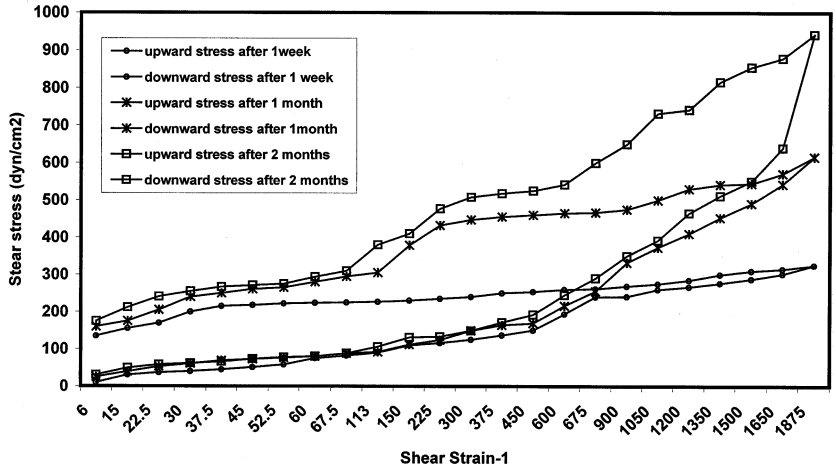

Fig. 5. Rheogram for 1% itraconazole liquid crystal cream (a) after 1 week (b) after 1 month (c) after 2 months.

Table 2
In vitro antimycotic activity of 1% itraconazole in different formulations using Agar-cup method and *C. albicans* as test organism

Formula	Inhibition zone diameter (mm)							
	Test 1	Test 2	Test3	Test 4	test 5	Mean	S.D.	CV%
Test (formula-a)	29	30	30	32	31	30.4	1.1401754	3.75058
control I (formula-b)	19	20	18	21	20	19.6	1.1401754	5.81722
control II (formula-c)	14	15	14	16	15	14.8	0.83666	5.65311

5.33×10^{-6}, 8.92×10^{-5} respectively. Although the inhibition zone values for control I and control II were lower than those of test, yet the controls were significantly different from each other, $P = 0.002192$. From the above mentioned results and by comparing the inhibition zone values of the test with the two controls, it is observed that our formula had the highest zone of inhibition. So it may be therefore concluded that the prepared formula exhibited better antimicrobial activity than both controls.

4. Conclusion

The results of the present study show that formulation of liquid crystals cream containing 0.1% itraconazole is successful as topical delivery system. The proposed formula a liquid crystalline emollient cream containing polyoxyethylene [21] stearyl ether as surfactant, cetostearyl alcohol as cosurfactant, silicon as an oil phase has advantages over other bases. Within the scope of development of topical liquid crystal formulations, we are maintaining its pharmacological properties while improving its tolerance to overcome its side effects and enhancing the efficacy of the existing drug The inhibition zone values of the liquid crystal (test) when compared to water soluble base (control I) and fatty soluble base (control II) using two-tailed unpaired Student t-test, was found to be that the test was significantly different from control I and control II, $P = 5.33 \times 10^{-6}$, 8.92×10^{-5} respectively.

It may be therefore concluded that incorporation of the drug in liquid crystal exhibited better antimycotic activity against candida albicans in comparison with control I and control II. The results confirmed the suitability of the ternary polyoxyethylene [21] stearyl ether/oil and water for itraconazole as antifungal topical formulation.

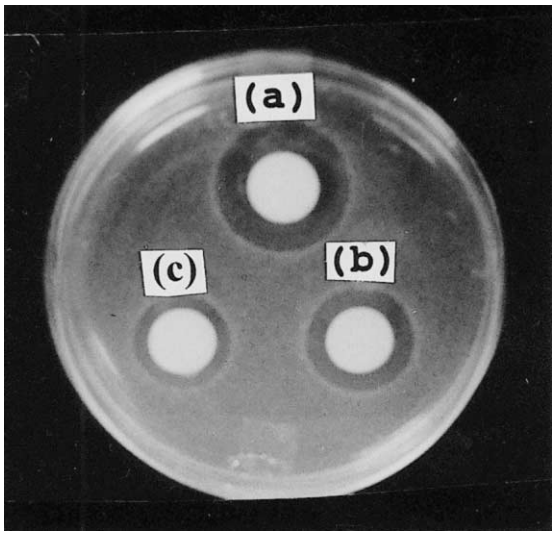

Fig. 6. Inhibition zone of 1% itraconazole cream (a) drug in liquid crystal, (b) drug in hydroxyethyl cellulose gel, and (c) drug in GMS cream.

These results suggested that the magnitude of compatability with surfactant is an important factor in determining the efficacy of itraconazole antifungal agents in skin. The total therapeutic effect of percutaneous preparations depends not only on the action of the drug itself, but also on other factors related to the structure of the vehicle.

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