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# LYOTROPIC LIQUID CRYSTALLINE SYSTEM FOR EFFECTIVE TOPICAL DELIVERY OF TOLNAFTATE

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## ABSTRACT

*The present investigation deals with the formulation, optimization and evaluation of liquid crystalline cream of Tolnaftate. Brij-78 used as a surfactant, Cetostearyl alcohol was used as a co-surfactant and Silicon oil as a oil phase. Liquid crystalline cream system, has a potential for efficient delivery of Tolnaftate (1%), as topical dermal drug delivery system. The liquid crystalline system enhance the diffusion of water insoluble drug Tolnaftate through the skin for effective result. Liquid crystals (LC) are substances that flow like liquids but maintain some of the ordered structure characteristics of crystalline solids. Based on the ways that LCs are generated, they can be classified into two types 1) Thermotropic LCs and 2) Lyotropic LCs. Incorporation of the drug in liquid crystal increased its antimycotic activity against different antifungal microorganisms. Used surfactant enhance the penetration of drug and also improve the solubility of drug. The objective of this study was to increase the diffusion coefficient of drug through the formulation, and also to improve the availability of drug at the site of action. The prepared liquid crystalline cream exhibited the expected, viscosity, drug content, pH, spreadability, in vitro drug release and in vitro antimycotic inhibitory activity. Liquid crystalline cream for tolnaftate was found to be stable cream. It was found to have better in vitro release profile characteristics, and in vitro antimycotic activity, it can be concluded that the formulation F5 has better potential of antimicrobial activity and to enhance the diffusion of drug through the cream.*

**Keywords:** Tolnaftate, LyotropicLiquid crystals, Brij 78, Silicon oil, Anisotropic

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## INTRODUCTION

The study of liquid crystals began in 1888 by an Austrian botanist named Friedrich Reinitzer.Liquid crystals are substances which exhibit a phase of matter possess properties between those of a conventional liquid and solid crystal. It is often called a mesomorphic state which is state of matter. In mesomorphic state the degree of molecular order is intermediate between the perfect three-dimensional, long-range positional and orientational order which are found in solid crystals and the absence of long-range order found in isotropic liquids, gases, and amorphous solids. It is also called as meso intermediate. A liquid crystals may flow like a liquid but have the molecules in the liquid arranges and/or oriented in a crystal like way. There are many different types of LC phases, which can be distinguished based on their different optical properties (such as birefrigrance).

When viewed under a microscope using a polarized light source, different liquid crystal phases will appear to have a distinct texture[5]. Each 'patch' in the texture correspond to a domain where the liquid crystal molecules are oriented in a different direction. Liquid crystals can be divided into thermotropic and lyotropic LCs. Thermotropic LCs exhibit a phase transition as temperature is changed, whereas lyotropic LCs exhibit phase transition as a function of concentration of the mesogen in a solvent (typically water) as well as temperature[1].

The distinguishing characteristic of the liquid crystalline state is the tendency of the molecules (mesogens) to point along a common axis, called the director (the molecular direction of preferred orientation in liquid crystalline mesophases). This is in contrast to molecules in the liquid phase, which have no intrinsic order. In the

solid state, molecules are highly ordered and have little translational freedom[1]. The characteristic orientational order of the liquid crystal state is between the traditional solid and liquid phases and this is the origin of the term mesogenic state.

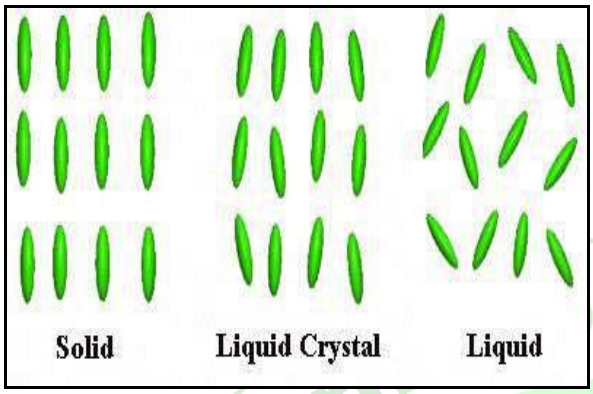


**Fig. 1. Average Alignment of the Molecules in Each Phase**

Most of the, liquid crystals are used as excipients to protect sensitive substances like vitamins, antioxidants, oils. They may enhance the stability of creams while creating a rheological barrier because of that viscosity is increases and coalescence decrease by modification of Van der Waals forces .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, Tolnaftate was chosen as antifungal agent. It has been effective in dermatophytoses (tinea cruris, pedis, corporis, athletes foot). Ternary water/ nonionic surfactant/ oil formulation were used to formulate 1% tolnaftate. Brij 78 was chosen as a surfactant. The oil selected was silicon oil which is commonly used in dermatological pharmaceutical formulations.

## MATERIAL AND METHOD

### Material:

Tolnaftate (Antifungal agent)and Brij 78 (surfactant) were obtained as a gift sample from Cox Research Center PVT LTD, Nashik, India, Cetostearyl alcohol (Cosurfactant), Silicon oil (Oil phase), Propylene glycol (Humectant)was used on the laboratory grade.

### Method:

A Lyotropic liquid crystalline emollient cream was prepared by containing Brij 78 as surfactant, cetostearyl alcohol as cosurfactant, silicon as an oil phase. The aqueous phase contains propylene glycol, preservative and water. The oil phase was melted at 70°C on water bath, 1% tolnaftate 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.

### Physical evidence:

The prepared formulation were subjected to physical evidence as follows:

### Organoleptic characteristic

The prepared cream was tested for colour, odour, texture and phase separation as well as feels upon application to observe stiffness, truthiness, freshness and tackiness of formulation[2].

### Homogeneity test

A small quantity of prepared cream was pressed between the thumb and index finger in order to notice the consistency of cream that any coarse particles being attached or detached on finger[2].

### 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].

### Occlusiveness

Prepared cream was taken in white glass vial and visually observed weather it is occlusive or not[2].

### Washability

A small quantity of cream was rubbed on the skin of back hand. The patch was washed with water and observed weather it is washable or not[2].

### pH

The pH of cream was determined to find out the irritant effect of formulations on skin and to study the compatibility of preparations with the skin. The electrode was dipped in cream for 10 seconds, and subjected to pH measurement by using a Calibrated digital pH meter.

A solution containing 1 gm of cream in 30 ml of Phosphate buffer solution (pH 7.4) was prepared and subjected to pH measurement by using a Calibrated digital pH meter[3].

### Viscosity measurement

Liquid crystalline systems were thought to have an intermediate behavior between liquid and solids. The performance of dermatological products depends to a great extent on their rheological behavior. Viscosity of liquid crystalline cream formulation was measured by using Brookfield viscometer using spindle no. 62 at different rpm. The viscosity of the cream can also be determined to estimate the gel strength[4].

### Drug content

Accurately 1gm of cream was measured and transfer to 100 ml of volumetric flask. To this 20-30 ml of Phosphate buffer solution (pH 7.4) was added to dissolve drug. The resultant solution Filtered through 0.45 micron membrane filter and suitably diluted with methanol. Absorbance was measured at 257nm using UV-spectrophotometer. The content was determined from calibration curve of tolnaftate in Phosphate buffer solution (pH 7.4)[5].

**Spreadability**

Spreadability was determined by modified wooden block and glass slide apparatus. The apparatus made up of a wooden block with glass slide and pulley. For determination of spreadability measured amount of cream was places on fixed glass slide, the movable glass slide with a pan attached to it, was placed over the fixed glass slide, such that cream were sandwiched between the two slides for 5 min. The weight was continuously removed. The time taken for the slides to separate was noted. Spreadability was found out using the following formula[6].

S=W x L/T

Where,

S=Spreadability, L=length of the glass plate (14.5 cm),

W=Weight tied to upper plate (50gm),

T=Time taken to separate the slide completely from each other.

**Light Microscopic Studies**

In order to study the texture of the anisotropic phases of liquid crystalline systems, the samples were investigated under polarized light microscope. A small quantity of the sample was placed on a clean glass slide and observed by microscope at 100x magnification[2].

**Drug - Excipients Interaction Study**

Tolnaftate was further identified and confirmed by using ATR-IR (PERKIN ELMER). The sample mixture was directly placed on polished surface of sample holder and ATR-IR instrument was runned and the bands ($cm^{-1}$) have been assigned.

The drug-excipients interaction study was carried out using Attenuated Total Reflectance Infrared spectroscopy (ATR-IR).

**Attenuated Total Reflectance Infrared Spectroscopy (ATR-IR).**

IR spectroscopy was also used to determine the molecular interaction between polymer and drug. Infrared spectra of drug, polymer, physical mixture and formulation were obtained using ATR-IR Spectrophotometer (PERKIN ELMER).

***In Vitro* Anti-Fungal Studies**

*In Vitro* antimycotic study was performed at Bac-Test Lboratory. The antimycotic studies were conducted using agar-cup method and candida albicans as a test organism. Sabouraud-dextrose agar medium was used. 20 ml of molten agar was poured in petri dish on a level surface. The plates were dried at room temperature, so that no drops of moisture remained on the surface of the agar. Colonies of candida albicans was withdrawn from slant of candida albicans. The suspension of candida albicans was prepared and transfer to the sterile agar plates. On solidification, 1 cm of hole was made with the help of cork borer. Filled it with an accurately weighed sample. The plates were incubated at 35±5°c in incubator for 24 hours[7].

***In vitro* drug release studies**

Various formulation prepared by changing process variables were subjected to in vitro release profile of tolnaftate in phosphate buffer solution (pH 7.4) as diffusion medium.

***In Vitro* drug release profile**

Diffusion studies were carried out by using franz diffusion cells. *In Vitro* drug release from the various liquid crystalline systems was performed in phosphate buffer solution (pH 7.4) as diffusion medium using cellophane membrane mounted on a cell membrane. The dialysis cell consist of donor and receptor compartments separated by a cellophane membrane. The donar phase contained formulation equivalent to 10 gm of drug incorporated into vehicle components whereas the receptor phase contained phosphate buffer solution (pH 7.4). Diffusion assembly was placed on magnetic stirrer and study was carried out at 37 °C ± 2 °C. Aliquots were withdrawn at specified time intervals, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8h and 10 h. At each time interval sample withdrawn was replaced with same amount of phosphate buffer solution pH 7.4 to maintain a sink condition. The sample were analyzed after suitable dilution by UV-spectrophotometer at 257 nm. A plot was generated showing the amount of cumulative % drug release verses time[3].

**RESULTS AND DISCUSSION**

**Physical Investigation**

All formule were examined under two day's observation for the performance of the formulation. It appear white, opaque, smooth, and 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. The cream were subjected to the sensitivity test and no erythema, pruritis or allergic reaction had occurred when applied to the skin

**pH Determination**

The pH was measured in each of the liquid crystalline cream of Tolnaftate, using a calibrated digital pH meter. All the formulations are within required pH range suitable for absorption and no irritation and compatibility with the skin was observed.

**Table. 1: pH of prepared *Liquid Crystalline Cream Formulations***

| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| pH | 6.7 | 6.5 | 6.8 | 6.6 | 6.7 | 6.4 | 6.9 | 7.1 | 6.8 |

**Measurement of Rheological Property:**

Viscosity of liquid crystalline cream formulation can be measured by using Brookfield viscometer using spindle no. 62 at various rpm. The viscosity of all formulations were mentioned in the table, in which F5 trial batch show the thixotropic and pseudoplastic flow.

**Table. 2: Viscosity of Prepared *Liquid Crystalline Cream Formulations***

| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Viscosity (Cps) | 3800 | 2900 | 2100 | 4200 | 3500 | 2700 | 3900 | 4500 | 3100 |

**Drug Content**

The drug content of all (F1-F9) formulations is given in table 7.11, it ranges in between 83.4-% - 88.9%.

**Table. 3: Drug Content of Prepared Liquid Crystalline Cream Formulation**

| Formulation code | *F1* | *F2* | *F3* | *F4* | *F5* | *F6* | *F7* | *F8* | *F9* |
|---|---|---|---|---|---|---|---|---|---|
| Drug content (%) | 86.5 | 83.4 | 87.7 | 85.4 | 88.9 | 84.4 | 86.6 | 85.9 | 83.4 |

**Spreadability**

The efficacy of topical therapy depends on the spreading ability of the formulation in an even layer to deliver a standard dose. The optimum consistency of such formulation helps to ensure that a suitable dose is applied or delivered to the target site. The delivery of the correct dose of the drug depends highly on the spreadability of the formulation so spreadability is directly proportional to efficacy. Based on this it was concluded that formulated cream was having more efficacy.

**Table.4: Spreadability of Prepared Liquid Crystalline Cream Formulation**

| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Spreadability (gm.cm/sec) | 21.4 | 21.11 | 20.18 | 19.47 | 22.12 | 22.94 | 20.83 | 22.57 | 21.09 |

**Polarize Light Microscopic Studies**

Freshly prepared and stored samples of the cream containing 1% drug was investigated under polarized light microscopy. Fig. shows a typical polarized light micrograph of liquid crystals.

**Fig. 2: Liquid Crystalline Cream under Polarized Light Microscope**

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, indicating a lamellar Structure.

**Drug-Excipients Interaction Study**

**Attenuated total reflectance Infrared Spectroscopy (ATR-IR)**

FTIR spectra were recorded for Tolnaftate, Brij-78, and silicon oil with drug. Pure Tolnaftate spectra showed sharp characteristics peaks at 2922.96, 1444.77, 1368.08 1159.19, $cm^{-1}$ etc. Physical mixture showing almost similar identical IR ranges of pure drug, which proves the compatibility of drug and used excipients i.e there is no interaction between drug and excipients.

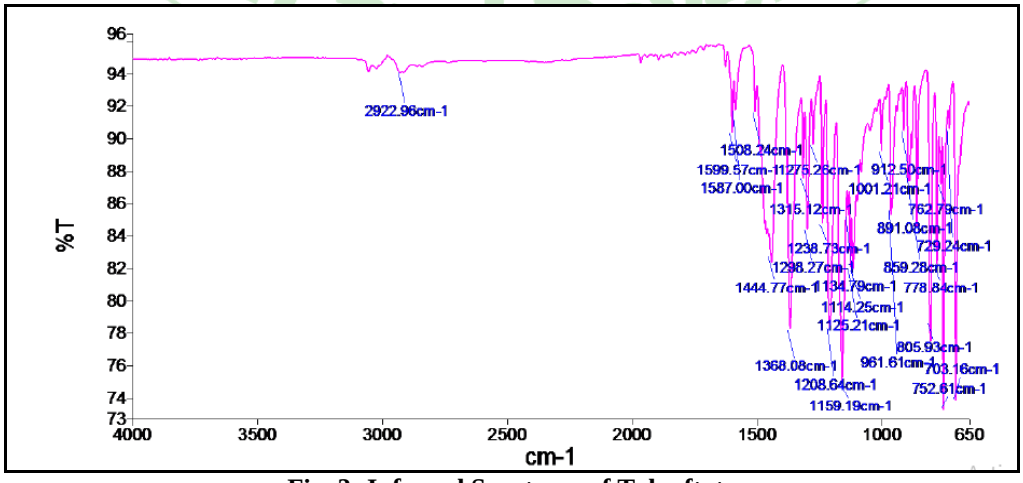


**Fig. 3: Infrared Spectrum of Tolnaftate**

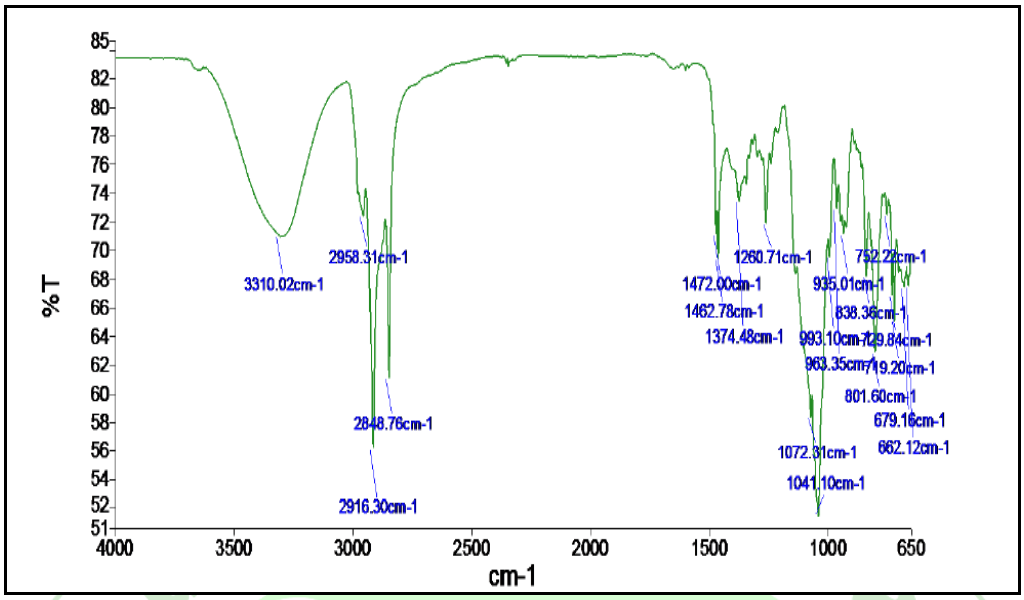


**Fig. 4. : Infrared Spectrum of Cream**

***In-Vitro*Anti-Fungal studies**

The antifungal activity of prepared liquid crystalline cream was determined using *Candida species.* The result suggest that 1 % of tolnaftate incorporated in optimized liquid crystalline system is sufficient to produced effective zone of inhibition.


**Fig. 5: Image of Zone of Inhibition**

The highest zone of inhibition was reported for optimized liquid crystalline formulation. This indicates that polyoxyethylenestearyl ether (Brij-78) effectively delivered drug at concentration exist in OLC formulation. Hence it may be concluded that the prepared formula exhibited better antimicrobial activity.

**In Vitro Drug Release Studies**

The *In-Vitro*drug release of the liquid crystalline cream were carried in phosphate buffer pH 7.4 from 0 to 10 h by diffusion medium (cellophane membrane). The plot of %cumulative drug release v/s time (h) was plotted and depicted as shown in fig.6 *In-Vitro* drug release study was conducted on the formulations for a period of 10 hours during which the highest drug release of 79.00 % was observed with formulation F5.

**Table. 5: *In-Vitro*Drug release of Tolnaftate *Liquid Crystalline Cream* Formulations (F1- F9)**

| Sr.no. | Time | % CR1 | % CR2 | % CR3 | % CR4 | % CR5 | % CR6 | % CR7 | %CR8 | %CR9 |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **2** | 30 | 9.10 | 10.58 | 14.22 | 7.44 | 15.78 | 13.26 | 5.10 | 8.84 | 9.15 |
| **3** | 60 | 15.39 | 18.23 | 20.42 | 13.59 | 21.10 | 22.08 | 9.94 | 14.58 | 13.02 |
| **4** | 90 | 22.54 | 25.50 | 27.63 | 19.51 | 28.27 | 28.57 | 12.49 | 19.56 | 20.59 |
| **5** | 120 | 28.19 | 29.90 | 32.85 | 23.69 | 34.09 | 34.88 | 16.56 | 25.25 | 26.26 |
| **6** | 180 | 34.09 | 38.31 | 44.98 | 31.56 | 46.69 | 45.90 | 20.92 | 31.93 | 35.03 |
| **7** | 240 | 40.92 | 45.83 | 56.01 | 37.80 | 58.21 | 57.03 | 24.53 | 37.27 | 40.25 |
| **8** | 360 | 44.61 | 54.45 | 62.84 | 45.77 | 65.24 | 63.44 | 27.86 | 41.13 | 49.59 |
| **9** | 480 | 51.69 | 60.28 | 69.14 | 50.84 | 72.89 | 68.75 | 31.55 | 50.91 | 56.15 |
| **10** | 600 | 55.00 | 65.00 | 72.00 | 53.00 | 79.00 | 75.00 | 34.00 | 57.00 | 62.00 |

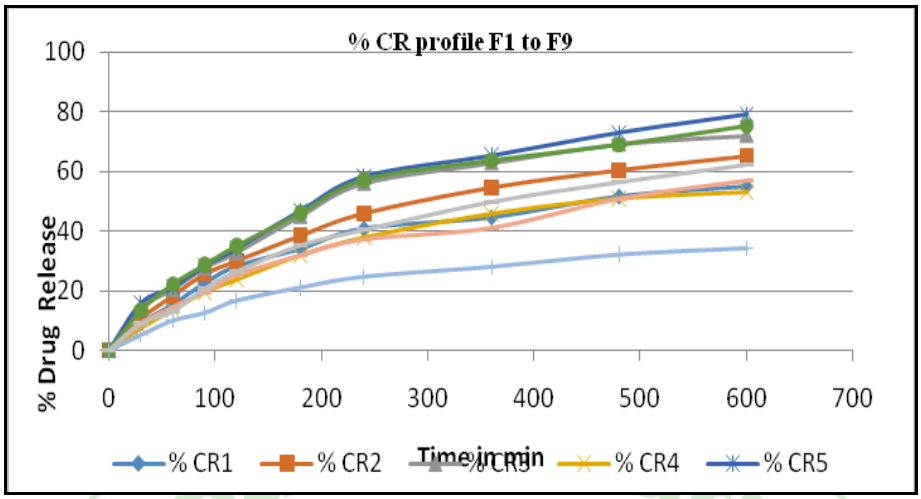


**Fig.6: Diffusion Profile of F1 to F9 Batches**

## CONCLUSION

The present investigation deals with the formulation, optimization and evaluation of liquid crystalline cream of tolnaftate. Liquid crystalline system has become the alternative of conventional dosage form asit's provide a great potential for development of less soluble drugs with enhanced diffusion rate. The results of the present study show that formulation of liquid crystals cream containing 1% tolnaftate is successful as topical delivery system. Within the scope of development of topical liquid crystal formulations, we are maintaining its pharmacological properties while improving its tolerance to overcome side effects and enhancing the efficacy of the existing drug. The liquid crystalline cream formulations exhibited well, viscosity, drug contents and drug release profile.

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