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FORMULATION AND EVALUATION OF PLURONIC LECITHIN CLOTRIMAZOLE ORGANOGEL FOR TOPICAL DELIVERY

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ABSTRACT

Clotrimazole is a synthetic, imidazole derivate with broad-spectrum, antifungal drug which has been used in many skin and nail infections caused by fungi. The aim of the present study is to prepare and evaluate novel topical drug delivery of clotrimazole by using pluronic lecithin based organogel. Formulations were developed using 30% oil phase and 70% aqueous phase. The formulated organogels were evaluated for appearance by psycho-rheological, *in vitro* diffusion study, drug content, viscosity, spreadability and pH. It was found that the pH of all the formulations is in the range of to 6-7 that suits the skin pH, indicating skin compatibility. This is the primary requirement for a good topical formulation. All formulation showed spreadability in the range of 13.83- 28.35gcm/sec. The finding of the study can be utilize for the development of organogel of the other drugs for the safer and effective topical delivery.

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INTRODUCTION

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use. Organogels are bicontineous colloidal system that coexist as micro heterogeneous solid (i.e. Gelator) and organic liquid phase.[1,2] In general, organogels formation is based in the spontaneous self assembly of individual gelator molecules into three-dimensional networks of randomly entangled fiber like structures. This three dimensional network holds micro domains of the liquid in a non flowing state mainly through surface tension. Lecithin Organogels, the jelly like phases, consist of a 3-dimensional network of entangled reverse cylindrical (polymer-like) micelles, which immobilizes the continuous or macroscopic external organic phase, thus turning a liquid into a gel.[3-7] The formation of transition at the micellar level in a low viscous newtonian liquid, consisting of lecithin reverse micelles in non polar organic liquid. However, these systems can also be called as polymer like micelles or wormlike or threadlike micelles.[7,8]

Clotrimazole is a synthetic imidazole derivative having broad spectrum of fungicidal, which has been used in many, skin and nail infections caused by fungi. It is known to be potent and a well tolerated topical antifungal agent. Although, topical formulation of the drug is available but, to investigate effective and well tolerated treatment for superficial fungal infection of the skin the above system and drug candidate was selected.[9,10]

The objective of the present study is development of a novel topical vehicle for the delivery of an antifungal agent in terms of effectiveness and elegance as compared to conventional ointment and creams, improved availability at the desired site by use of organogels and Improved patient compliance.

MATERIALS AND METHOD

Material

Clotrimazole was procured as a gift sample from Cipla Pharmceutical Pvt. Ltd., Mumbai, India. Poloxamer (Pluronic F127) were provided a gift samples by M/s BASF corporation, NJ, USA. Soya Lecithin and sorbic acid were procured from M/s Himedia labs Pvt. Ltd. Mumbai, India. Isopropyl myristate was a product of Central Drug House Pvt. Ltd, New Delhi, India. All other chemicals used were of analytical grade.

Methods [2,11-14]

The various formulations of Pluronic Lecithin Organogel (Table 1) were developed with different compositions. Oil phase was prepared by dispersing the specific amount of soya lecithin at room temperature in isopropyl myristate. The mixture was kept overnight at room temperature in order to dissolve its constituents. Then sorbic acid in appropriate quantity was added, finally drug and polyethylene glycol-600 was dissolved in oil phase, polyethylene glycol-600 was used for solubilization of clotrimazole. Aqueous phase was prepared by dispersing weighed amount of Pluronic F-127 and potassium sorbate in cold water. The dispersion was stored in refrigerator overnight for effective dissolution of Pluronic F-127. Finally, aqueous phase (70%) was slowly added in oil phase (30%) with stirring at 400 rpm using mechanical stirrer. The formulation shown in table no.1.

Table no. 1: Formulation of organogels.

Components	Content	F1	F2	F3	F4	F5	F6	F7	F8
Drug	Clotrimazole (%)	1	1	1	1	1	1	1	1
Oil Phase	Lecithin Soya (%)	2.5	2.5	5	10	2.5	2.5	5	10
	Sorbic Acid (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Polyethylene Glycol 600 (%)	-	10	10	10	-	10	10	10
	Isopropyl Myristate upto (%)	100	100	100	100	100	100	100	100
Aqueous Phase	Pluronic F-127 (%)	10	10	10	10	20	20	20	20
	Potassium Sorbate (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Purified water upto (%)	100	100	100	100	100	100	100	100

Organogel Characterization

Organoleptic characteristics[15]

Each formulation was tested for color, odor, texture and phase separation as well as feels upon application (stiffness, grittiness, greasiness and tackiness).

Homogeneity test

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

Conclusiveness

Prepared gel was taken in vial and visually observed weather it is occlusive or not.

pH Determination

The pH of formulated organogels was determined using pH meter. A solution containing 1 gm of organogel in 30 ml of neutralized distilled water was prepared and subjected to pH measurement. The results are given in the table 2.

Rheological Measurement

The rheological properties of organogel were measured using a thermostatically controlled Brookfield programmable rheometer (Model DV-1+ Brookfield viscometer) by using concentric cylinder spindle LV-4 at 100 rpm and at temperature 25ºC. The results are given in the table-2.

Spreadability[16]

Spreadability of formulations was determined by an apparatus suggested by Multimer *et al*. which was fabricated in laboratory and used for study. The apparatus consists of a wooden block, with a fixed glass slide and movable glass slide with one end tied to weight pan rolled on the pulley, which was in horizontal level with fixed slide. An excess of gel sample 2.5 g was placed between two glass slides and a 1000g weight was placed on slides for 5 minutes to compress the sample to a uniform thickness. The time (seconds) required to separate the two slides was taken as a measure of Spreadability. It was calculated using the formula,

$$S = ML/T$$

where, S is spreadability in gcm/sec, M is weight tied to upper slide, L is length of glass slide, T is time in seconds. The results are given in the table-2.

Drug Content[17]

The content of clotrimazole in the formulations was determined as per the method described by Willaimann et.al. For estimation clotrimazole content 1 gm of organogel was diluted to 100ml with phosphate buffer pH 7.4 and analyzed spectrophotometrically at 260nm.

Gel Transition Temperature

The gel transition temperature was determined in 10ml transparent vial containing a magnetic bar and each formulation was placed in water bath. The vials were heated at a constant rate while stirring. The gelation temperature was measured when the magnetic bar stopped moving due to gelation.

***In vitro* Drug Release Studies**[18]

The different formulations were subjected to *in vitro* drug release studies. The release of clotrimazole form organogel was determined as a function of time in phosphate buffer saline (pH7.4) using dialysis membrane-150 (Himedia) the release profile of clotrimazole from different formulations are given in table 2.

RESULT AND DISCUSSION

Formulation and Characterization of Pluronic Organogel Formulations

In the present work, pluronic lecithin organogel was prepared for topical delivery of clotrimazole with improved therapeutic performance by their penetration enhancing property. In order to achieve this objective, the formulations were prepared with soya lecithin, isopropyl myristate and polyethylene glycol 600 as a co surfactant. The formulations were characterized for their organoleptic properties, homogeneity, conclusiveness, pH, viscosity, gel transition, *in vitro* drug release studies and antifungal study.

The physiological observation shows that organogel formulations were washable, yellowish in color with no phase separation, smooth in feel and showed no clogging which indicate good texture of system. Freedom from grittiness reflects the degree of acceptability of clotrimazole formulation by the patients.

Table no. 2: Characterization of Organogels Formulation.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
pH	6.96 ±0.3	7.10 ±0.4	6.77 ±0.4	6.96 ±0.5	6.71 ±0.3	6.91 ±0.3	7.10 ±0.3	6.71 ±0.4
Viscosity (poise)	5620 ±0.7	5442 ±0.5	5310 ±0.1	5880 ±0.2	5415 ±0.2	5540 ±0.1	5780 ±0.7	5628 ±0.7
Spreadability (gms/s)	22.59 ±0.4	21.18 ±0.4	13.83 ±0.4	19.94 ±0.4	24.94 ±0.4	15.54 ±0.4	28.35 ±0.4	23.27 ±0.4
Dug Content (%)	98.13 ±0.3	97.41 ±0.2	98.76 ±0.3	97.93 ±0.4	98.62 ±0.4	97.58 ±0.2	99.39 ±0.3	97.93 ±0.3
Gel Transition Temperature (ºC)	26.4 ±0.03	30.3 ±0.03	27.8 ±0.04	30.2 ±0.04	30.1 ±0.03	30.3 ±0.03	32.5 ±0.04	30.3 ±0.05
Invitro Drug Release (%)	39.16 ±0.53	46.36 ±0.35	45.19 ±0.65	60.19 ±0.69	42.27 ±0.5	66.83 ±0.82	81.79 ±0.71	79.48 ±0.69

pH Determination

There was no significance difference in pH between the batches. The pH of all the formulations was found in the range of skin pH reflecting no risk of skin irritation.

Rheological Measurement

It was observed that in the prescence of pluronic, viscosity increases from 5310±190.16 to 5780±234.76 poise. The increase in viscosity might be due to formation of complex network as in gel, consistency depends on percentage of solids in relation to liquid and also could due to combination of pluronic and lecithin present in formulation.

Spreadability

The spreadability of formulations was found to be 13.83±0.006 to 28.35±0.028gcm/s, which revealed that the presence of pluronic increases the spreadability of formulation.

Drug Content

Clotrimazole content in organogel was determined by UV visible spectrophotometer. Drug content was found to be 97.41±0.023% to 99.65±0.019%. indicating due to prescence of pluronic which causes uniform distribution of drug throughout the base and also prevent its interaction with the components of base.

Gel Transition Temperature

Gelation temperature, defined as the temperature at which the liquid phase makes a transition to gel. The phase behaviour of organogels varies with changing the temperature conditions. The phase transition temperature also helps in optimizing the organogel composition. The gel transition temperature was found to be 26.4ºC to 32.5ºC, which is attributed to increase in viscosity of the base which decreases gel transition temperature and improves the adhesive properties of formulations.

***In vitro* Drug Release Studies**

The formulations were subjected to *in vitro* drug release studies in phosphate buffer saline (pH7.4) using dialysis membrane-150 (Himedia). The clotrimazole release was found to be decrease with an increase in lecithin content, an inverse correlation existed between the release rate and the gel viscosity values. But a significant decrease in clotrimazole was obtained as concentration increases in formulations. (Fig.1).

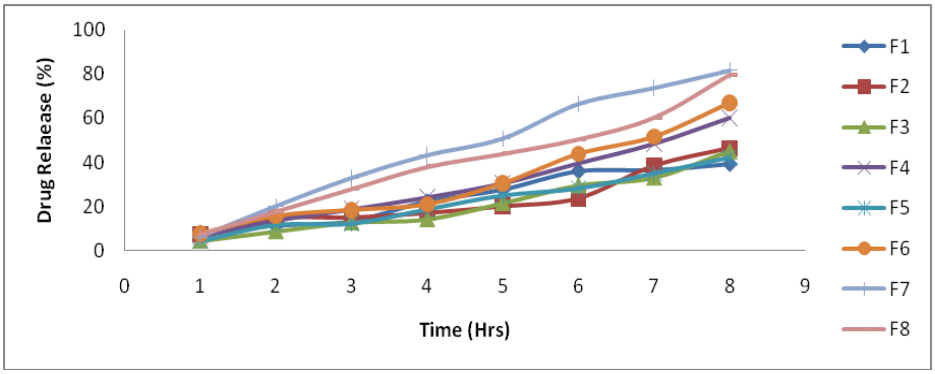

Fig.1: Comparative In Vitro Drug Release Study.

Further increase in concentration of organogelator decrease cumulative percentage drug release which might be due to extensive entanglement of long cylindrical micelles with each other, forming network like structure with increase in viscosity.

CONCLUSION

Pluronic organogel was thought to penetrate into skin, interact and disorganize the lipid to penetrate the lipid layers of stratum corneum. However, improved topical drug delivery has been attributed to the biphasic drug solubility, the desired content and modifications of skin barrier function by the organogel components. The finding of the present study suggest that the prepared clotrimazole organogel containing pluronic were observed to be safe, stable and cost effective drug delivery system. The topical organogel formulation of clotrimazole provides significant antifungal activity when applied topically.

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Conflict of Interest: Nil

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