Original Article

Formulation and Characterization of Clotrimazole Micro Emulsion for Topical Drug Delivery

Vamakshi Thaker[1], A.K. Singhai[2], Dilip Kumar Tiwari[3]

From, [1]M. Pharmacy, [2]Professor and Principal, [3]Asstt. Professor, Department of Pharmaceutical, Lakshmi Narain College of Bhopal (M.P.) India.

Correspondence to*:* Vamakshi Thaker, M. Pharmacy, Department of Pharmaceutical, Lakshmi Narain College of Bhopal (M.P.), India.
Email: vidhivamakshi@gmail.com

ABSTRACT

An antimycotic drug like clotrimazole is used for treating *Candida albicans* and other fungal infections. Clotrimazole seems to be a topical therapy treating vulvovaginal candidiasis, tineapedis, and oropharyngeal candidiasis. That is a synthetic azole antimycotic. By decreasing the production of ergosterol, this drug inhibits fungal growth. Clotrimazole has become a medication of interest for a variety of illnesses, including sickle cell anemia, malaria, and some cancers, in addition to its antimycotic properties. It is mixed with other molecules to create clotrimazole compounds with enhanced pharmacological effectiveness. Numerous novel pharmaceutical formulations enabling variable releases developed. Clotrimazole is a welltolerated, little-adverse drug. However, certain immunocompromised individuals are developing treatment resistance. In this study, we discussed the pharmaceutical chemistry, use, and pharmacology of clotrimazole.

Key words: Clotrimazole antifungal drug, Topical drug delivery system, Clotrimazole micro emulsion gel.

Clotrimazole is a synthetic imidazole derivative most often used to treat yeast, dermatophyte infections of the vagina, and skin. This drug works well against *Microsporum* spp., Candida spp, *Trichophyton* spp., and *Malazzesia furfur* in vitro (1). It also shows modest activity in vitro action against Gram-positive bacteria and, at extremely high doses, activity against Gram-positive bacteria *Trichomonas* spp. Clotrimazole shows successful results in individuals who already failed to get treated by certain other antifungal medications such as nystatin, and amphotericin B. In the case of trichomonal vaginitis, the results aren't promising. Topical application of clotrimazole help treat skin infections caused by Candida or dermatophytes (2).

Clotrimazole cream is equally efficient as Whitfield's ointment or tolnaftate in the treatment of dermatophytoses, and even as efficient as nystatin inside the treatment of cutaneous candidiasis in clinical studies. Clotrimazole topical formulations are typically well-tolerated, although in a few cases, local discomfort has prompted therapy discontinuation. (13)**.** Clotrimazole has a molecular formulation of C22H17ClN2 as well as a molecular weight of 344•8 g mol−1. Clotrimazole is in widespread use for the treatment of *Candida albicans* and other fungal infections. Its antimycotic properties were discovered in the late 1960s. As an active ingredient, it is marketed as a generic drug under various trade names and by various companies worldwide. In addition to its antimycotic activity, clotrimazole is used in the treatment of metronidazoleresistant *Trichomoniasis* to relieve symptoms (15) and displays activity against certain Gram-positive bacteria (16). It is a synthetic compound.

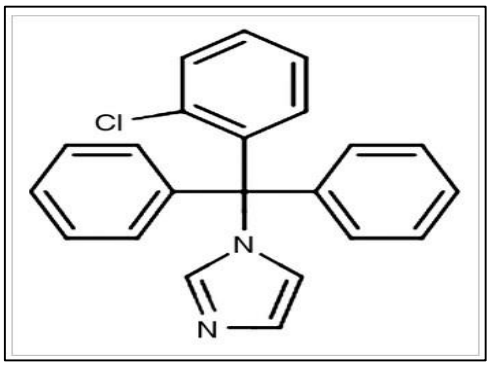


Figure 1: The Chemical Structure of Clotrimazole (1-[(2Chlorophenyl) Diphenylmethyl]-1H-Imidazole) [(1)].

MATERIALS AND METHODS

Polyethylene sorbitan mono-oleate (PSMO) and sorbitan mono-oleate (SMO) acquired by P. C. Drug Center Co. Ltd. RCI Labscan Limited has acquired isopropyl-alcohol (IPA) (7). These were bought from the Orbit pharmaceutical, Gujarat Isopropyl palmitate (IPP). Sigma Aldrich bought fumed silica.

During the tests, distilled water was utilized. All chemical products were medicinal and utilized without further purification.

Pre-formulation Study

Solubility **-** Solubility of clotrimazole determined in different oils, surfactants, and co-surfactant. Clotrimazole was added in excess to oils, surfactants, and co-surfactant and stirred for 24 h on a magnetic stirrer. Samples were centrifuged at 1500 RPM for 10 min after stirring, and the drug present in the supernatant get extracted at λ max 261 nm (8).

pH- A standard solution of clotrimazole, 1mg/ml prepared. Further, diluted with USP buffers of pH 1.2, 4.5, and 6.8, each up to 10ml (5). Incubated the solutions for 2 hour at 37° C. To achieve an adequate solubility level aqueous samples were prepared with acetonitrile as a co-solvent at an effective final concentration of 10% (v/v). The samples were assayed for drug content by the validated HPLC method.

FTIR Analysis- Test solution dissolved in 50mg of the substance to be examined in ethanol (96%) R and dilute to 5ml with the same solvent. Reference solution dissolves in 50mg of clotrimazole CRS in ethanol (96%) R and is diluted to 5ml with the same solvent. Plate thin layer chromatography F254 PLATE R. Mobile phase concentrated ammonia R1, propanol R, Toluene R (0.5:10:90 v/v/v)

Solubility of the Drug in Different Solvents- Solubility is calculated using the following protocol. Partially insoluble in water, soluble in ethanol (96%), and methylene chloride. In different oils such as oleic acid, lemon oil, olive oil, and methane oil, the solubility of clotrimazole was studied. The maximum solubility of clotrimazole in mentha oil was discovered among the oils tested. The analgesic and cooling effects of mentha oil itself are sensory. Mentha oil is used for the oil phase for the clotrimazole microemulsion (6). ***Stability -*** Based on visual identification microemulsion with clotrimazole remained as clear liquid for two months without the occurrence of phase separation or flocculation at room temperature and refrigerator temperature. The results of various studies performed on ME gel were found to be satisfactory so, both were found to be stable for two months (4, 5).

Drug Excipient Study- Accurately weighed amounts of clotrimazole (100 mg), and each selected excipient (500mg) were placed in a 5ml glass vial and mixed thoroughly. Closed vials containing blends were stored in ovens at 60°C and 40°C for 14 days. A standard clotrimazole sample without mixing with an excipient clotrimazole sample was kept under similar conditions. The amount of drug substance in blends was determined based on the expected drug to excipient ratio in the final formulation. Duplicate samples of drug–excipient blends were analyzed after 14 days by validated HPLC methods.

Preparation of CTM Micro Emulsion and CTM Micro Emulsion-Based-Gels- The desired micro emulsion and micro emulsion-based gels with 1 percent w/w of clotrimazole have been selected. To obtain clotrimazole micro emulsions, the medicine has been dissolved. For clotrimazole-based gel, fumed silica dispersed in clotrimazole micro emulsions and produced.

Preparation of Blank CTM Micro Emulsion and CTM Micro Emulsion Gel- Micro emulsion components in the preceding report, the region of micro emulsion chosen. The simple blending of IPP, 2:1 water and IPA, and 1:1 PSMO and SMO mixtures at 20% of concentrations produced two micro emulsions. 30% and 50%w/w for ME1 and in 20%, 40% w/w for ME2 1. Afterwards, 2.0 % 5 % of fumed silica were added into ME1 and ME2 to obtain micro emulsionbased gel designated as MBG1-1 to MBG1-2 and MBG2-1 to MBG2-2 respectively.

Table 1- Composition of Studied Micro Emulsion – Based - Gel Systems

Micro emulsion	Fumed 2.5% silica w/w	Fumed 5.0% silica w/w
ME 1	MBG1 1	MBG1 2
ME2	MBG2 1	MBG2 2

Characterization of Blank CTM Micro Emulsion and CTM Micro Emulsion Based Gel- Important characters of CTM Micro emulsion and CTM Micro emulsion-based gel are-

- The look has been seen visually.
- Spreadability was achieved by the spreading of a low to high skin stretchable and retainable quantity of each formulation over the skin with sensational consideration in the + to +++ range.
- Dilution tests and conductivity measurements have established the kind of micro emulsions.
- The dilution inspection should be carried out by dropping into the water of each micro emulsion, classified for miscibility or immiscibility.
- The conductivity meter CM-115 was tested (Orbit pharmaceutical, Gujarat).

Determination of Transmittance of Clotrimazole Micro Emulsions- The %transmittance was checked against distilled water using a UV-visible spectrophotometer at λ max 630 nm (1, 2).

T % = Antilog (2 - Absorbance)

Drug Release Kinetics- The drug release kinetic study was performed to find drug release mechanisms from dissolution parameters by using various kinetic model equations. The zero-order, first-order, Hixon Crowell, Korsmeyer Peppas, and Higuchi Plot models were tested.

Methods for Antifungal Activity- Following protocol was followed for measuring anti-fungal activity:

- The cup-plate method was used for anti-fungal formulation.
- Candida albicans suspension was poured into sterilized dextrose agar media (cooled at 40ºC) and was mixed thoroughly.
- 20ml of the above-mentioned suspension was poured aseptically in a pre-sterilized Petri dish and was allowed to solidify. The surface of the agar plate was pierced via a sterile cork borer.
- These wells were filled with an equal volume of the optimized batch of micro emulsion-based gel and marketed 1 % clotrimazole gel followed by incubation at 18-24ºC, for 72 h.
- Fungal growth was detected and the zone of inhibitions was measured using an antibiotic zone reader.

RESULTS

Pre-formulation Studies

Chemical Properties- It is a white powder or colorless crystalline powder. It has a melting point of 147-149° C. It is soluble in ethanol, acetone, and chloroform, but almost insoluble in water. It is odorless, tasteless, and subject to rapid decomposition in an acid solution. Clotrimazole hydrochloride has a melting point of 159° C.

pH- The pH of clotrimazole in different solutions at initial and 2hrs. It was observed that, at pH 1.2, pH 4.5, and pH 6.8. At initial time 98.94 ± 1.55, 98.85 ± 1.02, and 99.58 ± 1.72, respectively. The value observed at 2 hrs of 98.25, 98.25, and 99.35, respectively.

Table 2- pH Observed

TIME	pH 1.2	pH 4.5	pH 6.8
Initial	98.94 ± 1.55	98.85 ± 1.02	99.58 ± 1.72
2 hrs	98.25	98.25	99.35

FTIR Analysis- The FTIR Spectra of the clotrimazole and optimized clotrimazole microemulsion gel were recorded with KBr on an infrared spectrophotometer as shown in the figure.

Solubility in Different Solvents- CLT experimental solubility values in buffers pH 2.0 and 7.4, 1-octanol and hexane expressed in molarity (S) in the temperature range (293.15-313.15) K. The temperature dependences of the drug solubility in the studied solvents are shown in the figure 3, 4. Stated that studied solvents the compound solubility increased at higher temperatures. Clotrimazole is stable in the buffer solution pH range of 1.2 - 7.5, but it degrades in strongly acidic and basic media and at high temperatures (9, 10).

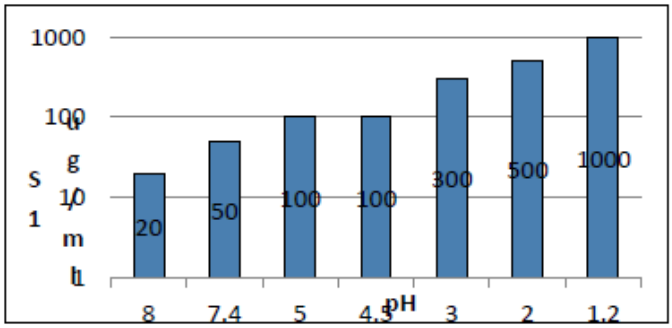


Figure 2 - Solubility data of CLT in buffer solutions at different pH and temperature.

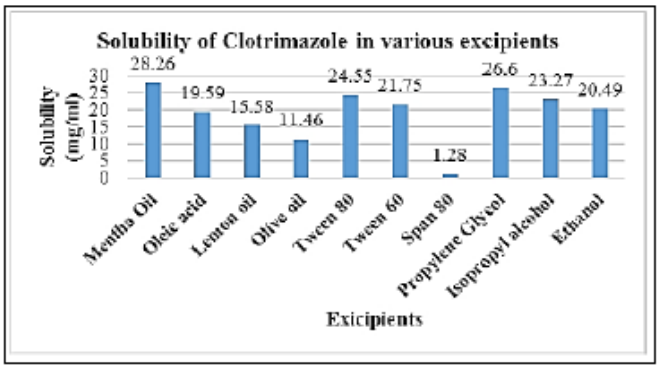


Figure 3 - Solubility of clotrimazole in various oils, surfactants and co-surfactants.

Stability- Optimized micro emulsion & micro emulsion gel were subjected to a stability study for two months at room temperature and refrigeration conditions (2-8°C). During the period of storage, the ME was subjected for % transmittance, % assay & pH, while I gel was subjected for % transmittance, % assay, pH, consistency & viscosity (physical). Results are shown in **Table 3**

Table 3- Result of stability study of micro emulsion at room temperature

TEST	Initial time	1month	2month
Transmittance %	99.6 ± 0.06	99.6 ± 0.21	99.4 ± 0.18
Assay %	99.1 ± 0.26	98.8 ± 0.15	98.82 ± 0.13
pH	5.50 ± 0.19	5.50 ± 0.14	5.50 ± 0.14
Result of stability of Micro emulsion gel at room te mperature			
Assay %	99.26 ± 0.68	99.2 ± 0.28	99.2 ± 0.26
pH	6.10 ± 0.25	5.92 ± 0.38	98.82 ± 0.13
Transparency	Transparency & clear	Transparency & clear	Transparency & clear

Viscosity	Very good	Very good	Very good
Result of stability stud y of micro emulsion at refrig eration temperature			
Transmittance %	99.9 ± 0.10	99.5 ± 0.10	99.4 ± 0.09
Assay %	99.6 ± 0.22	99.1 ± 0.30	99.0 ± 0.30
pH	5.46 ± 0.22	5.4 ± 0.20	5.42 ± 0.20
result of stability of M icro emulsion gel at refriger ation temperature			
Assay %	99.6 ± 2.42	98.9 ± 1.23	98.6 ± 1.13
pH	5.99 ± 0.20	5.99 ± 0.14	5.97 ± 0.12
Transparency	Transparency & clear	Transparency & clear	Transparency & clear
Viscosity	Very good	Very good	Very good

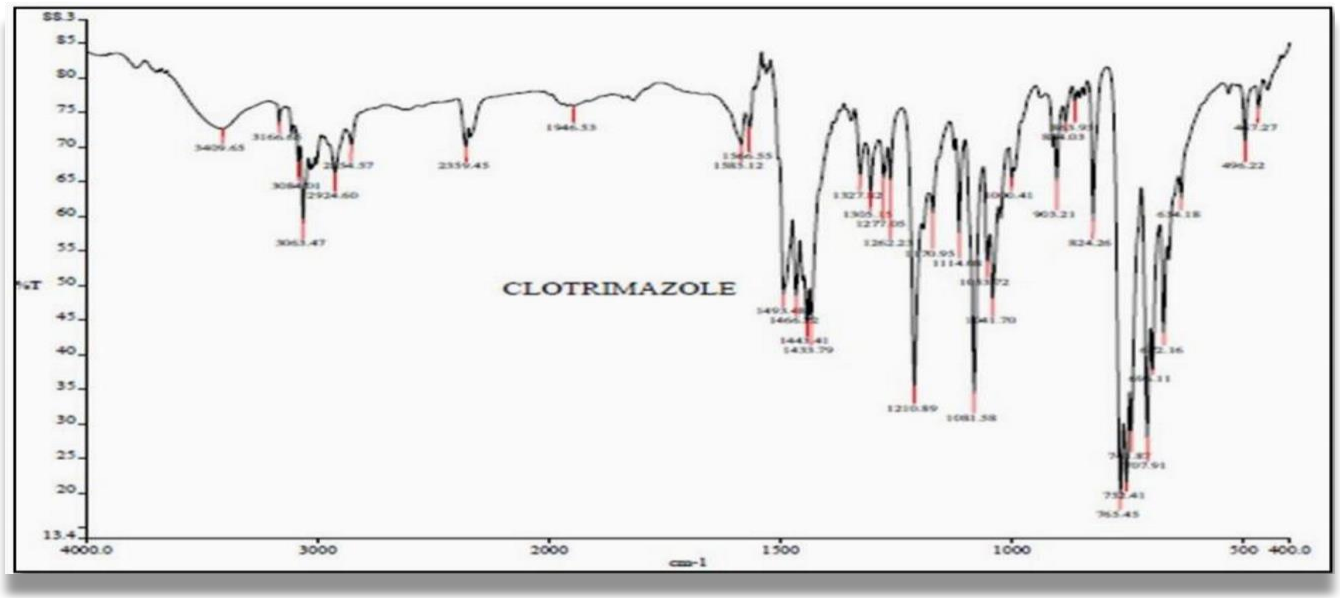


Figure 4 - FTIR Spectroscopy of clotrimazole drug.

Drug Excipient Chemical Compatibility- The total number of drug excipient blends in the study may be very high; therefore, excipient rank-ordered with their solubility for CLZ were selected primary screening. For example, oils such as capryl 90, lauroglycol 90, and capmul MCM C8 exhibiting higher solubility for clotrimazole were selected. As summarized in the table, every excipient clotrimazole had degraded approximately 5-15% in 14 days at both storage conditions. The rate of degradation increased with an increase in temperature. A similar degradation peak of clotrimazole was evident in chromatograms of all samples. The representative chromatograms of the sample stored at 60o C for 14 days are shown in the figure. Which shows a well-resolved degradation product of clotrimazole. In the solution state, the stability of clotrimazole is pH-dependent.

Preparation of CTM Micro Emulsion & CTM ME Gel- Following steps were followed in preparing CTM micro emulsion and CTM ME-based gel: The micro emulsions and micro emulsion based-gels which had desirable appearance were selected and were added with 1% w/w of clotrimazole. The drug was dissolved in micro emulsions to obtain clotrimazole micro emulsions. Fumed silica was dispersed in clotrimazole micro emulsions for the preparation of clotrimazole micro emulsion-based gel.

Preparation of Blank Micro Emulsions and Micro Emulsion Based-Gels- Following steps were followed in preparing blank micro emulsion and ME-based gel: Micro emulsion components in the preceding report, the region of micro emulsion was chosen. The simple blending of IPP, 2:1 water and IPA, and 1:1 PSMO and SMO mixtures at 20% of concentrations produced two micro emulsions. 30% and 50% w/w, respectively for ME1 and in those of 20 %, 40 %, and 40 % w/w, respectively for ME 2 1. Afterwards, 2.0 % and 5 % of fumed silica was added into ME1 and ME2 to obtain micro emulsion-based gel designated as MBG1-1 to MBG1-2 and MBG2-1 to MBG2-2, respectively.

Table 7- Physical properties of clotrimazole micro emulsions and micro emulsion based-gels

Formulation	Conductivity (µS/cm)	pH	Spread-ibilty
ME1C	16.70± 0.17	6.92 ±0.03	+
ME2C	53.37 ±1.96	6.84 ±0.01	+
MBG-2-2C	31.37 ±0.15	6.78 ±0.02	+++

Characteristics of Clotrimazole Micro Emulsions and Micro Emulsion-Based Gels- Following characteristics were observed: 1%w/w clotrimazole was incorporated in ME1, ME2, andMBG2-2, and ME1-C, ME2- C, and MBG2-2-C, were

obtained respectively. No significant visual changes were observed. However, conductivity values of clotrimazole-loaded samples were low in comparison to their blank counterparts, while pH and spreadability showed remarkable change. The samples were water-in-oil type; therefore, clotrimazole located in the external oil phase, that resulted in lower conductivity. The rheological behaviour ofME1-C andME2-C still showed as Newtonian flow, also the MBG2-2-C still were shear-thinning like their blank counterparts. The viscosity of MBG2-2-C was raised slightly in comparison to its blank counterpart.

Characteristics of Blank Micro Emulsions and Micro Emulsion-Based Gels- The obtained micro emulsions (ME1 and ME2) were clear, pale yellowish liquids with little smell of alcohol and were immiscible with water. The results of dilution and conductivity exhibited that both ME1 and ME2 were water-in-oil types since their HLB value was 9.65.

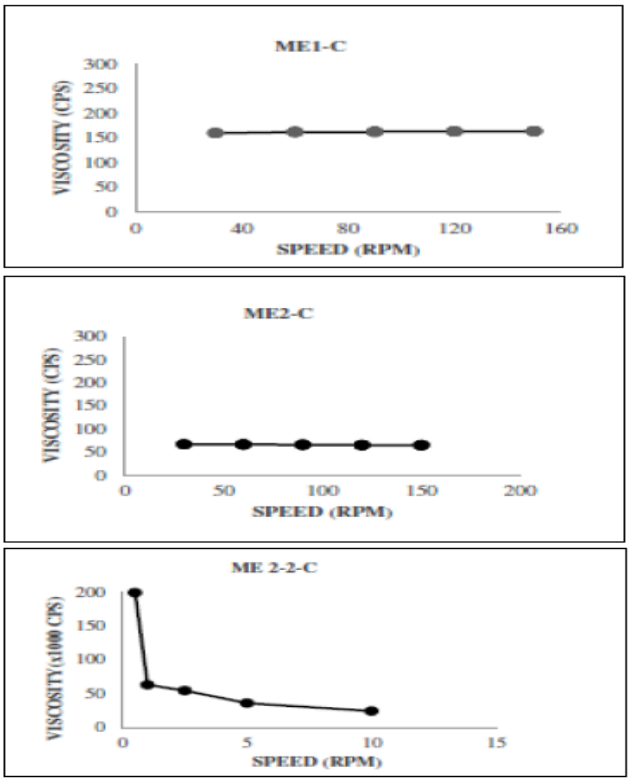


Figure 5 - Characteristics clotrimazole micro emulsions and micro emulsion based-gel

Table 8- Characteristics of blank micro emulsions and micro emulsion-based gels

Formulation	Conductivity (µS/cm)	pH	Spread-ability
ME1	20:60 ± 0:20	6.96 ±0.07	+
MBG1-1	26.83 ±0.15	6.99 ±0.02	+
MBG1-2	23.73± 0.55	6.90± 0.06	++
ME2	63.63± 2.90	6.98 ±0.09	+
MBG2-1	74.77 ±1.05	6.86± 0.03	++
MBG2-2	50.43 ±1.42	6.88 ±0.14	+++

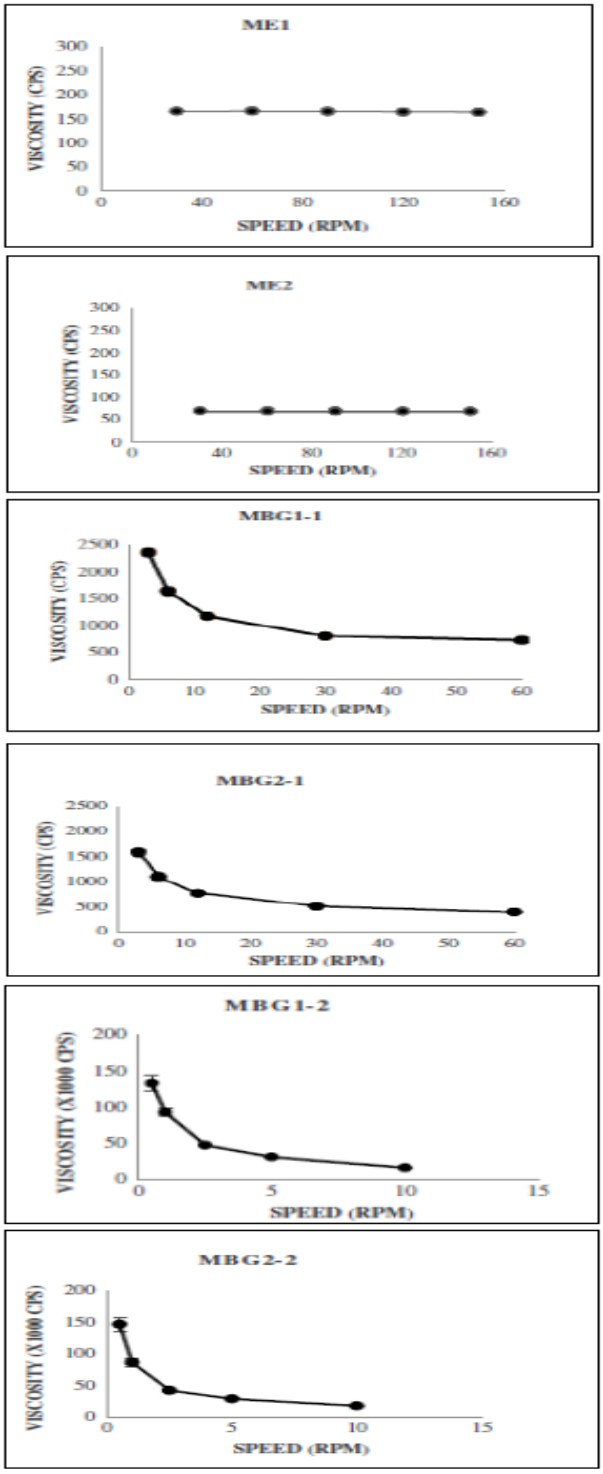


Figure 6- Characteristics of blank micro emulsions and micro emulsion based-gels

Figure 7A: Clotrimazole formulation assay-based results 7B: Clotrimazole formulation software based results

The pH of the formulations FA and FB was found to be 6.6 ± 0.07 and 6.1 ± 0.4respectively. The pH has been adapted to the appropriate physiological pH of 6.1-6.6. In USP, clotrimazole results were determined to be not less than 90.0 percent and not more than 110.0 percent 20. "Test findings using the established analytical technique. The F2 formulation of F2 drugs discovered 98.9 ± 0.46% whereas, the F3 formulation produced 100.3 ± 0.71 %. Fig. shows FB as an optimal formulation based on the desired assessment.Researchers also determined that clotrimazole is often a suitable phenomenon for hydrogel integration. It also shows that the solubility problem of hydrophobic drugs also isn't addressed by alcoholic content. A hydrogel without any hard solvents that may irritate can be produced by co-solvents. It was discovered to be compatible with solvents as Carbomer was used as a gelling agent. The approach devised does not require the removal of polymer over the day and so saves time. Has an increased propensity and is much more patient adaptive, therefore more clinical studies are necessary.

Drug release kinetics study- The kinetic research on drug release. The formulation of hydrogel based on micro emulsion is an effective promoter of the localization of clotrimazole to the skin. It was shown that the drug permeability of the optimized formula based on micro emulsion (in vitro) was below (92.04 percent) its optimal hydrogel formulation based on micro emulsion (ex vivo) (96.12 percent). This might be because of the drug partitioning into the oil phase of the hydrogel-based on micro emulsion that lowers drug release.

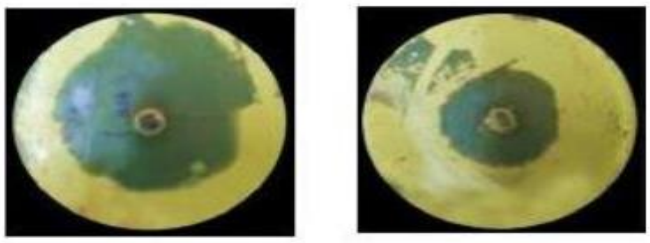
Antifungal activity- The values of the mean zone of inhibition (in vitro antifungal activity) of optimum micro emulsion-based hydrogel batch and marketed formulation (15). For topical antifungal medicines, such as clotrimazole, effective formula is required. Their thermodynamically and isotopically stable characteristics are caused by surfactants and co-surfactants that lower interfacial tension from the oil to the water phase.

Table 8- Drug Kinetics Release Study

Kinetic model		Zero order	First order	Hixon crowell	Corse mayer papers	Higuchi plot
In vitro study	R^2Value	0.920	0.965	0.985	-0.229	0.831
	Slope	0.104	0.002	0.011	1.338	0.247
	Intercept	-9.810	0.310	0.626	-4.522	10.00
Ex vivo study	R^2Value	0.929	0.948	0.981	-0.269	0.836
	Slope	0.108	0.002	0.011	1.158	0.241
	Intercept	-8.798	0.482	0.918	-4.008	10.200

Table 9- Zones of inhibition by various gels

Sample	Zone of Microbial growth inhibition
Placebo	0
CLT-ME	43.67 ±2.31
CLT-ME gel	41.67 ±2.88



(a) (b)

Figure 8 - Zone of inhibition of (a) optimized batch & (b) marketed product

DISCUSSION

Clotrimazole o/w micro emulsion by the titration technique throughout their experiment. Surfactants and co-surfactants have been combined and applied wisely to the water drop. The medicine was dissolved in the oil phase and stirred continually into the aforementioned solution. The solution allowed for clear and transparent liquid micro emulsion to be formed. The phase titration technique was used to manufacture clotrimazole loaded o/w micro emulsion. Surfactants and co-surfactants have been combined and applied wisely to the water drop. The drug was dissolved in the oil phase and stirred continually into the mentioned solution (14). All located clear and transparent liquid solutions.

The greater clotrimazole solubility in the oil phase is essential since clotrimazole is a low water-soluble medicine. In different oils including oleic acid, lemon oil, olive oil, and mentha oil, the solubility of clotrimazole was studied (4). The maximum solubility of clotrimazole in mentha oil has been discovered among the oils that have been tested. The analgesic and cooling effects of mentha oil itself are sensory. Mentha oil has thus been used for the oil phase for the clotrimazole micro emulsion (11, 12). The maximal solubility of clotrimazol in tween 80 was shown. Tween 80 was therefore used as the surfactant for the formulation of clotrimazole. Micro emulsion for other co-surfactants including IPA and ethanol, clotrimazole demonstrated the highest solubility of propylene glycol. The skin is well permeated by propylene glycol. The co-surfactant is, therefore propylene glycol.

Nevertheless, the further development of clotrimazole as a pharmaceutical is an area of intense research at present. There are prospects both for its exploitation in new indications and for

the development of new formulations. A scaffold based on clotrimazole is being used as a pharmacophore in the design and synthesis of novel antimalarial drugs that are cheap and easy to synthesize [22]. Palladium–clotrimazole complexes that exhibit enhanced cytotoxicity against tumour cell lines, in comparison with clotrimazole alone, are under investigation as novel antineoplastic agents [23]. Indeed, several other metal – clotrimazole complexes, such as ruthenium– clotrimazole and platinum –clotrimazole, also display promising antineoplastic characteristics [24]. There is also intense interest in using clotrimazole and its metabolite as lead compounds in the strategic design of novel treatments for sickle cell disease, on the basis that they can reduce erythrocyte dehydration *in vivo* by inhibiting the so-called Gardos, calcium-dependent potassium channel that malfunctions in this disease.

CONCLUSION

In conclusion, clotrimazole is an effective, safe, and welltolerated drug with unusual chemistry that is widely used in the treatment of skin, vulvovaginal and oropharyngeal fungal infections. It is sold in most developed countries worldwide under a variety of trade names, and a large number of clotrimazole formulations are available.

Although emerging resistance to clotrimazole may limit the future use of this drug in certain patient subpopulations, in the general population, its widespread use is likely to continue for the foreseeable future. The ongoing development of clotrimazole as a pharmaceutical is currently focused on finding new clinical indications for the drug, its use as a lead compound in structure-based drug design studies, and the optimization of formulated products to enhance drug delivery. New approaches to the formulation of clotrimazole include a buccal bio-adhesive film containing clotrimazole, which was found to inhibit oral candidiasis for up to 6 h (18), and a thermos-sensitive vaginal gel formulation formed by complexation of clotrimazole with beta-cyclodextrin, which has been shown to reduce the release rate of clotrimazole in comparison with standard preparations (17).

This type of slow-release formulation may exhibit increased efficacy over other vaginal delivery systems, as traditional vaginal creams, pessaries and tablets tend to have short residency times in the vagina due to the natural cleansing process that takes place there. The use of liposomes containing clotrimazole may also provide increased residency in the vagina, thereby improving gel formulations for treatment (19). RS 100 nano-capsules have recently been studied in the treatment of ***C. Albicans*** and ***C. glabrata***, and these have been reported as more active than free clotrimazole alone (20). Given the scale of the current market for vulvovaginal clotrimazole preparations, novel formulations that can demonstrate an advantage over pre-existing preparations could potentially attract a large revenue stream. Nano-fiber mats for oral applications are also superior in efficacy and have reduced toxicity over lozenges and powders in current use, although further pharmaceutics investigations are needed (21).

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