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Formulation and Evaluation of Clotrimazole Emulgel

Arpita Srivastava*, Alok Mukerjee, Ipshita Pandhey, Nimesh Kumar Dubey
United Institute of Pharmacy, Prayagraj, U.P.- INDIA

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ABSTRACT

Clotrimazole is an imidazole derivative with a broad spectrum antimycotic activity, widely used for the treatment of Candida albicans. It acts by inhibiting biosynthesis of Ergosterol, an important component of fungal cell membranes. It is widely used for the treatment of local candidiasis, oral thrush, and vaginal yeast infections. It is also a favoring agent for various diseases such as cancer, sickle cell anemia, neuroprotective effect and anti-inflammatory effect in patients with rheumatoid arthritis. Topical application includes fungal infections such as ring worm, athlete's foot and jock itch. Emulgels are emulsions, either of the oil-in-water or water-in-oil type, which are gelled by emulsion has been used widely in cosmetics and in pharmaceuticals preparations. The USP defines gel as semisolid systems containing either suspensions made up of either small inorganic particles, or large organic molecules interpenetrated by a liquid. Gel having a property to form cross linked network where it takes small drug particles and provides its release in a controlled manner. Through its mucoadhesive properties it prolongs the contact period of medication over the skin. Characterization of clotrimazole emulgel was done by physical examination, pH determination, viscosity testing, in- vitro release study, drug content determination, swelling index. The in-vitro % cumulative drug release of clotrimazole F1 To F5 was found 11.27%, 39.2%, 119%, 28.2%, 31.5%. At 50 times F2 gave a highest release. Finally the formulation F2 can be concluded that are suitable for topical application as antifungal agent.

Keywords- Clotrimazole, Emulgel, Ergosterol, Imidazole.

I. INTRODUCTION-

Clotrimazole is an imidazole derivative with a broad spectrum antimycotic activity, widely used for the treatment of Candida albicans. It acts by inhibiting biosynthesis of Ergosterol, an important component of fungal cell membranes. It is widely used for the treatment of local candidiasis, oral thrush, and vaginal yeast infections. It is also a favoring agent for various diseases such as cancer, sickle cell anemia, neuroprotective effect and anti-inflammatory effect in patients with rheumatoid arthritis. Topical application includes fungal infections such as ring worm, athlete's foot and jock itch. Clotrimazole action leads to increased membrane permeability and apparent disruption (division) of enzyme systems bound to the membrane. Clotrimazole is an effective, safe and well tolerated drug with unusual chemistry that is broadly used in the treatment of skin, vulvovaginal and oropharyngeal fungal infections. It has broad antifungal activity against pathogenic yeasts and also for filamentous fungi. According to WHO, Clotrimazole is an effective antifungal agent in topical infections, harmless than any other antifungal agents being listed in its essential drugs list currently and it is commonly recognized safe. The commercial available cream of Clotrimazole has the limitations of lower skin retention, poor residence ability and deposition at the target site. Clotrimazole has limitations such as poor water solubility, bioavailability and the short half life (2 hours) as reported by Crowley et al 2014. Clotrimazole show poor bioavailability when administered orally because of low aqueous solubility and slow dissolution in water. Hence, to improve its bioavailability, an effort was made to develop transdermal Clotrimazole. Topical preparation of Clotrimazole are generally well tolerated, but local irritation has necessary withdrawal therapy in some cases. So, an effort has been made to formulate transdermal gel to overcome these limitations and to optimize delivery of drug through the skin upon the variation of different penetration enhancers. Emulgels can be defined as the emulsions, either of the o/w or w/ o type, which are thicken by mixing the gelling agent. Emulsion has been used widely in cosmetics and in pharmaceuticals preparations.. Through its mucoadhesive properties it prolongs the interact duration of medication over the skin. Within

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biphasic liquid dosage forms Emulsion is a controlled release system, where drug particles is entrapped in internal phase and passes in to the skin through external phase and slowly get absorbed internal phase. acts as a reservoir of drug and slowly release the drug in a controlled way through the external phase to the skin. Since Emulgel having the characteristics of both emulsion and gel it acts as dual control release system.. Present days, they are being used for controlled delivery applications.

II. MATERIALS AND METHODS

Clotrimazole was gifted from Hetro Pharmaceuticals, Baddi. Carbopol 934,• liquid paraffin, tween 20, span 20, propylene glycol, ethanol, methyl paraben, propyl paraben were provided by college. Purified water was used for all equipments.

PREFORMULATION STUDY

SOLUBILITY STUDY:

10 mg of drug (Clotrimazole) was taken and dissolved in 10 ml of various solvents, then the solubility was visually analyzed.

MELTING POINT ANALYSIS: 10 mg of drug was taken for melting point analysis using melting point apparatus (Fisher- Johns).

CALIBRATION CURVE: 10 mg of drug is dissolved in100 ml methanol. After that absorbance was taken at 260 nm by UV-Spectrophotometer.

DRUG IDENTIFICATION: Identification of clotrimazole was done by FTIR.

FORMULATION OF EMULGEL:

The gel phase was prepared by dispersing Carbopol 940 in purified water with continuous stirrer for 5 minutes at 2000 rpm. The gel phase was cooled and left overnight. The oil phase of the emulsion was prepared by dissolving span 80 in light liquid paraffin although the aqueous phase was prepared by dissolving tween 20 (F_1 ,F_2 ,F_3) and tween 80 (F_4 ,F_5,F_6) in purified water. Methyl paraben and propyl paraben were dissolved in propylene glycol although Clotrimazole drug was dissolved in ethanol; both are then mixed with the aqueous phase. The aqueous phase and the oil phases were separately heated to 70^0 C, and then the oil phase was added to the aqueous phase with continuous stirring till cooled to room temperature. The emulsion and gel were both mixed together in equal ratio with gentle stirring till cooled to room temperature. The emulsion and gel were both mixed together in equal ratio with moderate stirring till getting the emulgel.

COMPOSITION AND CODES OF CLOTRIMAZOLE FORMULATIONS (%W/W):

Components	**Formula's Code**					
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
Clotrimazole	1	1	1	1	1	1
Carbopol 940	1	1	1	1	1	1
Liquid paraffin	4	4	6.5	6.5	4	4
Tween 20	-	-	-	0.5	0.5	0.5
Tween 80	0.5	0.5	0.5	-	-	-
Propylene glycol	4.9	4.9	4.9	5	5	5
Span 80	0.8	0.8	0.8	1.4	1.4	1.4
Methyl paraben	0.04	0.04	0.04	0.04	0.04	0.04
Propyl paraben	0.2	0.2	0.2	0.2	0.2	0.2

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Ethanol	2.4	2.4	2.4	2.4	2.4	2.4
Purified water	Qs	Qs	Qs	Qs	Qs	Qs

CHARACTERIZATION

PHYSICAL APPEARANCE AND pH DETERMINATION:

The prepared Clotrimazole emulgel were examined visually for their tone, consistency, homogeneity and pH. The pH value of the prepared emulgels was measured by digital pH meter (Abron).

DRUG CONTENT DETERMINATION:

Drug content determinations were examined by dissolving 500 mg of clotrimazole emulgel in 5 ml of methanol in a beaker. Then formulation was dilute by methanol and absorbance was taken at 260 nm using UV- Spectrophotometer (Shimadzu UV 1700).

IN-VITRO RELEASE STUDY:

The in-vitro drug release studies determined by using a Franz diffusion cell . The emulgel (Clotrimazole) was applied on dialysis membrane which was placed between donor and receptor compartment of the Franz diffusion cell. Phosphate buffer pH 7.4 was used as a dissolution media. Hot water was circulating in water jacket and the temperature of the cell was maintained at 37^0 C, using a magnetic bead the whole assembly was fixed on a magnetic stirred repeatedly. A similar blank set was run simultaneously as a control. 5ml was isolated at appropriate time intervals and exchanged with equivalent amounts of refreshing dissolution media. Samples were analyzed spectrophotometrically at 260 nm using ultraviolet spectrophotometer and the cumulative % drug release was calculated.

SWELLING INDEX: The swelling index of prepared sample was performed by taking 1 gm of emulgel (Clotrimazole) on porous aluminium foil and keeping it aside undisturbed (unmoved) in a 50 ml beaker. At distinct duration of time, the sample was removed from beaker and place it on a moisture less place for some time and weighed it again. Swelling index was calculated by using following formula:

SW% = [Wt – Wo] * 100/ Wo

Where, SW% = Equilibrium percent swelling Wo = Initial wt. of emulgel at time zero

Wt = Weight of swollen emulgel after time

RHEOLOGICAL STUDIES:

The viscosity of the different emulgel formulations was determined at 25^0C using Brookfield viscometer with spindle 52 and connected to a thermostatically controlled circulating water bath. The viscosities were determined.

III. RESULTS AND DISCUSSION

PREFORMULATION STUDY:

SOLUBILITY STUDY: The solubility study of clotrimazole drug was examined by dissolving 10 mg of clotrimazole in 10 ml of light liquid paraffin, propylene glycol, methanol, methyl paraben, propyl paraben and water.

The solubility of Clotrimazole drug was studied in different type of solvents which are given below:

SOLVENTS	SOLUBILITY
Light liquid paraffin	+++
Propylene glycol	+
Methanol	+++
Methyl paraben	+
Propyl paraben	+

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Water	–

Table-1 Solubility of Clotrimazole

The solubility of clotrimazole was found to be highly soluble in light liquid paraffin and methanol but less soluble in propylene glycol, methyl paraben and propyl paraben and insoluble in water.

CALIBRATION CURVE OF CLOTRIMAZOLE:

Preparation of Standard Stock Solution: Weighed 10 mg of clotrimazole and transferred into the volumetric flask (100 ml). Volumetric flask was contained 2 ml of methanol. After that drug was fluidify in 2 ml of methanol. The volume was balance with methanol upto the mark to get final solutions containing 100 µg/ml of clotrimazole . Then that solution was imposed to ultrasonication for about 10 to 20 minutes and then filtered through 0.2 µm (N66) membrane filter paper. To obtain standard calibration curves, sample was diluted in series again with methanol. After that absorbance of clotrimazole solution was taken at 260 nm using UV-Spectrophotometer (Shimadzu UV 1700).

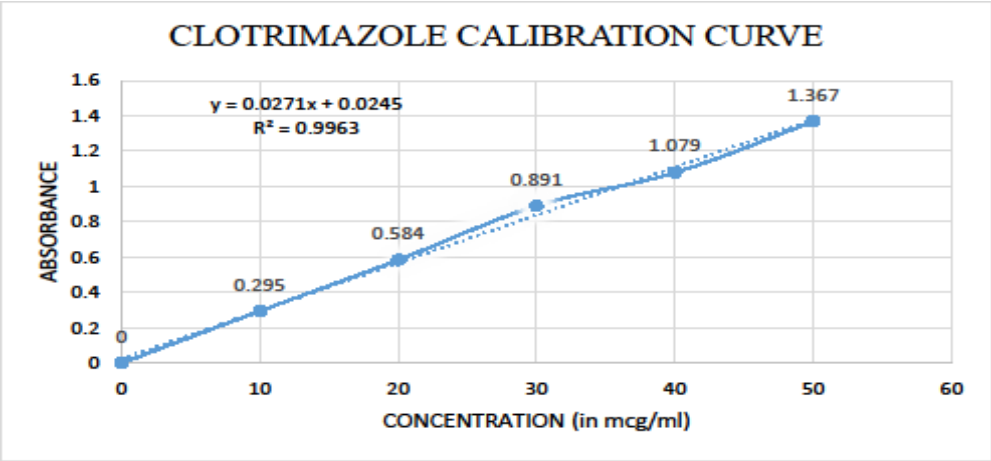

Fig-1 Calibration curve of Clotrimazole drug in Methanol

MELTING POINT ANALYSIS: 50 mg of drug was subjected to melting point apparatus **(Fisher–John's apparatus);** the melting point of clotrimazole was found to be148^0 C.

IDENTIFICATION: 50 mg of drug was identified by means of FTIR at 260 nm.

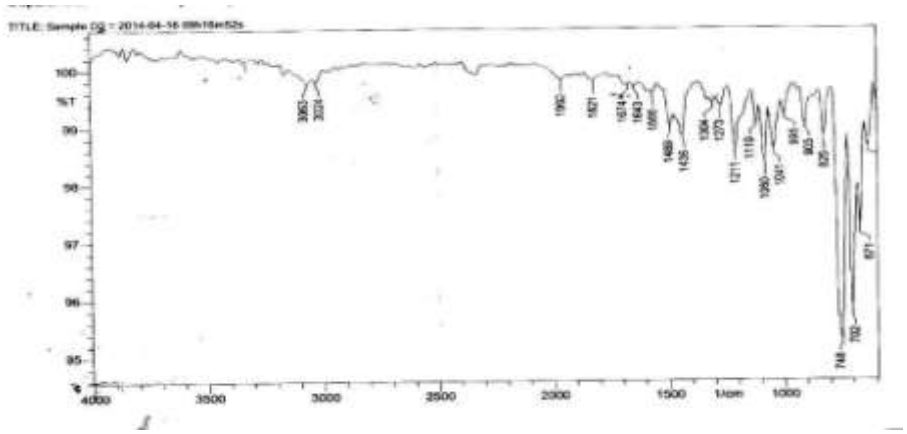

Fig-2 FTIR SPECTRA OF CLOTRIMAZOLE DRUG

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PHYSICAL EXAMINATION:

APPEARANCE:

Clotrimazole emulgel formulations which were prepared, inspected visually for homogeneity, color, consistency and pH. All formulations from F_1 to F_6 showed white color formulations showed gleaming appearance. Formulations from F_1 to F_6 showed appropriate homogeneity and consistency.

Phase separation was examined by centrifuge machine. 3ml of emulgel sample was taking in small test tubes , place the 6 test tubes in a centrifuge machine than subjected to centrifugation at the speed of 3000 rpm. After 10 minutes sample phase separation was not observed in test tubes containing samples of emulgel.

Formulations	Color	Consistency	Homogeneity	Phase Separation
F_1	Shiny white	+++	+++	None
F_2	White	+++	+	None
F_3	White	++	++	None
F_4	Shiny white	+++	++	None
F_5	Shiny white	+++	++	None
F_6	Shiny white	+++	+++	None

Table-2 Shows the appearance characteristics of the Emulgel Formulations

The color, consistency and homogeneity of all 6 formulations was found to be excellent. Phase separation was not found in any formulations.

pH DETERMINATION: pH determination of emulgel formulation (clotrimazole) was determined by using **Abron pH meter**. The electrode of pH meter was cleaned with distilled water and made it dry with the help of tissue paper, then immerse the electrode and temperature probe in beaker containing emulgel formulations. After that wait for few minutes then note the readings of pH of samples (F_1- F_6) which were displayed on pH meter. Experiments was performed in triplicates.

Formulation	pH
F_1	6.12±0.50
F_2	6.36±0.52
F_3	6.32±0.36
F_4	6.51±0.40
F_5	6.34±0.68

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F_6	5.64±0.59

Table-3 : pH of emulgel formulations (F_1- F_6)

The pH values of formulations F_1 to F_6 was found in the range of 5.64-6.51% which were considered avoidance of skin itching upon application to skin. The pH sample of F_4 was found to be more suitable.

DRUG CONTENT DETERMINATION: Drug content determination was performed by dissolving 500 mg of clotrimazole emulgel in 5 ml of methanol in a beaker. Then the formulations were diluted by the methanol and absorbance was taken at 260 nm using UV- Spectrophotometer (Shimadzu UV 1700). The drug content was calculated by using the slope and the intercept obtained by linear regression analysis of standard calibration curve.

BATCH NO.	% DRUG CONTENT(µg/ml)
F_1	44.8%
F_2	70.84%
F_3	26.85%
F_4	13.68%
F_5	13.63%
F_6	30.7%

Table-4 : Drug content of emulgel formulations from F_1 to F_6 are given below:

The drug content of emulgel formulations was determined and the results was found in limits with range of 30.7%- 70.84%. The drug content of F_2 was found to be 70.84% which were considered as a best drug content dose.

IN-VITRO RELEASE STUDIES: In-vitro release study was determined by Franz diffusion cell apparatus. 1 gm of emulgel was placed on the donor compartment of cell . Phosphate buffer pH 7.4 was placed on a receptor compartment. The medium was agitated using a magnetic stirrer. 5 ml of sample were withdrawn from the receptor compartment at 10- 50 minutes of duration of time. The withdrawn sample was replaced with fresh sample. After that, absorbance of sample was taken by the UV- Spectrophotometer at 260 nm.

Time (min)	F_1	F_2	F_3	F_4	F_5	F_6
0	-	-	-	-	-	-
10	11.27	8.08	36.79	7.943	11.63	10.31
20	16.87	13.7	40.5	11.3	15.7	14.35

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30	22.5	20.1	46.55	16	20.4	18.61
40	29.75	31	52.5	20.7	25.7	21.66
50	37.76	39.2	58.7	28.2	31.5	26.84

Table-5 : Data for in-vitro cumulative% drug release of all prepared formulation from F_1 to F_5 is given as follows:

Highest% cumulative drug release 58.7% at 50 minutes which were observed in F_3 formulation. So F_3 was considered as a optimized dose of emulgel formulation.

SWELLING INDEX: 1 gm of emulgel (clotrimazole) was scrapped with Millipore filter paper placed on a beaker containing phosphate buffer of pH 7.4 . After 4 hours remaining amount of sample was weighed with electronic balance. The weight of swollen gels was determined by using the following formula:

SW% = [Wt – Wo] * 100/ Wo

Where, SW% = Equilibrium percent swelling Wo = Initial wt. of emulgel at time zero
Wt = Weight of swollen emulgel after time

Swelling index of all prepared formulation from F_1-F_6 are given below:

Formulations	**Swelling Index**
F_1	31.54%
F_2	28.43%
F_3	32.14%
F_4	34.21%
F_5	28.23%
F_6	40.02%

Table-6 : Swelling index of emulgel formulation (F_1. F_6)

The swelling index of F_6 was found to be 40.02% which was considered as a highest swelling index.

RHEOLOGICAL STUDIES: The viscosity of the emulgel formulation from F_1 to F_6 was determined by Brookfield viscometer (spindle 52). The 40 ml samples were placed on a beaker which was connected to a water bath, spindle of viscometer was rotated. After that recorded viscosities was noted.

Formulations	**Min* η**	**Max*η**
F_1	6390	1100
F_2	65.68	27.66
F_3	6309	1070
F_4	97.83	27.83

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F_5	7615	1225
F_6	6684	1080

Table-7 : Viscosities (cp) of Clotrimazole emulgel formulations high and low rate of shear.

The recorded viscosities of F_1 toF_6 formulations at both higher and lower shear rate were collected. F_1(1100) , F_3 (1070) F_5 (1225) and F_6 (1080) was found to be highest viscosities whereas F_2(65.68) and F_4(97.83) was found to be lower rate of shear.

IV. CONCLUSION

Clotrimazole exhibited good solubility in light liquid paraffin than propylene glycol. So this co-solvent was although chosen to be used in the emulgel formulation. Concentration of oils and surfactants increasing the size of globules. Clotrimazole emulgel formulation was prepared by using Carbopol 940, six formulated batches show glossy and white appearance.. The solubility of drug in the oil phase is important for emulgel to maintain the drug in solubilized form. pH value indicates the suitability of emulgel for topical application. The pH value of (F_1 to F_6) formulation ranged from 5.66-6.51. The pH of the proposed of the formulation is friendly to the skin. The emulgel containing surfactant, co-surfactant and emulsifiers showed excellent physical and chemical stability. Cumulative % release data revealed that formulation F_3 containing the Tween 80 was the optimum formulation which showed 58.7 % drug release after 5 hours. The viscosity of F_1 (1100), F_3 (1070) and F_6 (1080) was found to be highest.

It was concluded on the basis of results of evaluation that emulgel will be a solution for incorporating hydrophobic drugs in water soluble bases. Formulation containing the highest conc. of emulsifiers, the optimized formulation having highest % cumulative drug release after 5 hours. Thus, emulgel showed a promising future for topical delivery of drugs.

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