FORMULATION AND EVALUATION OF FLUCONAZOLE OINTMENT

[1]Haleema.S. Siddiqui, [1]Mr.R. Balaji Reddy, [2]Nausheen Fathima, [3]M. Mahboob Shareef, [4]Mohammed Mustafa

Department of Pharmaceutics,
Deccan school of pharmacy, Darussalam, Aghapura.
Affiliated Osmania University, Hyderabad-500027

***Abstract*: The key focus of this research study was to develop a fluconazole ointment using polyethylene glycol (water soluble) ointment base. Five formulations where each contains 0.5%w/w of fluconazole and 25%w/w of PEG 4000 with varying concentration of PEG 400 were formulated by the method of fusion. The prepared fluconazole ointments were examined visually, pH, Viscidness, Drug content, In-vitro drug release and Antifungal potency where dermatophyte fungi strain was used. Upon evaluation the formulation F5 showed highest % of drug content and antifungal activity and satisfactory results in all assessment parameters and best expressed by Higuchi model indicating that optimum concentration of PEG 4000 and PEG 400 form a potent ointment base for azole antifungals. Through this research study we intend to show PEG ointment base as a safe, efficacious ointment base for Fluconazole and similar azole antifungals that can prove to be effective against fungal dermatological infections.**

***Keywords*: Fluconazole, Polyethylene glycol, Dermatophyte fungi, Antifungal activity**

INTRODUCTION: Nowadays dermatological infections are treated with antimicrobials formulated in broad range of semisolid dosage forms comprising of ointments, creams, gels, pastes, aerosols, solutions [1]. The skin has become a significant site of drug delivery due to easy access, greater surface area and non-invasive, pain free nature of therapy where bioavailability is systemic or local [2]. The therapy can be stopped without any complications if any adverse effects occur[3].Ointments are homogenous, semisolid dosage form applied to the skin or mucous membrane[4].Few authors have postulated diverse formulations of azole antimycotic ointments [5-7]. Hydrocarbon, absorption bases and water-soluble bases are various types of ointment base that facilitates the manufacture of optimum formulation.

Polyethylene glycols (PEGs) are being employed in topical pharmaceutical preparations due to their chemical stability, hydrophilicity, safety and washable property. Current research work is underway for optimal release of antimicrobial drugs from water soluble PEG base maintaining bioavailability, efficacy and safety for improved treatment [8]. The primary goal of this research study was to prepare Fluconazole ointment containing water soluble base PEG 4000 and 400 in combination and to evaluate its drug content and antifungal activity.

MATERIALS:

Fluconazole was procured from Chandra Labs, Hyderabad. PEG 4000 from Chemical Crunch, Mumbai and PEG 400 from Bangalore Fine Chem (BFCLAB). All other excipients of analytical grade were utilised for this study.

METHOD:

The topical ointment of fluconazole comprising of water-soluble base was developed by the process of fusion. Water soluble bases selected are Polyethylene glycol 4000 and PEG 400 and are heated in descending order of their weights and mixed thoroughly. The drug Fluconazole 0.5%w/w was added and dissolved in propylene glycol and then incorporated into the PEG ointment base.

Six ointment formulations were prepared of the following composition tabulated in the table

INGREDIENTS	F1	F2	F3	F4	F5
Fluconazole	0.5 gm	0.5 gm	0.5 gm	0.5 gm	0.5 gm
Polyethylene glycol 4000	25	25	25	25	25
Polyethylene glycol 400	20	25	30	35	40
Menthol	1	1	1	1	1
Propylene glycol	15	15	15	15	15
Methyl paraben	0.5	0.5	0.5	0.5	0.5
Propyl paraben	0.5	0.5	0.5	0.5	0.5
Water	q. s	q. s	q. s	q. s	q. s

Table1: Formulation composition of respective Fluconazole ointment with water soluble base

EVALUATION OF FLUCONAZOLE OINTMENTS:

1.PHYSICAL EXAMINATION:

Physical appearance of six formulations was observed visually and Spreadability by spreading 1g of prepared ointment on a clean glass surface[10].

2.pH DETERMINATION:

The ointment formulations were evaluated for their pH using pH meter[9].

3.VISCOSITY MEASUREMENT:

The drug release from six fluconazole PEG ointment formulations depends on the viscosity that is evaluated using Brookfield viscometer[9]

4.DRUG CONTENT:

An accurately weighed amount of each formulation was dissolved in 5ml 0.1 N NaOH, filtered using a nylon membrane filter disk (0.45µm). Then they were suitably diluted and assayed spectrophotometrically for drug content λmax at 303nm against blank. [11]

5.In VITRO DRUG RELEASE STUDY:

The 6 formulations for in-vitro release were examined using dialysis method.1 gram sample of each formulation positioned on a cellophane membrane submerged in 25ml of phosphate buffer 7.4(receptor medium) for 24 hours and spread on the glass tubes lower end sealed using a rubber band and, in a beaker maintained for 3 hours at 37 ± 0.5ºC in a thermostatic shaking water bath (50 rpm). 5 ml sample of each prepared formulation was removed at intermissions of 1, 2, 3, 4, 5, and 6 hours and substituted by equivalent volume of buffer solution.[9].

6.ANTI-FUNGAL ACTIVITY:

The anti-fungal potency of the prepared fluconazole PEG ointment base was evaluated using Agar cup plate method. Strains of Trichophyton rubrum, one of the most common dermatophyte fungi was selected for the study. Spores of the selected strain were mixed with Sabourad Agar media and allowed to solidify. Wells of 1cm depth were created and 0.5gm of each formulation was added and incubated for 7 days and the zone of inhibition was calculated.[9].

7.DRUG RELEASE KINETICS:

Fluconazole release kinetics expressed by Zero order, First order, Higuchi model and Peppas model[9].

RESULTS AND DISCUSSION:

1.Physical Examination:

The 6 prepared fluconazole ointments are white coloured viscous in nature with suitable consistency and Spreadability.

2.pH Determination:

The following pH values (6-7) indicate that on application each formulation will not lead to any skin irritation.

S. No	Formulation	pH
1.	F1	6.21±0.1
2.	F2	6.68±0.29
3.	F3	7.17±0.4
4.	F4	6.70±1.2
5.	F5	6.51±0.6

Table 2: pH of Fluconazole ointments

3. Viscosity Determination:

The table 3 represents the viscosity evaluated for the prepared formulations.

S. No	Formulation	Viscosity(cps) at rpm
1.	F1	30,890±14.2
2.	F2	31,218±10.8
3.	F3	32,600±15.1
4.	F4	33,129±20.4
5.	F5	34,254±15.8

Table 3: Viscosity of Fluconazole ointment

4. Drug Content:

The results indicate that the range of drug content of prepared formulation was 97-99% which infers uniform distribution of drug.

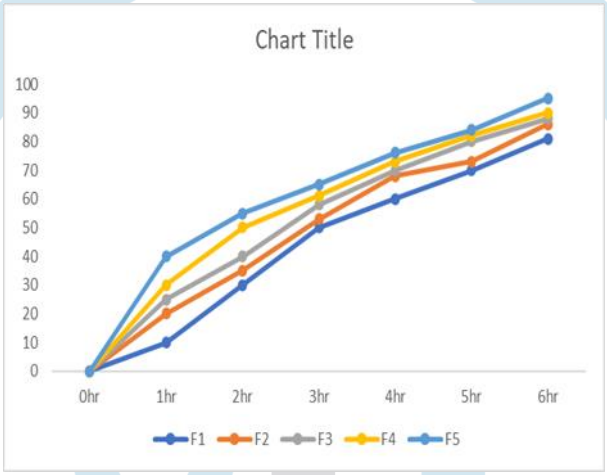
S. no	Formulation	Drug content
1.	F1	97.1±0.58
2.	F2	98.3±0.61
3.	F3	98.5±0.43
4.	F4	98.7±0.32
5.	F5	99.8±0.51

Table 4: Drug content of Fluconazole Ointments

5. In-vitro Drug release study:

Key evaluation of API release from the formulation essential during drug development process

Fig 1-In Vitro release of Fluconazole from PEG ointment base



S. No	Formulation	%CDR (6hr)
1.	F1	85.089±1.01
2.	F2	87.021±1.67
3.	F3	89.181±0.72
4.	F4	90.038±0.96
5.	F5	92.016±0.52

Table 5: In-vitro drug release of fluconazole ointments

6. In Vitro Antifungal Study:

The average value of zone of inhibition of three plates for each formulation was determined.

S. No	Formulation	Zone of inhibition diameter(mm) Trichophyton rubrum
1.	F1	25
2.	F2	29
3.	F3	34
4.	F4	37
5.	F5	39

Table 6: Zone of inhibition of prepared Fluconazole ointments

7. Drug Release Kinetics of Optimized Formulation (F5):

Optimized formulation (F5) was subjected to Zero, first order, Korsmeyer peppas model and Higuchi model. From the following results it can be inferred that Higuchi model best expressed the formulation (F5).

Table 7: Data of fluconazole release kinetics

CONCLUSION:

Using Water soluble ointment base PEG 4000 and PEG 400 in combination we have been able to successfully formulate fluconazole ointment for topical application for antifungal therapy against Dermatophyte fungi. The optimized formulation was F5 as it showed highest drug content, drug release and antifungal activity. With the right concentration of PEG 4000 and PEG 400 they act as a potent, safe and efficacious ointment base for incorporating azole antifungal drugs. Thus, this water-soluble base is a potential vehicle and serves a new route for topical drug delivery.

Formulation	Zero order Regression equation(R^2)	First order (R^2)	Higuchi model (R^2)	Korsmeyer Peppas (R2)
F5	0.941	0.037	0.998	0.612

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