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Design and Characterisation of Emulgel of an Antifungal drug

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Abstract:

Emulgel is the recent technology in novel drug delivery system used for control release of emulsion and gel for the purpose of topical use. The stability of emulsion is increased, when it is incorporated into gel. Ketoconazole is a lipophilic antifungal drug has been used in the treatment of dermatophytic infection. The goal of the present study was to design and Characterisation of Emulgel of an Antifungal Ketoconazole drug to incorporate hydrophobic or poorly water soluble drug in formulation and delivered through gels and which will increase skin penetration of drug. This study was conducted to develop emulgel formulations of Ketoconazole using different types of gelling agents like carbapol 940 and carbopol 934. The in-vitro diffusion studies were carried out for all formulations. All gels showed acceptable results of properties like color, homogeneity, consistency, pH, viscosity, spreadability, extrudability and drug content etc. Formulation containing Carbapol 934 having good spreadability, homogeneity and soothening effect. In these all aspect the formulation F5 satisfied all the pharmaceutical parameter of emulgel and appears to be good topical agent.

Keywords: Ketoconazole (Ktz), Topical Drug Delivery System, Emulgel, Carbopol 934, Carbapol 940

I. INTRODUCTION

Topical drug delivery is the term used for localized treatment of dermatological condition where the medication is not targeted for systemic delivery; examples include treatment of dermatological conditions like eczema or psoriasis by topical application. Examples of drugs delivered topically include corticosteroids, antifungals, antivirals, antibiotics, antiseptics, local anesthetics, and antineoplastics.

Gels being newer class of dosage form are created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles, which may obtained from natural or synthetic origin. The higher constitution of aqueous component shows greater dissolution of drugs, and permits easy migration of the drug through a liquid vehicle as compared with the ointment or cream base. In spite to advantageous gels show a major limitation in the delivery of hydrophobic drugs. So avoid this limitation, emulgel is prepared. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. To deliver the various drugs to the skin, both oil-in-water and water-in-oil type of emulsions are used as vehicles.

For dermatological use Emulgels show several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, long shelf life, bio-friendly, transparent & pleasing appearance.. Molecules can basically penetrate into skin through intact stratum corneum, sweat ducts and sebaceous follicle. The surface of the uppermost layer of skin that is stratum corneum presents more than 99% of the total skin surface and that is available for percutaneous drug absorption. Passage through this outer most layer is the rate limiting step for percutaneous absorption. The percutaneous absorption include the concentration gradient, it provides the driving force for drug movement across the skin, release of drug from the vehicle that is partition coefficient, and drug diffusion across the layers of the skin that is diffusion coefficient. Emulgel having many advantages like Incorporation of hydrophobic drugs, Better loading capacity, Production feasibility and low preparation cost, Better stability, Controlled release etc.

II. MATERIAL AND METHODS

Materials:

Ketoconazole and Carbopol 940 purchased from Yarrow Chem Products, Mumbai. Liquid paraffin, Glutaraldehyde, Triethaloamine, Span 20, Tween 20, Propylene glycol procured from Loba Chemie, Mumbai. Carbopol 934 purchased from Research Lab fine chem. Industries

Methods:

Method of Preparation of Ktz-loaded Emulgel:

Preparation of gel base: Sock Carbapol in water for 24 hrs, add Triethanolamine in it.

Preparation of Emulsion: Prepared oil phase by Mixing of span 20 in liquid paraffin and Aqueous phase by drug dissolved in ethanol, Tween 20 mixed with distilled water, Methyl paraben and propyl paraben dissolved in propylene glycol (Mixed these three solutions with each other so as to form aqueous phase). Both oily phase and aqueous phase heat upto 70 to 80 ℃ separately. Add oil phase into aqueous phase with continuous stirring. Cool at room temperature.

Preparation of Emulgel: Add emulsion into gel base.

Characterization of Emulgel:

1. **Physical Apperance:** [14]
   The prepared Emulgel formulation of Ketoconazole was inspected for their Physical Apperance including colour, consistency, homogeneity.
2. **pH measurement:** [14]
   1g of emulgel was dissolved in 100 ml distilled water and kept aside for two hours. The pH of developed formulations was determined using pH meter.
3. **Viscosity**: [15]
   Brookfield Viscometer was used to determine viscosity of prepared Emulgel formulation. For the determination of viscosity, prepared Emulgel formulation was added to the beaker and settled it for 30 mintue at 25-30 °C. Adjust the spindal in that way

that spindal does not touch the bottom of the jar and rotate at a moderate speed 100 RPM for 10 mintue. The viscosity reading was noted.

4. **Spreadability:** [3]

Spreadability is determined by apparatus which is suitably modified in the laboratory and used for the study. Spreadability was measured by two glass slides and a wooden block, which was provided by a pulley at one end on the basis of Slip and Drag characteristics of gels. A ground glass slide was fixed on this block. An 1 gm of gel of different formulations were placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide. Excess of the gel was scrapped off from the edges. The top plate was subjected to pull of 20gms. If time taken for the separation of two slides is less then better the spreadability.

Spreadability is calculated by using the following formula:

$S = M \times L/T$

Where, S is the spreadability, M is the weight in the pan (weight tied to the upper slide), L = is the length moved by the glass slide T = time taken to separate the slide completely from each.

5. **Extrudability:** [12]

It is a usual empirical test to measure the force required to extrude the material from tube. The extrudability is based upon the quantity of emulgel and this emulgel extruded from collapsible tube on application of weight in grams required to extrude at least 0.5cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability.

The extrudability is determined by using the following formula.

Extrudability = Applied weight to extrude emulgel from tube (in gm) / Area (in cm^2)

6. **Drug Content:** [9]

Drug concentration in emulgel was measured by UV spectrophotometer. Drug content was measured by dissolving specific quantity of emulgel in solvent with the help of Sonication. Absorbance was measured after suitable dilution at 242 nm in UV/VIS spectrophotometer.

7. **In-vitro Diffusion Study:** [3]

Simple diffusion cell was used for the drug release studies. Ketoconazole emulgel was applied onto the surface of egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber of diffusion cell was filled with freshly prepared solution of phosphate buffer pH 5.5. The receptor chamber was stirred by magnetic stirrer. The samples were collected at suitable time interval. Samples were analysed for drug content by UV visible spectrophotometer at 242 nm after appropriate dilutions. The cumulative amount of drug released across the egg membrane was determined as a function of time.

8. **Motic Digital Microscopy:**

Prepared Antifungal Emulgel can be placed on glassslide at room temperature and then the surface morphology of the Emulgel can be studied by Motic Digital Microscopy. The morphology of Ketoconazole Antifungal Emulgel was examined with a Motic Digital Microscopy. The sample was mounted on a glass slide and observed under 10X object.

9. **Antifungal activity of optimized formulation:** [13, 16, 21]

Antifungal activity was checked by agar well diffusion method. Certain volume of *fungus* suspension was poured into sterilized sabouraud's agar media (cooled at 40 ºC) and mixed systematically. About 20 ml of this suspension was poured aseptically in petri dish and kept till the solidification. The surface of agar plates was pierced by using a sterile cork borer. The prepared wells were filled with an equal volume of optimized batch of antifungal emulgel formulation after that it was incubated at 18-24 ºC, for 72 hrs. Fungal growth was found and the zone of inhibitions was measured using antibiotic zone reader.

10. **Zeta potential measurement of optimized formulation:** [25]

Zeta potential of emulsion of optimized formulation and optimized formulation of Emulgel determined by Malvern zetasizer. Sample dissolved in purified water and agitated to get homogenous dispersion then analyze it on zetasizer.

11. **Fourier transform infrared spectroscopy of Optimized formulation:**

FTIR of Optimized formulation of emulgel was performed. The spectra were scanned over wavelength region of 4000 to 400 cm-1 at resolution of 4 cm-1.

III. RESULT AND DISCUSSION:

1. **Physical Apperance:**

The physical observation of prepared Ketoconazole emulgel formulations are shown in Table 2.

2. **pH measurement:**

The pH values of all prepared formulations were ranged between 6.0 to 6.4 which was shown in Table 2. The formulations are considered acceptable to avoid the risk of irritation upon application to the skin because adult skin pH is 5.5.

3. **Viscosity:**

The tests were performed at 100 rpm for 10 min. Results are shown in table 2.

4. **Spreadability:**

The values of spreadability indicate that the Ketoconazole emulgel is easily spreadable by small amount of shear. The spreadability of all prepared batches from F1to F6 are shown in table 2.

5. **Extrudability:**

The emulgel formulations were filled into collapsible metal tube or aluminium collapsible tube. The tube was pressed to extrude the material and the extrudability of formulation was observed. Results are

shown in table 2.

6. **Drug Content:**
The drug content of all prepared batches from F1to F6 was shown in table 2.

7. **In-vitro Diffusion Study:**
The in-vitro diffusion studies were carried out for all formulations using PBS (pH 5.5). In- vitro diffusion of all formulation is shown in table 3.

Table 1. Composition of Ktz-loaded Emulgel formulations

Ingredients (% w/w)	F1	F2	F3	F4	F5	F6
Ketoconazole	1	1	1	1	**1**	1
Carbopol 934	-	-	-	0.5	**1**	1.5
Carbopol 940	0.5	1	1.5	-	-	-
Liquid paraffin	2.5	2.5	2.5	2.5	**2.5**	2.5
Span 20	0.3	0.3	0.3	0.3	**0.3**	0.3
Tween 20	0.4	0.4	0.4	0.4	**0.4**	0.4
Propylene glycol	2.5	2.5	2.5	2.5	**2.5**	2.5
Ethanol	1.25	1.25	1.25	1.25	**1.25**	1.25
Methyl Paraben	0.01	0.01	0.01	0.01	**0.01**	0.01
Propyl Paraben	0.05	0.05	0.05	0.05	**0.05**	0.05
Glutaraldehyde	0.05	0.05	0.05	0.05	**0.05**	0.05
Purified Water	q.s.	q.s.	q.s.	q.s.	**q.s.**	q.s.

Table 2. Evaluation of Antifungal Emulgel formulation

Parameters	F1	F2	F3	F4	F5	F6
Colour	White	White	White	White	**White**	White
Consistency	Excellent	Excellent	Excellent	Excellent	**Excellent**	Excellent
Homogeneity	Good	Good	Good	Good	**Good**	Good
pH	6.1	6.2	6.2	6.1	**6**	6.4
Viscosity (cp)	2231	2221	2236	2341	**2346**	2339
Spreadability(gm.cm/sec)	26	25	26	22	**27**	25
Extrudability(g/cm^2)	13	16	11	16	**13**	16
Drug content (%)	74	73	74	77	**81**	79

Table 3. In-vitro Diffusion Study

Time (Hrs)	% Drug Diffused					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	**0**	0
1	15.47	15.70	16.17	26.33	**32.55**	24.66
2	19.40	18.42	19.87	27.8	**40.48**	31.14
3	23.85	24.41	25.14	33.09	**45.24**	37.07
4	29.24	29.72	29.90	41.46	**51.35**	41.71
5	33.17	33.24	34.29	45.46	**57.48**	43.80
6	40.06	41.51	42.14	51.24	**64.09**	51.50
7	49.24	46.62	49.45	57.39	**66.90**	57.26
8	51.32	54.07	57.38	62.52	**68.91**	60.87

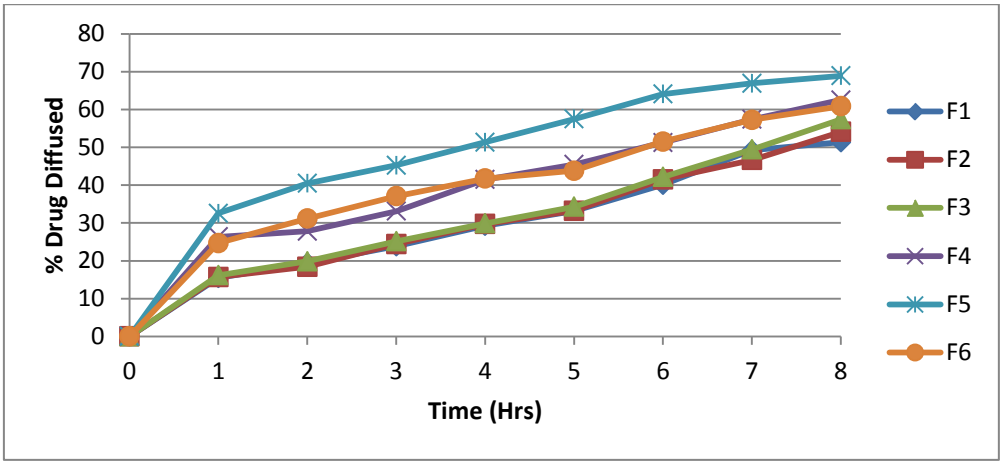

Figure 1. Comparative drug release profile of F1- F6

8. Motic Digital Microscopy:

Image of Antifungal emulgel (Optimized formulation F5) by Motic Digital microscope showed in figure that three dimensional cross-linked network within the liquid.

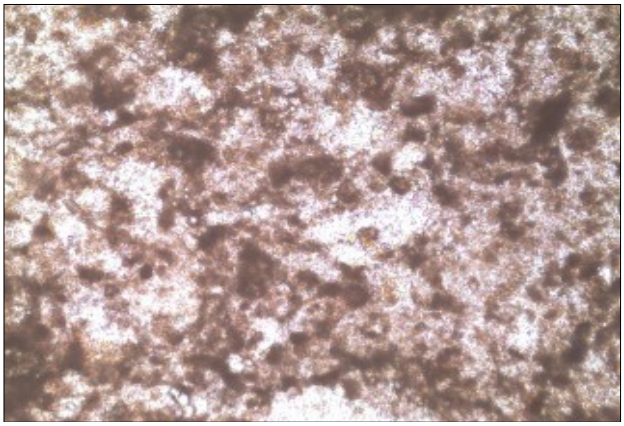

Figure 2. Motic microscopic image of optimized Emulgel formulation F5

9. Antifungal activity of optimized formulation:

Photograph showing Zone of inhibition of optimized batch F6 of Ketoconazole Emulgel

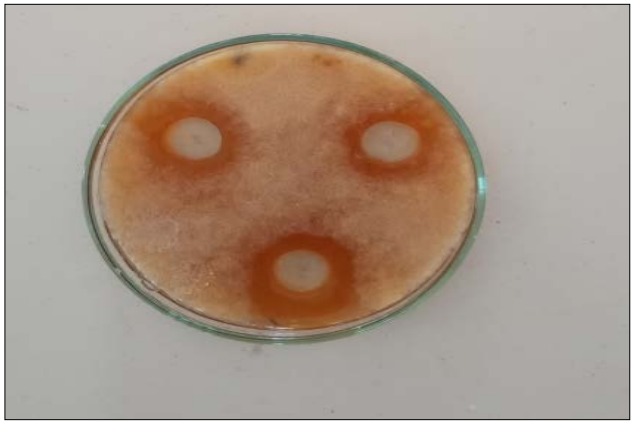

Figure 3. Antifungal activity of Ketoconazole Emulgel (F5)

The zone of inhibition was measured for antifungal activity of drug that is shown in table 4

Table 4. Inhibition zone of optimized formulation (F5)

Optimized formulation (F5)	Inhibition zone (cm)
	0.4-0.6 cm

10. Zeta potential measurement of optimized formulation:

Zeta potential of emulsion of optimized formulation and optimized emulgel formulation F5 was found to be -25.0 mV and -23.2 mV respectively, was shown in fig. The zeta potential of emulsion of optimized formulation and optimized Emulgel formulation F5 was shown good stability.

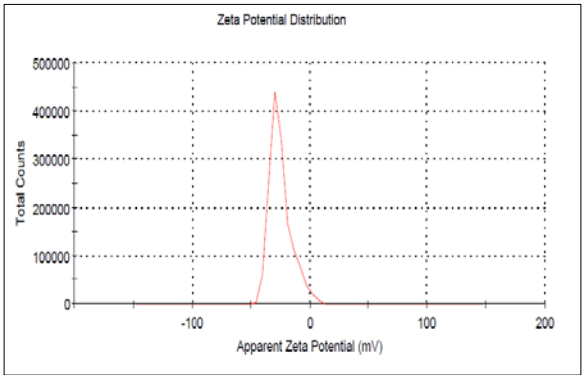

Figure 4. Zeta potential of emulsion of optimized formulation F5

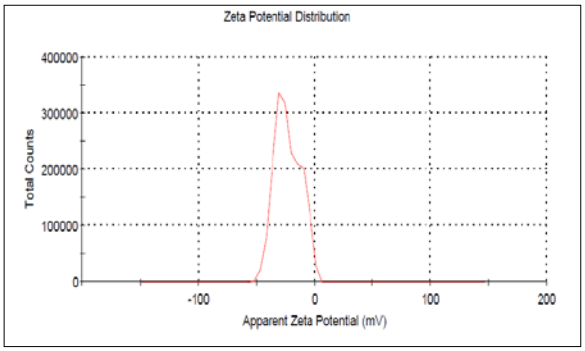

Figure 5. Zeta potential of optimized Emulgel formulation F5

11. Fourier transform infrared spectroscopy of Optimized formulation:

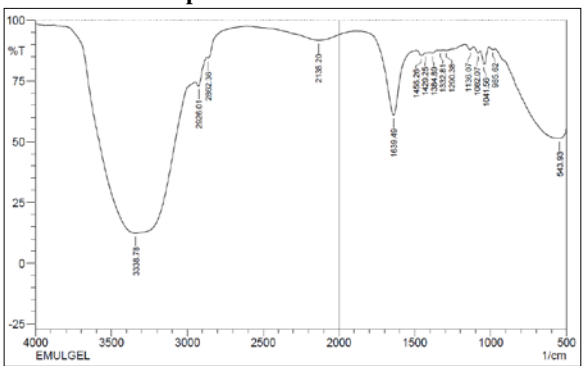

Figure 6. Fourier transform infrared spectroscopy of Optimized formulation F5

Table 5. Interpretation of IR spectrum of Optimized formulation F5 of Ketoconazole emulgel

Sr.No.	Observed value(cm^{-1})	Functional group sassociated
1	1639.49	C=O stretching
2	1290.38	C-O stretching
3	3338.78	C-H stretching
4	2926.01, 2862.36	C-H stretching

IV. CONCLUSION:

In the present study, an attempt has been made to formulate the topical drug delivery system of Ketoconazole Emulgel. Ketoconazole is widely used antifungal agent mostly used for fungal disease. The Ketoconazole was firstly characterized for its

identification by using physical characterization test like melting point, UV absorption in methanol, FTIR and DSC. Emulgel was developed using gelling agent carbopol 934, and carbapol 940. Span 20 and tween 20 used a emulsifiers. Propylene glycol used as a penetration enhancer.Methyl paraben and propyl paraben used as a preservative and Ketoconazole as hydrophobic drug. All the formulation designed and evaluated for the post formulation studies like color, pH, viscosity, spreadability, Extrudability, drug content, *In-vitro* drug diffusion and Antifungal studies etc. All the result observed was within official limit. Ketoconazole Emulgel formulation containing Carbapol 934 shown acceptable value as compared to Carbapol 940 so that the F5 formulation selected as an optimized formulation. No phase separation was observed in F5 optimized formulation. Drug content was found in the range of 81% , Spreadability in range of 27 g.cm/sec, Extrudability 13g/cm^2, Viscosity 2346 Cps, *In-vitro* drug release is 68.91 % , Antifungal activity for Aspergillus Niger shown 0.4-0.6 cm zone of inhibition. pH of all the formulation was found in the range of 6 to 6.4 that suits the skin pH indicating skin compatibility. This is the primary requirement for a good topical formulation. From the *In – vitro* drug diffusion study we have concluded that the Emulgel prepared from Carbapol 934, controls the drug release for longer period of time which will be helpful. Zeta potential of emulsion of optimized formulation and optimized emulgel formulation F5 was found to be -25.0 mV and -23.2 mV respectively. The zeta potential of emulsion of optimized formulation and optimized Emulgel formulation F5 was shown good stability.

From the above study we have concluded that the topical Ketoconazole Emulgel prepared from the Carbapol 934 having good spreadability, homogeneity and soothening effect. In these all aspect the formulation F5 satisfied all the pharmaceutical parameter of emulgel and appears to be good topical agent.

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