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RESEARCH ARTICLE……!!!

FORMULATION AND EVALUATION OF ITRACONAZOLE EMULGEL FOR TOPICAL DRUG DELIVERY

Asmit Kamble*, Rahul Adnaik, Mangesh Bhutkar

Rajarmbapu College of Pharmacy, Kasegaon, Dist: Sangli, Maharashtra, India.

KEYWORDS:

Emulgel, Itraconazole.

For Correspondence:

Asmit kamble *

Address:

Rajarambapu College of

Pharmacy, Kasegaon,

Tal. Walwa, Dist. Sangli.

E-mail:

asmitkamble@gmail.com

ABSTRACT

The aim of the present research work was to investigate the potential of emulgel in enhancing the topical delivery of Itraconazole. Emulgel formulations of Itraconazole were prepared using two types of gelling agents namely: Carbopol 934 and Carbopol 940. The influence of the type of the gelling agent and the concentration of both the oil phase and emulsifying agent on the drug release from the prepared emulgel was investigated using a 23 factorial design. The prepared formulations were evaluated for their physical appearance, viscosity, drug release, globule size, skin irritation test, antifungal activity, transmission electron microscopy and stability. Commercially available Itraconazole cream was used for comparison. All the prepared emulgel showed acceptable physical properties concerning color, homogeneity, consistency, spreadability, and pH value. The antifungal activity and drug release were found to be higher for optimized formulation as compared to the marketed Itraconazole cream. The result of studied reveled that the optimized batch shows 95.08% release in 48 hours andstable for around three. The result of microbial assay compared with marketed product, the result shows46.6% inhibition of optimized batch where as marketed preparation shows only 32.3% inhibition. Whileresult of skin irritation test shows no edema and erythema.No irritation was observed on the skin of the rabbits. Stability studies showed that the physical appearance, rheological study, in vitro drug release, and antifungal activity in all the prepared emulgel remained unchanged upon storage for 3 months. In general conclusion, it was suggested that the emulgel formulation succeed the drug release for sustained drug delivery in a controlled manner in comparison with cream.

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INTRODUCTION:

Emulgel are emulsions, either of the oil-in-water or water in oil type, which are gelled by mixing with a gelling agent. Emulsified gel is stable one and better vehicle for hydrophobic or poorly water soluble drugs . They have a high patient acceptability since they possess the advantages Topical drug delivery and antifungal activity of both emulsions and gels. Direct (oil-in-water) systems are used to entrap lipophilic drugs,whereas hydrophilic drugs are encapsulated in the reverse (water-in-oil) systems]. Therefore, they have been recently used as vehicles to deliver various hydrophobic drugs to the skin. In the local market, Emulgel are available: Voltarenemulgel (Novartis Pharma, Switzerland), containing diclofenac diethylamine and Miconaz-H emulgel (Medical Union Pharmaceuticals, Egypt), containing miconazole nitrate and hydrocortisone.

Topical drug administration is a localized drug delive Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. The emulsion gels are hydrogels containing randomly distributed oil micro droplets. Topical drug delivery systems have been used for centuries for the treatment of local skin disorders, one side the topical applications of the drug offer the potential advantages of delivering the drug directly to the site of action and delivering the drug for extended period of time at the effected site that mainly acts at the related regions. On the other hand, topical delivery system increases the contact time and mean resident time of drug at the applied site leading to an increase in local drug concentration while the pharmacological activity of Emulgel formulations may not change as rapidly as the solution form. Several antifungal agents are available on the market in different topical preparations (e.g. creams, ointments, and powders for the purpose of local dermatological therapy).One of these antifungal agents is Itraconazole, which has both antifungal and antibacterial properties. It is applied locally in mild uncomplicated dermatophyte and other cutaneous infections. Both oil-in-water and water-in-oil emulsions are extensively used for their therapeutic properties and as vehicles to deliver various drugs to the skin. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. In addition, the formulator can control the viscosity, appearance, and degree of greasiness of cosmetic or dermatological emulsions. Oil-in-water emulsions are most useful as water washable drug bases and for general cosmetic purposes, while water-in-oil emulsions are employed more widely for the treatment of dry skin and emollient applications.

Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, compatible with several excipients, and water-soluble or miscible.

MATERIALS AND METHODS [2]

Materials: Itraconazole was obtaines as a gift sample from Gufic Bioscience Ltd Mumbai, Carbopol 934, Light liquid paraffin,Tween 20, Span 20, propylene glycol, methyl paraben and propyl paraben were purchased from lobachemie , Mumbai. Ethanol was procured from Rajarambapu College of Pharmacy, Kasegaon. Double distilled water was used for all experiment.Allchemicalswerepharmaceuticalgradeand used without furthermodification.

Emulgel preparation: [3]

Table no 1: Emulgel preparation

CONTAINS	F1	F2	F3	F4	F5
DRUG(mg)	200	200	200	200	200
Propylene glycol(ml)	1	1	1	1	1
Carbapol 940(mg)	300	400	500	600	700
Tween 80	0.5	0.5	1	1	1
Propyl paraben(mg)	0.03	0.03	0.03	0.03	0.03
Liquid paraffin(ml)	1.5	1.5	1.5	1.5	1.5
Span 80	1	1	1	1	1
Triethanolamnie	Qs	Qs	Qs	Qs	Qs
Ethanol	2	2	2	2	2
Purified water QS	Qs	Qs	Qs	Qs	Qs

Characterization of Emulgel [4]

Physical appearance:

The prepared Itraconazole emulgel formulations were inspected visually for their color, homogeneity, consistency and pH. The pH values of 1% aqueous solutions of the prepared emulgel were measured by a pH meter (Digital pH meter).

Table no: 2 pH of Emulgel

Batch no.	pH
F1	5
F2	5.5
F3	5.6
F4	5.7
F5	5.5

Spreadability: One of the criteria for an emulgel to meet the ideal quantities is that it should possess good spreadability. It is term expressed to denote the extent of area to which gel readily spread on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from emulgel and placed in between the slides under the direction of certain load. It is calculated by using the formula.

Table no : 3 Spreadability:

Formulation code	Diameter(cm)
F1	4.2
F2	4.8
F3	5.7
F4	4.1
F5	4.8

Rheological Study: The viscosity of different emulgel formulation was determined at 250^{o}C using a brook field viscometer (Brookfield DV-E viscometer). The emulgel were rotated at 10 (min.) and 100 (max.) rotation per minute with spindle 4.

Table no 4: Rheological Study:

Batch no.	Viscosity (centipoise)
F1	1739.45
F2	1395.44
F3	2288.56
F4	1340.42
F5	1556.32

Drug Content Determination:[5] Drug concentration in emulgel was measured by UV spectrophotometer. Itroconazole content in emulgel was measured by dissolving Known quantity of emulgel in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution at 282 nm in UV/VIS spectrophotometer (UV-1800, Shimadzu Corporation, Japan).

Table no 5: Drug Content Determination:

Batch no.	Drug content
F1	91.13±0.16
F2	93.78±0.27
F3	95.12±0.67
F4	90.76±0.79
F5	94.24±0.46

In Vitro Release Study: [6]

Diffusion cell (with effective diffusion area 3.14 cm2 and 15.5 ml cell volume) was used for the drug release studies. Emulgel (1gm) was applied onto the surface of cellophine membrane evenly. The cellophine membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to

solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collectedat suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer at 282 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval .The cumulative amount of drug released across the cellophine membrane was determined as a function of time.

Table no 6: In Vitro Release Study:

Time in hrs	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	12.26±.0.13	11±0.16	12.29±0.026	16.38±0.19	24.77±0.14
2	14.05±.26	12.26±0.22	24.88±0.50	20.02±0.05	30.02±0.16
3	15.01±.31	13.63±0.33	27.38±0.37	20.98±0.53	32.61±0.56
4	15.5±.22	13.77±0.007	31.1±0.9	23.9±0.49	33.63±0.53
5	16.2±.15	14.6±0.31	31.13±0.10	26.97±0.53	34.51±0.58
6	17.35±0.12	15.02±0.006	33.81±0.57	28.95±0.51	35.22±0.59
7	20.01±0.21	16.21±0.12	36.35±0.17	32.26±0.13	37.26±0.45
8	21.97±0.60	17.36±0.37	39.7±0.25	39.63±0.31	40.22±0.32
9	22.51±0.48	21.22±0.48	43.61±0.79	43.51±0.25	44.06±0.61
10	30.65±0.30	23.41±0.59	46.97±0.92	48.87±0.45	47.11±0.21
11	34.33±0.16	27.6±0.52	55.83±0.92	50.88±0.13	48.22±0.22
12	36.36±0.18	30.61±0.64	61.77±0.94	52.2±0.27	48.52±0.31
13	41.08±0.23	33.41±0.22	65.1±0.02	50.26±0.0	50.26±0.52
14	45.36±0.28	35.76±0.32	71.32±0.50	51.27±0.50	51.27±0.42
15	48.96±0.27	41.95±0.51	77.56±0.37	53.85±0.37	53.85±0.41
16	53.51±0.41	48.0±0.41	79.33±0.79	55.82±12	55.82±36
17	58.12±0.23	53.01±0.35	81.37±0.68	63.81±32	56.63±25
18	63.53±0.32	57.4±0.42	84±0.42	65.1±56	58.38±52
19	66.02±0.61	61.45±0.12	86.27±0.57	67.7±54	62.03±33
20	67.88±.056	66.96±0.33	87.38±0.46	70.15±41	63.14±33
21	67.89±.0.32	70.7±0.18	89.15±0.61	70..16±12	63.15±65

Skin irritation test: [7]

A set of 8 rats was used in the study in set of two Experimental (4)and Control (4). The emulgel was applied on the properly shaven skin of rat. Undesirable skin changes, i.e., change in color, change in skin morphology were checked for a period of 24 h to development of Erythema and Edema was monitored.

Table no 7 Skin irritation test:

No. of Rat	**Erythema**			**Edema**		
	8 hr	16 hr	24 hr	8 hr	16 hr	24 hr
1.Experimena(4)	No	No	No	No	No	No
2.Control(4)	No	No	No	No	No	No

Stability studies:

The prepared Itraconazole emulgel formulations were stored away from light in collapsible tube at 25±2°C, 40±2°C and 4±2°C for 3 months. After storage, the samples are tested for their physical appearance, pH, rheological behavior, drug release, skin irritation test and microbiological assay.

Table no 8: Stability studies:

Sr no.	Properties	Observation
1	Color (Initial)	White
2	Color (After one month)	White
3	pH (Initial)	5.6
4	pH (After one month)	5.3
5	% drug content	89%

RESULTS

Physical examination: The prepared Itraconazole emulgel formulations were white viscous creamy preparation with a smooth and homogeneous appearance. The pH values of all prepared formulation ranged from 5.4 to 5.8, which are considered acceptable to avoid the risk of irritation upon application to the skin because adult skin pH is 5.5.

Spreadability: The values of spreadability indicate that the emulgel is easily spreadable by small amount of shear. Spreadability of F3 was 3.1cm/sec, indicating spreadability of emulgel containing itroconazole was good as compared to the marketed gel.

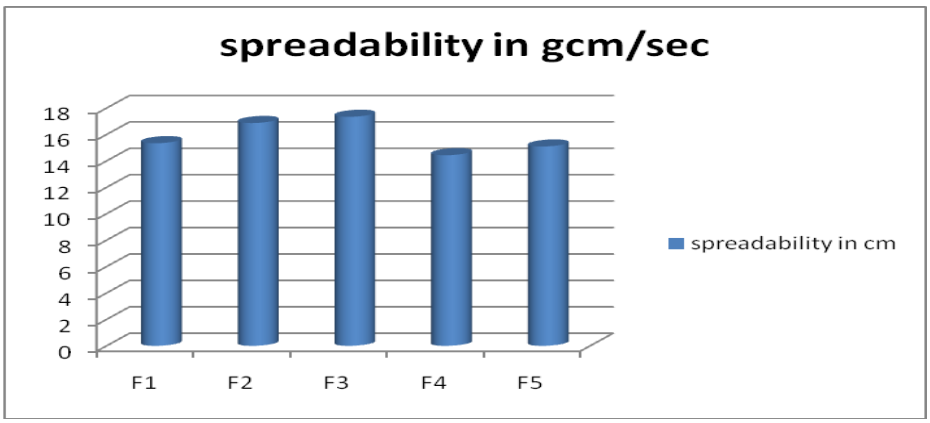

Fig 1- Spreadability of the various emulgel formulations (Mean ± S.D.)

Rheological studies: [8]

The measurement of viscosity of the prepared emulgel was done with Brookfield viscometer (Brookfield DV-E viscometer). The highest viscosity was found in Emulgel F3 it may be due to low level of the liquid paraffin concentration and emulsifying agent concentration. The lowest viscosity was found in formulation F2 .

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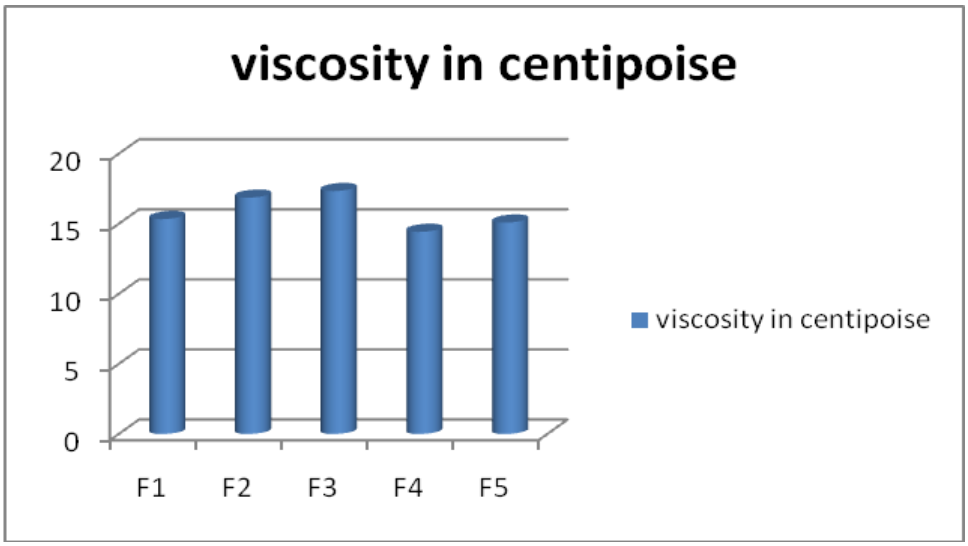

Fig 2- viscosity of itraconazole emulgel (Mean ± S.D.)

Drug content determination:

The drug content in emulgel was found in range of 67.87 ± 1.82% to 89.28± 1.20%. The higher drug content found in F3 i.e. 89.28 ± 1.20% it may be due to the concentration of liquid paraffin.

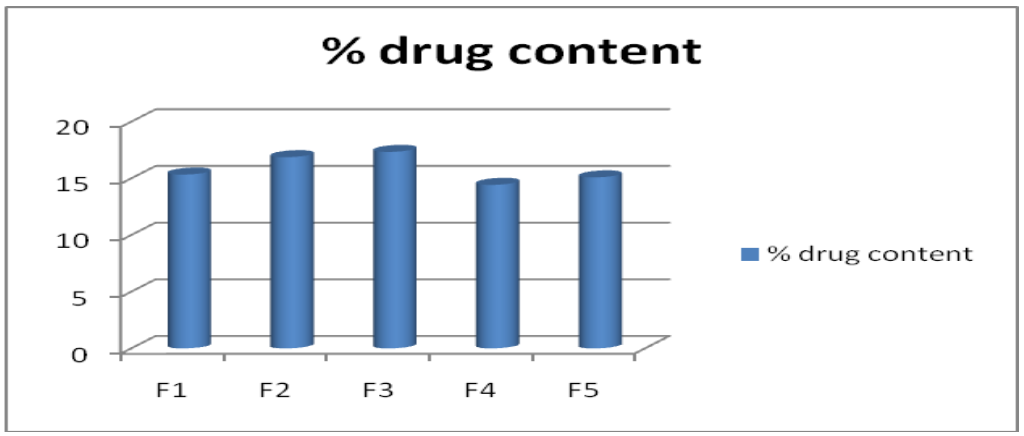

Fig. 3-Drug content of itraconazole emulgel in %

Drug Release:[9] The in vitro release profiles of Itraconazole from its various emulgel formulations are represented in . The better release of the drug from all emulgel formulation can be observed and the emulgel formulation can be ranked in the following descending order Where the amounts of the drug released after 21 hours were 67.89, 70.7, 89.15, 70.16, 63.15 respectively.

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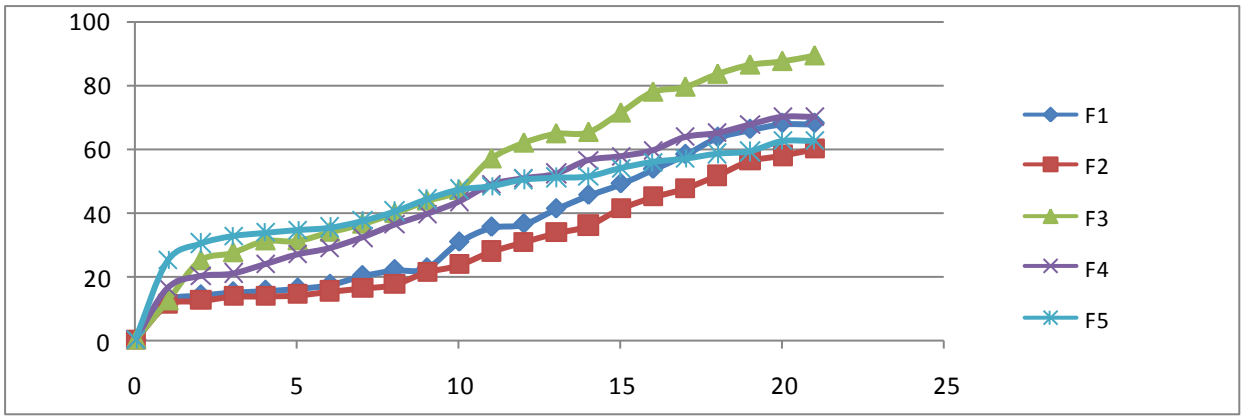

Fig no 4 Drug release of itraconazole emulgel

Stability studies:

Stability studies of optimized formulation were performed as per ICH guideline (International Conference on Harmonization). It can be observed that the emulgel formulation showed no major alteration in relation to the pH, microbiological study, consistency, skin irritation test and in vitro release study. The formulation shows stability for the period of 3 months. No significant changes in the pH of formulations were observed for 3 months in all storage conditions.

Discussion:

Topical application of the drug at the affected site offers potential advantage of delivering the drug directly to the site of action. The present work deals with the formulation and evaluation of Itraconazole topical gel using gelling agent like carbapol 940 in ten different concentrations and all the raw materials are of standard grad as supplied by manufacturer. The standard drug Itraconazole used. Itraconazole topical gel formulation was prepared by using carbapol 940 in ten different concentrations the formulated five batches shows white in appearance. optimized batch F3 shows white in appearance. pH of all five batches was found between 5 - 5.7 PH of optimized batch F3 was found 5.6 which lies in normal PH of skin.

Viscosity is important parameter for characterizing the gels as it affect spreadability, extrudability and release of the drug, all the formulated batches should increase viscosity as the concentration of gelling agent increased optimized batch F3 show ideal viscosity. Extrusion of the emulgel from the tube is an important during application and for the patient compliance. Emulgels with high consistency may not extrude from the tube easily, where as low viscous gel may show quickly extrudabilty of emulgels. Optimized batch F3 show better extrudability than other five batches. Formulation with less concentration of gelling agent was found to be good and with high concentration of gelling agent it was satisfactory. Optimized batch F3 show ideal gelling agent concentration 500mg all the prepared emulgel formulations showed uniformity of emulgel content.

All the pepaired batches shows uniformity in drug content. Optimized batch F3shows 95.12% drug content which indicate uniform drug dispersion in emulgel. Invitro realease studies were carried out by using phosphate buffer PH 5.5 realease of Itraconazole from all prepaired emulgel formulations was found to be satisfactory and found to be satisfactory and extended over longer period of time. In optimized batch F3 drug diffusion occurs through the fluid phase and hence they offer little resistance to drug diffusion and realese.

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