Original Article

Formulation And Evaluation Of Emulgel Of An Antifungal Drug For Topical Drug Delivery

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Abstract

Topical drug delivery system improved bioavailability, reduced side effects, more uniform plasma levels, longer duration of action, resulting in a reduction in dosing frequency and improve therapy due to plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage form. Emulgel are generally used where the other systems of drug administration fails to directly treat cutaneous disorders such as fungal infections, acne, psoriasis etc.

Materials and methods: Fluconazole emulgel was optimized based on Design-Expert® software using central composite design (CCD) making Fourteen formulations using jojoba oil and liquid paraffin, Methylparaben, Propylparaben and Triethanolamine.

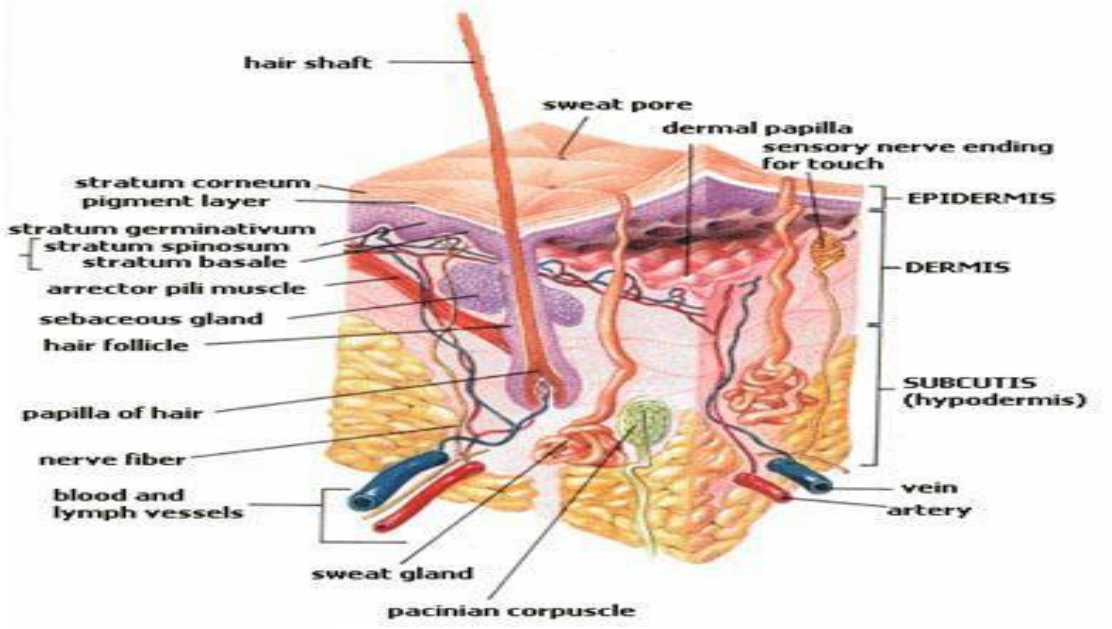
Results and Discussions: - The spreadability test range find from 8.9 g.cm/min to 14.87 g.cm/min for the formulations F1 and F14, respectively. Formulations having low amount of jojoba oil and liquid paraffin had the high spreadability index. As the viscosity of the gel increased, the release of the drug was expected to be slower. Complete drug release (100%) was achieved at the 3rd hr for the formulations F1, F8, F7 and F14 released more than 80 % of the drug and *in vitro* results showed that an emulgel formulation can be a potential candidate for the delivery of fluconazole for the skin disease, with better *in vitro* physical, using jojoba oil and liquid paraffin as drug carriers. SEM analysis of emulgel shows the uniform structure of emulgel formulation.

Keywords: - Emulgel ,oil ,gel, fluconazole, paraffin

INTRODUCTION:-

Human beings since many ages get encountered with various types of diseases affecting their health and well being. Route of administration depends on sort and seriousness of the disease. For skin disorders, the topical route is generally favored. Topical drug delivery system are with improved bioavailability, reduced side effects, more uniform plasma levels, longer duration of action, resulting in a reduction in dosing frequency and improve therapy due to plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage form. Topical drug delivery system has fewer side effects than oral medications or supplements. It is an alternative to people who cannot or prefer not to take medications or supplements orally. Topical drug delivery system cannot achieve high levels drugs in blood or plasma. This system cannot be developed if drug or formulation has tendency to causes irritation to skin **(Khullar R *et al.*, 2012).**

Topical drug delivery system can be defined as the application of a drug containing formulation to the skin to treat cutaneous disorder directly. The topical drug delivery system is generally used where other routes (like oral, sublingual, rectal, parental) of drug administration fails or in local skin infection like a fungal infection. The main advantage of the topical delivery system is to bypass first pass metabolism. Topical drug administration is simplest and easiest route of localized drug delivery anywhere in the body by routes as ophthalmic, rectal and vaginal skin (**Yadav *et al.*, 2016).**
Figure shows the diagram of skin along with its skin layers and other components.



Antifungal Class of Drugs :-

Polyene Antifungals	Imidazole, Tri-azole, and Thi-azole Antifungals
Amphotericin B	Imidazoles
Candicidin	Miconazole
Filipin	Clotrimazole
Hamycin	Epoxiconazole
Natamycin	Econazole
Nystatin	Ketoconazole
Rimocidin	Itraconazole

TOPICAL ROUTE AS DRUG DELIVERY

Topical delivery via skin is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin. It includes the application of drug through skin directly to treat cutaneous disorder by the pharmacological effect to the surface of the skin or within the skin. Drugs given via skin must have properties like low molecular weight (600 Daltons), adequate solubility in oil and water and have high partition coefficient. Main demerits of topical dosage form are diffusion and dissolution of drug in the delivery of hydrophobic drugs, and permeation through stratum corneum layer of the skin is for hydrophilic drugs. Therefore, to overcome these limits, emulgel are the system of choice. **(Singla *et al*,. 2012)**

Factors Considered When Choosing a Topical Formulation

1. **Effect of the vehicle.**
2. **Match the type of preparation with the type of lesions.**
3. **Match the type of preparation with the site**
4. **Irritation or sensitization potential.**

EMULGEL

Emulgel having advantage of both gels and emulsion act as a controlled drug delivery system for topically applied drugs. They are emulsion of either oil in water type or water in oil type which are gelled by mixing with a gelling agent. **(Singla *et al.*, 2012)**

In order to improve emulsion stability and ability to penetrate stratum corneum it is jellified in a gel base and the resulting formulation is known as Emulgel. From the four classes of BCS classification of drugs class II drugs show poor solubility and high permeability. Emulsified gel has proven a stable one and better vehicle for hydrophobic or poorly water-soluble drugs **(Upadhyaya S. *et al.*, 2014).**
Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate in the skin in addition **(Kaushal R. *et al.*, 2013).**

Advantages of Emulgel

- Avoidance of the systemic adverse effects of drug i.e. first pass metabolism in the body
- Systemic circulation is minimized or prevented

- Improve patient compliance and acceptability
- Suitable for self-medication
- Provide target drug delivery on the body
- Ability to easily terminate medication when needed
- Can easily pass through skin having dual behavior i.e. hydrophobic as well as hydrophilic
- They are convenient to apply on hairy skin due to absence of greasiness and lack of residues upon application
- Better stability and release of drug
- Better loading capacity
- Production possibility and low preparation cost
- No intensive sonication needed
- Emulgel can be used to prolong the effect of drugs having shorter t1/2
- Substitute for oral route
- Avoidance of GIT absorption
- pH associated deactivation

Table 1: Various Marketed Preparation of Emulgel with their Manufacturers

PRODUCT NAME	API	MANUFACTURER
Acent Gel	Acelofenac	Intra Labs India Pvt. Ltd.
Cloben Gel	Clotrimazole, Beclomethasone	Indoco Remedies
Clinagel	Clindamycin Phosphate Alloantoin	Stiefel pharma
Excex Gel	Clindamycin Adapalene	Zee Laboratories
Kojjivit Gel	Kojic Acid, Dipalmiate Arbuti	Micro Gratia Pharma
Lupigyl Gel	Metronidazole	Lupin Pharma
Miconaz-H-Emulgel	Miconazole Nitrate, Hydrocortisone	Medical union Pharmaceutical
Nadicin Cream	Nadifloxacin	Psycho Remedies
Pernox Gel	Benzoyl Peroxides	Cosme Remedies Ltd.
Topinate Gel	Clobetasol Propionate	Systopic Pharma
Voltren Emulgel	Diclofenac Diethyl Ammonium	Novartis Pharma
Zorotene Gel	Tezarotene	Elder Pharma
Diclomax Emulgel	Diclofenac Sodium	Torrent Pharma

Formulating an Emulgel

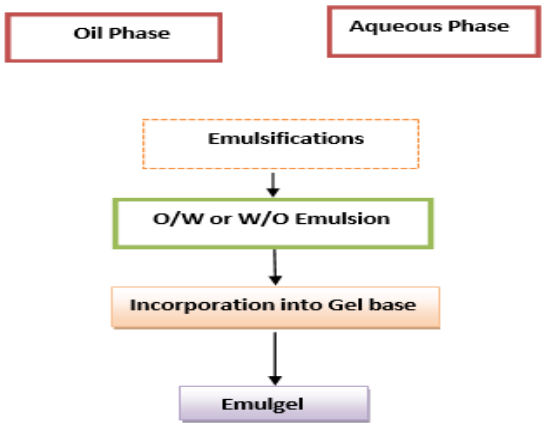
Preparation of emulgel comprises of simple and short steps which increase feasibility of the production. There are no specialized instruments needed for the production of emulgel. Moreover, materials used are easily available and cheap. All these; decrease the production cost of emulgel. The rheological properties and the breakdown behavior of gels filled with emulsions droplets can be varied by changing the interactions between oil droplets and gel matrix, the oil content and the oil droplet size **(Jain, *et. al.*, 2010).**

Steps Involved in Emulgel Formulation

- **Emulsification**
- **Incorporation of the Emulsion into a Gel Base**

Important constituents of the emulgel are the aqueous phase, the oil phase and the gelling agents. Commonly used aqueous agents are water and alcohols.Gelling agents are agents used to increase the consistency of any dosage form that can also be used as thickening agents. The selection of polymer for preparing gel is normally based on the character of external phase**. (Baboota *et al.*, 2011).**

Widely used oils in oral preparations are non-biodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g., olive, Arachis, Cottonseed, and Maize oils) as nutritional supplements **(Panwar, *et al.*, 2011).**



Flow Chart Showing Preparation of Emulgel

HERBAL OILS AS PENETRATION ENHANCERS

Essential oils and their constituents have been widely investigated as safe and suitable skin penetration enhancers for both hydrophilic and hydrophobic drugs.

List of Herbal oils

Angelica Oil	**Cyperus Oil**	**Cinnamon Oil**
Clove Oil	**Chaunxiong oil**	**Oregano Oil**
Lavender Oil	**Tea Tree Oil**	**Geranium Oil**
Chamomile Oil	**Cedar Wood Oil**	**Cinnamon Oil**
Frankincense Oil	**Lemongrass Oil**	**Pines**
Rosemary	**Jojoba Oil**	**Camellia Seed Oil**
Babchi Oil	**Geranium Oil**	**Patchouli oil**
Peppermints Oil		

Jojoba oil

Jojoba oil is the liquid produced in the seed of the *Simmondsia chinensis* (Jojoba) plant, a shrub, which is native to southern Arizona, southern California, and northwestern Mexico. **(Shahin M *et al.,* 2011).**

Jojoba Plant (Simmondsia Chinensis)

STATISTICAL DESIGN

Design of Experiment (DoE)

The design of experiment (DOE) is an effective procedure for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions. DoE begins with determining the objectives of an experiment and selecting the process factors for the study.

To study the effect of differential factors, conditions and their interactions on the response observed in experiments **(Gabrielsson *et al.,* 2002).**

Types of Experimental Designs

1. Full-Factorial designs

i) Two-level full factorial designs
ii) Three-level full factorial designs

2. Fractional factorial designs
3. Plackett-Burman designs
4. Response Surface Method

i) Central-Composite design
ii) Box-Behnken design

5. Taguchi Method

Response surface methods like Central-Composite designs (CCD) and Box-Behnken design (BBD) have been widely applied in optimizing drug delivery. In the present work, CCD was selected for optimizing the formulation of fluconazole emulgel.

CENTRAL COMPOSITE DESIGN

A central composite design is an experimental design, useful in response surface methodology, for building a second order (quadratic) model for the response variable without needing to use a complete three-level factorial experiment. After the designed experimental is performed, linear regression is used, sometimes iteratively, to obtain results **(Myers *et al.,* 1971).**

Implementation

1. A factorial design in the factors studied, each having two levels.
2. A set of axial points, experimental runs identical to the centre points except for one factor, which will take on values

both below and above the median of the two factorial levels and typically both outside their range. All factors are varied in this way.

3. A set of centre points, experimental runs whose values of each factor are the medians of the values used in the factorial portion. This point is often replicated in order to improve the precision of the experiment **(Myres *et al.*, 1971).**

The aim of the present work was to formulate and evaluate the emulgel of an antifungal drug i.e. Fluconazole for topical delivery and to study the role of carbopol-940 as gelling agent and jojoba oil as penetration enhancer in the formulation.

4.10 SELECTION OF TECHNIQUE

The methodology of preparation of emulgel involves the three steps.

STEP 1. Formulation of O/W or W/O kind of emulsion: oil tie of the emulsion was set up by dissolving emulsifier e.g. cross 80 in oil vehicle like liquid paraffin while the watery stage is set up by dissolving hydrophilic emulsifier like tween 80 in refined water. Added substances like methyl paraben and propyl paraben are separated in humectants like propylene glycol. The medicine was separated in watery dissolvable like ethanol. Both the plans of the solution and added substances are mixed with watery stage with consistent blending. Both the smooth and liquid stages were freely warmed to 70° C then the smooth stage was added to the watery stage with constant blending. This mix was cooled to room temperature to shape an emulsion.

STEP 2. Formulation of Gel base: the gel stage is set up by dissolving the polymer in the separated water with enduring mixing at moderate pace using the mechanical shaker and the pH was adjusted to 6-6.5 using triethanolamine.

STEP 3. Incorporation of emulsion into gel base with steady blending: the gel stage is mixed into the emulsion stage to the extent of 1:1 to procure emulgel.

Preliminary Studies

Identification of Drug (FTIR-Study)

The identification of the obtained sample was confirmed by presence of functional groups by utilizing FT-IR technique. Firstly the background was scanned and then crystal window closed. Samples were finely ground KBr then pressed into pellet and IR spectra were taken in transmission over the range of 4000-500 cm^{-1} at ambient temperature. The sample was pressed and scanned. In the Spectra that were appeared on the screen the baseline was corrected. The drug was identified by infrared spectroscopy and characteristic peak obtained compared with standard spectra of pure drug reported in official monograph.

Solubility Studies

The solubility of Fluconazole was tested in various solvents like chloroform, acetic acid, acetone, ethanol, methanol, dilute HCl and sodium hydroxide. A sufficient quantity (10mg) of drug dissolved in each investigated solvent at room temperature. The solubility was only observed by visual inspection **(IP, 2014)**

Calibration Plot

Accurately weighed 10 mg of Fluconazole is transferred into a 100 ml volumetric flask and dissolved in 30 ml of ethanol. It was made up to the mark with methanol to give a stock solution having 100 µg/ml concentrations. For calibration curve, serial dilutions were made for Fluconazole in the range of 10, 20, 30, 40 and 50µg/ml concentrations were prepared by diluting the stock solution with methanol. The absorbance values of above solutions were measured in the wavelength at λ max 260 nm against ethanol as blank and calibration curve was prepared.

OPTIMIZATION

A systematic experimental design and optimization was carried out using a standard RSM design called a Central Composite Design (CCD) for estimating the effect of independent variables (concentration of gelling agent, concentration of jojoba oil and concentration liquid paraffin) on dependent variables % Cummlative Drug Release and Spreadability using Design-Expert ® software (Version 11.0, Stat-Ease Inc., Minneapolis, MN, USA). The responses of the 20 experiments were analyzed numerically by fitting linear, interaction (2FI), and quadratic polynomials (models) to the responses. The highest order
polynomial was selected where the additional term is significant ($P < 0.05$), has insignificant lack of fit, exhibits low standard deviation (SD), high "R-Squared" values, and a low "PRESS.". The general form of the model is represented as in the following:

$$\mathbf{Y = \beta 0 + \beta 1A + \beta 2B + \beta 3C + \beta 4AB + \beta 5AC + \beta 6BC + \beta 7A2 + \beta 8B2 + \beta 9C2 \ldots\ldots\ldots}$$

Where $\beta 0$, the intercept, is the arithmetic average of all quantitative outcomes of twenty runs,
$\beta 1$ to $\beta 9$ are the coefficient computed from the observed experimental values of Y, and A, B and C are the coded levels of the independent variable(s).The terms AB, AC, AB and $A2$, $B2$ and C2 are the interaction and polynomial terms, respectively. The main effects (A, B and C) postulate the average result of changing one factor at a time from its low to high value. The interaction term (AB, AC and BC) show how the response changes when two factors are changed accordingly. The polynomial terms ($A2$, $B2$, and C2) symbolize nonlinearity. The polynomial equation was used to draw conclusion after considering the intensity of coefficient and the mathematical sign it carries, that is, positive or negative.

A positive sign signifies synergism **(Chakraborty, *et al.*, 2013).**

The model was used to generate the response surface plots, three-dimensional displays of the response surface, and predicted response(s) for any set of factors. The adequacy of the model equations to represent the relationship between the responses and the measured components were statistically validated using ANOVA provision in the software. After feasibility and grid searches, a multiple response optimization was done by setting factor ranges to the actual levels and the "Goal" at maximum values for spreadability. The lowest acceptable value (the lower limit) and the higher limit were set to get the desirability equation. Equal emphasis to upper or lower bounds was given for each response with a weight of 1 where desirability was varied from 0 to 1 in linear fashion. And all responses were given medium setting of importance level as compared to one another. The software was also used to optimize the process graphically to see a broader operating window, with the same requirements as in the numerical optimization. It produced the "overlay" plot of response contours for each response shaded out regions not meeting the specifications, leaving an operating window or "sweet spot" (colored yellow) where the factors was set to satisfy the requirements on all the responses.

FORMULATION OF EMULGEL

The composition of fluconazole emulgel formulations is shown in Table 6. The gel in formulations F1 to F14 was prepared by dispersing Carbopol 940 in purified water with constant stirring at a moderate speed then the pH was adjusted to 6 to 6.5 using TEA. In formulations F 1 to F 14 the gel was prepared by dispersing carbopol in heated purified water (80°C), and the dispersion was cooled. The oil phase of the emulsion was prepared by dissolving Span 80 in light liquid paraffin and jojoba oil while the aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl paraben and Propyl paraben were dissolved in propylene glycol whereas fluconazole was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel **(Magdy I. Mohamed 2004).** The different batches were made keeping the different concentration of Liquid Paraffin, Jojoba oil and Carbopol 940. Table 6 shows the formulation with dependent and independent factor of fluconazole emulgel.

EVALUATION OF EMULGEL

Characterization of Fluconazole Emulgel

A. Physical examination:

The prepared emulgel formulations were inspected visually for their optical clarity, color, homogeneity, fluidity, and phase separation after 24 h of preparation **(Mohamed, 2004; Singh, *et al.*, 2014).**

B. pH

The pH values of 1% aqueous solutions of the prepared emulgel were measured by a calibrated pH meter (Systronics, New Delhi) **(Mohamed, 2004)**

C. Spreadability

The spreadability of the emulgel formulations was determined 48 h after preparation by measuring the spreading diameter of 0.5 g emulgel which was placed within a circle of 1 cm diameter pre-marked on a glass plate over which a second glass plate (75 gm) was placed (Eq. 2.1). A weight of 425 g was allowed to rest on the upper glass plate for 5 min where no more spreading was expected **(El-Houssieny & Hamouda, 2010, Soliman, 2010).** The increase in the diameter due to spreading of the gels was noted. The spreadability (g.cm.min- 1) was calculated by using the formula:

S = m. l/t

Where S is spreadability, m is the weight of the upper plate and rested on it (g), l is the diameter of the spreading emulgel (cm), and t is the time taken (min) **(Jelvehgari, et al., 2007).**

D. In vitro Drug Release Study:

To compare the *in-vitro* release profiles of formulations was done using inert membranes on Franz Diffusion Cell. These membranes usually have a porous substructure made of hydrophobic matrix and are thus considered simple models of the human skin. Although the permeabilities of such membranes against drugs are in absolute terms, higher than the human skin, the data obtained are nonetheless instructive as they merely reflect the relative permeability of the various formulations. Pieces of synthetic membrane (Spectra/por) were soaked in 0.2 M potassium dihydrogen phosphate buffer pH=7.4, for 24 h before mounting in a Franz-type diffusion cell. About 200 mg of sample was placed on the donor side, fully covering the membrane. The whole assembly was placed in a water bath, maintained at 321°C and continuously well stirred. Care was exercised to remove any air bubble from the underside of the membrane and the receiving solution. At specified time intervals (0, 5, 10, 20, 30, 60, 90, 120, 150 and 180 min) 2 ml samples were removed from the receiver compartment, i.e. partial sampling and refilled with an equal volume fresh buffer **(Shah, 1999).** All samples were analyzed for fluconazole content spectrophotometrically using a wavelength of 260 nm **(Siamak Parsaee *et al.*, 2002)**

CHARACTERIZATION OF EMULGEL

SEM (Scanning Electron Microscopy)

The scanning electron microscope (SEM) is one of the most versatile instruments available for the examination and analysis of the microstructure morphology and chemical composition characterizations. It uses high electron beam but the beam is scanned over the surface and the back scattering of the electros is looked it In this technique sample is mounted on a stub of metal with adhesive, coated with 40-60 nm of metal such as gold and palladium.

These signals include secondary electrons (that produce SEM images) backscattered electrons (BSE) diffracted backscattered electrons (EBSD that are used to determine crystal structures and orientations of minerals) photons (characteristic X-rays that are used for elemental analysis and continuum X-rays) visible light and heat. Secondary electrons and backscattered electrons are commonly used for imaging samples: secondary electrons are most valuable for showing morphology and topography on samples and backscattered electrons are most valuable for illustrating contrasts in composition in multiphase samples **(Parsaee et. al., 2002).**

RESULTS AND DISCUSSION

PRELIMINARY STUDIES

FT-IR Studies

That FT-IR Study of the Drug, Carbopol940 and Physical Mixture was done using FT-IR spectrophotometer (BRUKER GERMANY). Figures 12, 13 and 14 given below shows the FT-IR pattern of fluconazole drug, carbopol 940 and Physical Mixture of Fluconazole and Carbopol 940.

For fluconazole, the vibrations of the various functional groups present in the molecule could be attributed to a broad band due to hydrogen bonded O–H stretching vibrations in the range of 3,600–2,500 cm-1 ; 1,619 and 1,514 cm-1 bands due to C=C stretch aromatic ring; 1,502 and 1,420 cm-1 bands due to triazole ring stretch; 1,273 cm-1 for C–F stretch; 1,138 cm-1 for triazole ring breathing; 1,020 cm-1 for C–H aromatic ring; 967 and 846 cm-1 for C–H triazole ring

SOLUBILITY STUDIES OF FLUCONAZOLE

The solubility studies of fluconazole was done in different solvent system like ethanol, oil, water and chloroform on observing the solubility of fluconazole was more in ethanol than other solvents.

CALIBRATION PLOT

The calibration plot of Fluconazole drug was studied in different concentration i.e. 10, 20, 30, 40 and 50 µg/ml at **λ max** 260 nm. On plotting the calibration plot between absorbance and calibration the value of R^2 was 0.9993 observed. The calibration plot was further used to calculate the % cumulative drug release of the emulgel formulations.

PHYSICAL APPEARANCE

The formulate emulgel were examined for their physical appearance. They were transparent to white opaque and from viscous gel preparations to flowable liquids with a smooth homogeneous appearance. Table 8 shows the physical appearance of all formulations of emulgel.

Table 8: Physical Appearance

Formulation	Appearance	Consistency
F1	Transparent	Flowable
F2	Transparent	Flowable
F3	Opaque	Gel
F4	Opaque	Gel
F5	Transparent	Flowable
F6	Transparent	Flowable
F7	Transparent	Gel
F8	Transparent	Flowable
F9	Opaque	Gel
F10	Opaque	Gel
F11	Transparent	Flowable
F12	Opaque	Gel
F13	Opaque	Gel
F14	Transparent	Flowable

6.5. pH STUDY

The formulate emulgel were examined for their pH. The pH values of all prepared formulations ranges from 6.0 to 6.5 which are considered acceptable to avoid the risks of irritation upon skin. Table 9 shows the pH of all formulations of emulgel.

Table 9: pH Study of Fluconazole Emulgel

Sr. no.	Formulation	pH
1.	F1	6.2 ± 0.06
2.	F2	6.5 ± 0.06
3.	F3	6.2 ± 0.17
4.	F4	6.4 ± 0.15
5	F5	6.5 ± 0.17
6.	F6	6.2 ± 0.35
7.	F7	6.4 ± 0.07
8.	F8	6.2 ± 0.15
9.	F9	6.5 ± 0.35
10.	F10	6.5 ± 0.17
11.	F11	6.5 ± 0.10
12.	F12	6.5 ± 0.12
13.	F13	6.5 ± 0.15
14.	F14	6.6 ± 0.20

6.6. OPTIMIZATION

For Emulgel formation a systemic experimental design and optimization was done using Central Composite Design. The Design was used to find the optimum Concentration of Liquid Paraffin, Jojoba oil and Gelling agent on the % Cummulative Release and Spreadability. 14 formulations were prepared in accordance with the design and effect of 3 factors i.e. concentration of liquid paraffin (a) concentration of gelling agent (b) and concentration of jojoba oil (c) was investigated on the two response variables viz. % cumulative release and spreadability. The result of two response variables is given in table 10.

The responses of the 14 experiments were analyzed numerically by fitting linear, two-factor interaction (2FI), and quadratic polynomials (models) to the responses. The highest order polynomial was selected where the additional term is significant ($P < 0.05$), has insignificant lack of fit, exhibits low standard deviation (SD), high "R-Squared" values, and a low "PRESS.". The general form of the model is represented as in the following:

$$\mathbf{Y = \beta 0 + \beta 1A + \beta 2B + \beta 3C + \beta 4AB + \beta 5AC + \beta 6BC + \beta 7A2 + \beta 8B2 + \beta 9C2\ldots\ldots\ldots\ldots}$$

Where $\beta 0$, the intercept, is the arithmetic average of all quantitative outcomes of twenty runs, $\beta 1$ to $\beta 9$ are the coefficient computed from the observed experimental values of Y, and A, B and C are the coded levels of the independent variable(s).The terms AB, AC, AB and A2, B2 and C2 are the interaction and polynomial terms, respectively. The main effects (A, B and C) postulate the average result of changing one factor at a time from its low to high value. The interaction term (AB, AC and BC) show how the response changes when two factors are changed accordingly. The polynomial terms (A2, B2, and C2) symbolize nonlinearity. The polynomial equation was used to draw conclusion after considering the intensity of coefficient and the mathematical sign it carries, that is, positive or negative. A positive sign signifies synergism **(Chakraborty, et al., 2013).**

The generated polynomial equations were used for the Analysis of the response and analysis of variance was done using statistical parameters like sum of degree of freedom, means sum of square and F value using software design expert. The significance of the developed model was judged based on P value, F value, correlation coefficient (R^2) and adjusted correlation coefficient (adjust R^2).

Table 10: Central Composite Design

Run	Liquid Parrafin	Jojoba Oil	Carbapol 940	% Cummlative Drug Release	Spredibility
1.	7	8	1.5	88.12	13.35
2.	10	8	2	77.30	12.59
3.	8.5	15	1.75	64.23	9.65
4.	7	15	2	62.73	9.37
5.	7	15	1.5	72.08	11.78
6.	11	11.5	1.75	74.02	12.03
7.	8.5	11.5	1.75	90.48	14.87
8.	8.5	11.5	2	89.56	13.88
9.	10	15	1.5	68.34	9.97
10.	7	8	2	65.73	9.77
11.	8.5	8	1.75	76.41	12.43
12.	5	11.5	1.75	70.51	11.52
13.	10	15	2	60.43	8.99
14.	10	8	1.5	82.98	13.12

The significance of the developed models was developed on the basis of p-value. The high value of R^2 also represents the significance of the model developed. The F- values indicates the effect variance is much higher than the error variance. The solution for optimized batch was obtained by fixing the parameters using the desirability approach for numerical optimization and desired responses viz. higher % cumulative drug release and maximum spreadibilty. The suggested model for % drug release was α quadratic model and table 11 shows the model suggested by Design Expert.
The 3 D surface plots showed the effect of formulation factors on the response variables. As the concentration of Jojoba oil increases the % cummlative release in formulation increases and same is with the concentration of liquid paraffin. The figure 16 shows the response surface plot of % Cumulative release.

Table 11: Experimental levels of the Independent Variables for Optimizing Fluconazole Emulgel

Factor	Name	Units	Type	Minimum	Maximum	Coded low	Coded high
A	Liquid Paraffin	%	Numeric	5	9.94	-1	+1
B	Jojoba Oil	%	Numeric	5	14.88	-1	+1
C	Carbopol - 934	%	Numeric	1.50	2	-1	+1

Table 12: Suggested Model for Percent Drug Release by Design Expert

Source	Sequential p- value	Lack of Fit p- value	Adjusted R^2	Predicted R^2	
Linear	0.0032	0.6720	0.4860	0.3533	
2FI	0.6742	0.5916	0.4355	-0.2090	
Quadratic	**0.0377**	**0.9952**	**0.6728**	**0.6353**	**Suggested**

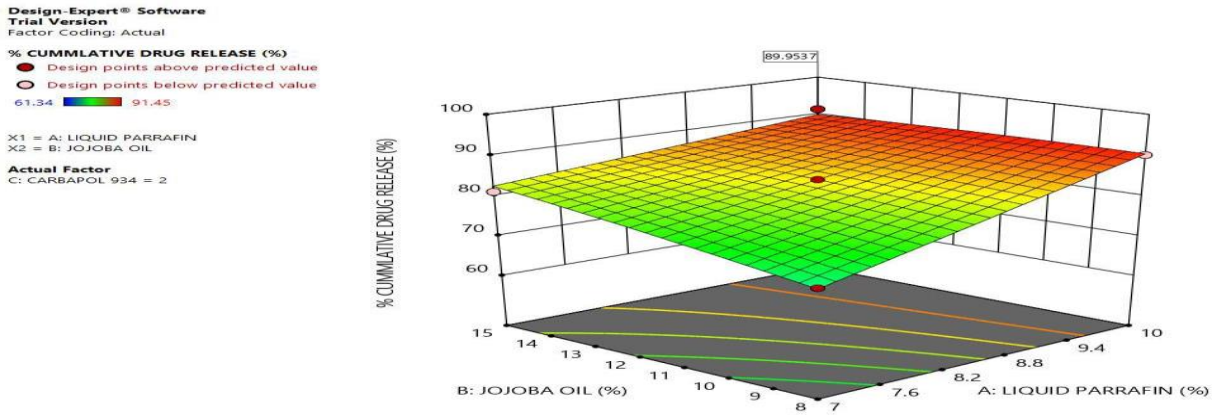


Figure 16: Response Surface Plot of % Cummulative Drug Release

Table 13: Suggested Model for Spreadability

Source	Sequential p- value	Lack of Fit p- value	Adjusted R^2	Predicted R^2	
Linear	**0.0011**	**0.8124**	**0.5515**	**0.3886**	**Suggested**
2FI	0.3867	0.8336	0.5592	0.2301	
Quadratic	0.2852	0.9366	0.6010	0.4598	

The suggested model for Spreadability was linear model. Table no. 13shows the suggested model of spreadability. The 3 D surface plot of spreadability is given in figure 17.The increase in concentration of Jojoba oil helps in increase in the Spreadability. The concentration of liquid paraffin shows the positive effect on the spreadability.

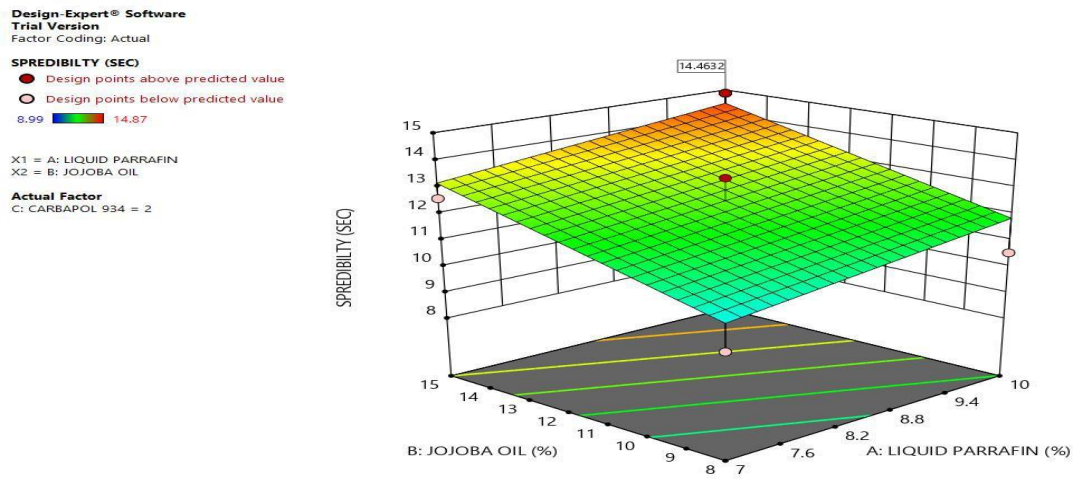


Figure 17: Response Surface Plot of Spredibility

6.7 SPREADIBILTY STUDY

The important factors to consider, during evaluating the spreadibility of a formulation, include the rate and time of shear produced upon smearing and the temperature of the target site. The parallel-plate method is the most widely used method for determining and quantifying the Spreadibility of semisolid preparation. It provides accurate, reproducible, and statistically relevant data. The advantages of the method are simplicity and relative lack of expense. On the other hand, the method is not very precise and sensitive, and data which it generates must be manually interpreted and presented. The spreadibility of fluconazole emulgel formulation following the spreadbility test was found to range from 9.37 to 12.59 g./cm. Low concentration of jojoba oil and liquid paraffin showed the less spredibility and with high concentration of jojoba oil and liquid paraffin the spradibilty values increases. Figure no18- shows the spreadibilty of formuations of emulgel.

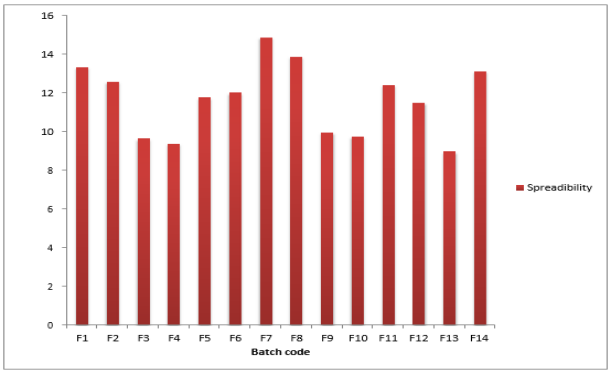


Figure 18: Spredibility Index of Emulgel Formulations (F1-F14)

IN VITRO DRUG RELEASE

The dissolution study of all the formulations of emulgel was done in Franz Dissolution apparatus using phosphate buffer pH 7.4. It is expected that drug release might be influenced by gel viscosity. The effect of oil phase concentration, when increased from 8 % w/w to 15% w/w, showed significant decrease in the amount of drug release from these bases. This result may be explained according to the concept of escaping tendency of drugs; it was supposed that increasing the thermodynamic activity which can be expressed in terms of relative solubility of drug lead to enhance the releasing of drugs from vehicle. Formulation F7 shows the maximum release of drug i.e 90.48 and formulation F13 shows the very less release i.e.

60.43. As the concentration of gelling agent increases the drug gets encapsulated in gel more but at very high concentration i.e. 2 % the release of drug become less, this may due to highly bound in the gel structure of emulgel. Table14 and 15 Shows the release profile of formulations F1-F7 and F8-F14 and figures 19 And 20 Shows the graphs of dissolution study.

Table 14: *In Vitro* Release Data of Formulations of Fluconazole Emulgel (F1-F7)

Time (min)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
5	7.76	10.32	9.12	9.31	8.87	12.84	10.43
10	14.72	17.38	18.54	20.12	18.31	25.87	21.92
20	22.93	26.38	29.53	26.23	28.82	32.65	28.87
30	32.54	35.42	40.32	33.68	37.34	39.75	36.83
60	38.29	41.38	47.55	42.83	41.93	50.66	38.29
90	45.23	49.42	53.23	48.45	54.06	57.34	49.98
120	55.87	57.61	58.45	52.54	66.51	63.98	59.56
150	62.43	70.23	60.34	59.23	71.31	68.42	65.78
180	88.12	77.3	64.23	62.73	72.08	74.02	90.48

Table 15: *In Vitro* Release Data of Formulations of Fluconazole Emulgel (F8-F14)

Time (min)	F 8	F 9	F 10	F 11	F 12	F 13	F 14
0	0	0	0	0	0	0	0
5	9.54	6.87	9.49	10.33	11.23	13.23	11.54
10	19.09	14.72	18.83	18.56	19.32	22.92	19.23
20	27.48	22.65	27.48	22.78	25.68	26.78	25.78
30	35.22	27.62	39.23	36.45	32.78	34.71	33.98
60	40.23	30.29	40.23	43.72	39.48	39.98	40.68
90	45.88	43.76	45.88	49.62	46.21	43.79	54.92
120	61.62	51.71	52.78	58.94	56.29	51.32	62.93
150	70.65	57.87	59.3	64.65	62.76	56.52	73.12
180	89.56	68.34	65.73	76.41	70.51	60.43	82.98

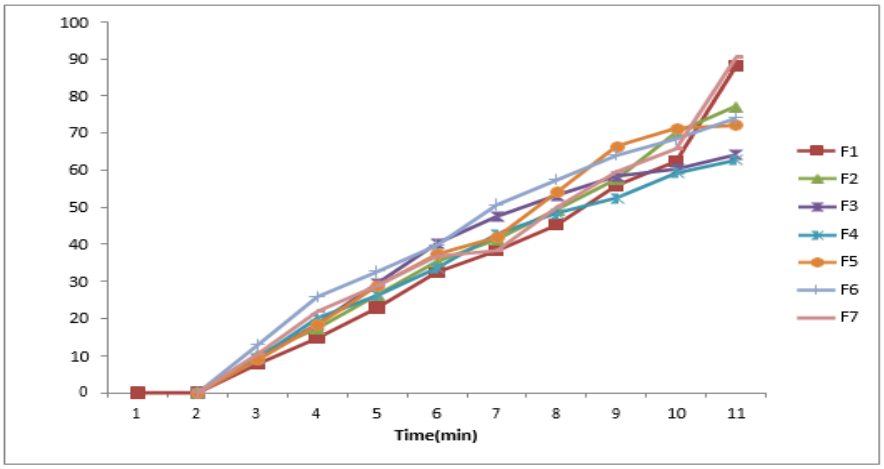


Figure 19: Dissolution Profile of Emulgel Formulations (F1-F7)

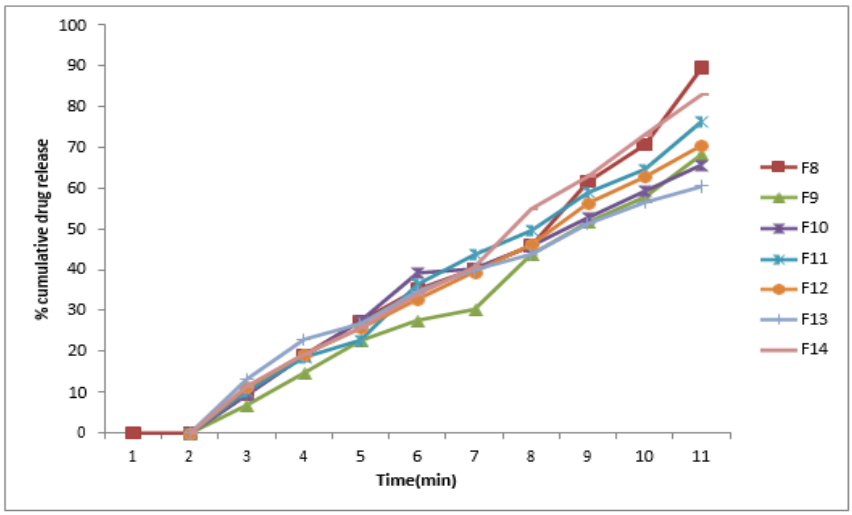


Figure 20: Dissolution Profile of Emulgel Formulations (F8-F14)

CHARACTERIZATION OF SCANNING ELECTRON MICROSCOPY

1. Scanning Electron Microscopy (SEM):

The morphological characterization of optimized batch was studied using scanning electron microscopy. The figure 21 showed the surface characterization of optimized batch of Emulgel.

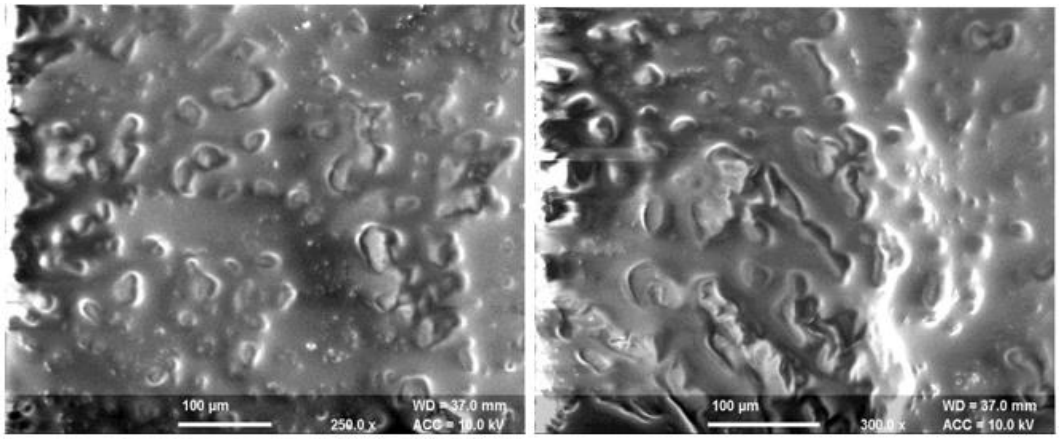


Figure 21: SEM Image of Optimized Batch of Fluconazole Emulsion

DISCUSSION

Gels are currently receiving increasing attention, especially hydrogel formulations, for topical application of drugs since they have an attractive appearance and develop pleasant cool feeling. They are easy to apply and remove and generally provide faster drug release compared with ointment and cream. Gels for topical use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non- staining, compatible with several excipients, and water-soluble or miscible. The pharmacological activity of gel formulations may not change as

rapidly as the solution form Eumlgel are emulsion gels which are hydrogels containing randomly distributed oil microdroplets. They are emulsions either of oil-in- water or water-in-oil type, which are gelled by mixing with gelling agent. They have been recently used as vehicles to deliver various drugs to the skin.

Fluconazole is poorly water soluble drug which presents several challenges to maintain potency, uniformity, and usability characteristics when used for extemporaneously compounded preparation. Fluconazole emulgel was optimized based on Design-Expert® software. The experiment was studied with a standard RSM design called a central composite design (CCD). One of the challenges that appear in the formulation of drug as an emulgel preparation is the choice of the type of base and concentration used. Fourteen formulations were prepared using jojoba oil and liquid paraffin as the oil phase at 1:1 ratio and Carbopol - 940 as a gelling agent.

Methylparaben (0.18% w/w) together with Propylparaben (0.02% w/w) have been used for the preservation of the formulations due to their additive effects. Triethanolamine used as a buffering system to convey the final formulation to a pH of around 6.8, which is considered acceptable to avoid the risk of irritation upon application to the skin. The formulated emulgel were examined for their physical appearance, pH and spreadibility. They were transparent to white opaque and from viscous gel preparations to flowable liquids with a smooth homogeneous appearance. The pH values of all prepared formulations ranged from 6.0 to 6.9, which are considered acceptable to avoid the risk of irritation upon application to the skin. The spreadability of fluconazole emulgel formulation following the spreadability test was found to range from 8.9 g.cm/min to 14.87 g.cm/min for the formulations F1 and F14, respectively. Formulations having low amount of jojoba oil and liquid paraffin had the high spreadability index. This may be due to the effect of the concentration and physical characteristics of the oil and liquid paraffin used in the emulgel on the contact angle of preparation on the substrate and lubricity, which is directly related to the coefficient of friction. As the viscosity of the gel increased, the release of the drug was expected to be slower. Initial release of the drug is significantly affected by the concentration of gelling agent in all cases. Complete drug release (100%) was achieved at the 3rd hr for the formulations F1, F8, F7 and F14 released more than 80 % of the drug. Percentage of drug released in dissolution medium showed extremely significant difference when the gelling agent concentration is varied. Formulations having concentration of gelling agent 1.75 % shows different release, this is due to different amount of jojoba oil and liquid paraffin.

In constructing the regression models, it was assumed that the responses were represented adequately with the independent variables in the β parameters and that the errors were (roughly) normal and (approximately) independently distributed with a mean of 0 and some constant variance. Diagnostic plots of the case statistics were used to check if these assumptions were valid. To optimize all the responses with different targets, a multi criteria decision approach like the numerical optimization technique by the desirability function and graphical optimization technique by the overlay plot were used. The optimized formulation was obtained by applying constraints on dependent variable responses and independent variables. The optimization of the emulgel was also decided to have maximum spreadability and % cumulative drug release features not less than 285 g.cm.min-1 and 12 min, respectively. The recommended concentrations of the independent variables were calculated by the Design Expert software from the above plots which has the highest desirability near to 1.0. Desirabilities range from zero to one for any given response. The program combines the individual desirabilities into a single number and then searches for the greatest overall desirability. The optimized concentration was obtained by using design expert software as clears in the 2D and 3D response surface prediction curve. The average % relative error between the predicted values and experimental values of each response was calculated and compared and these experimental findings are in close agreement with the model predictions which confirmed the predictability and validity of the model.

7. CONCLUSION

In this study, the *in vitro* results showed that an emulgel formulation can be a potential candidate for the delivery of fluconazole for the skin disease, with better *in vitro* physical, using jojoba oil and liquid paraffin as drug carriers. Fluconazole is incorporated in jojoba oil and liquid paraffin at 1:1 ratio can be emulsified with Tween 80 with oil to surfactant ratio on the micellization of the surfactant. Furthermore, since both the oil phase and the surfactant system are good solvents for clotrimazole, drug loading poses no challenge during formulation.

The jellifying of drug incorporated emulsion is the distinctive step of an emulgel formulation. Carbopol-940 can be incorporated in the aqueous phase of the emulsion up to a concentration of 1.5%-2% resulting in better physical property and showing Non-Newtonian shear thinning pseudo plastic behavior. The pH of the final formulation can be affected by the incorporation of a buffering system such as triethanolamine.

Computer based full Central Composite Design can be successfully used to optimize emulgel system setting concentration of oil phase and gelling agent as independent variables. From these variables, gelling agent concentration has more prominent effect on *in vitro* drug release and spreadability followed by surfactant concentration. When the formulation consist of oil phase 11.5 % and gelling agent 1.75% concentrations the drug will be released almost completely at the 3rd hr and demonstrate much better spreadability and drug release. SEM analysis of emulgel shows the uniform structure of emulgel formulation.

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