Formulation and Characterization of Antifungal Gel containing Fluconazole

Dr. J.N. Mishra Director, Mr. Amit Kumar Shukla Assistant Professor, *Rakesh Kumar Nishad Corresponding Author, Department of Pharmaceutics, Kailash Institute of Pharmacy and Management Gorakhpur.

ABSTRACT

Fluconazole is used for the treatment of local and systemic fungal infection as is a triazole derivative. The oral use of fluconazole produces several side effects hence it is not much recommended frequently. Fluconazole topical gel preparation are yet not available Commercially in the market, thus this formulation reduce the dose of drug and to avoid the side effects like liver damage and kidney damage provide better patient compliance. The gel was formulated by changing the polymer ratio. There no interaction between the drug and excipients and purity of drug confirmed by FT-IR study. drug content, pH determination, viscosity measurement, in vitro diffusion, antifungal activity and skin irritation all the factors were evaluated for gel formulations. The amount of drug diffused from formulation F1 was 97.857 ± 0.977 in4 1/2 h which was higher among all the gel formulation best fitted to Higuchi model. F1 formulation did not show any skin irritation as the viscosity of the F1 formulation was within the limits. It was found to be Gel formulation F1 stable at 30 ±2°C and 65± 5 RH. was not stable at 40 ± 2°C and 75 ± 5 RH and %CDR was decreased. Safe and efficient delivery of drug to skin application was found to be much beneficial in limiting the drug to desired site of action in the skin and reduced side effects associated with ordinary treatment.

***Keywords**; Fluconazole, Fungal infection, Polymer ratio, Topical gel.*

INTRODUCTION:-

Dermatological problem is one of the most common fungal infections of skin in present time. There is a wide variety of treatment for fungal infections in solid, semisolid and liquid dosage form. The transparent clear gel is the most common choice of drug for topical treatment of dermatological diseases as well as skin care.

In topical drug delivery system gel formulation is most acceptable formulation because they are less greasy and easily removable. It provide better application and stability in comparision to ointment and cream.[(2)] For topical administration skin is the most acceptable organ of human body. It is most suitable drug delivery system anywhere on the body, ophthalmic, armpit, rectal, vaginal and skin topical route. It expanded both cosmetic and pharmaceutical preparations. [(3)]

To restore the fundamental functions, enhances or to alter the pharmacological functions of underlined tissues a no. of medicated products are applied on skin surface or mucous membrane. Such products are reffered as topical or dermatological products such as HPMC 4000 CPS, methyl cellulose, carbapol 934 and natural polymers etc. [(4,5)]

In the late 1800s the name of some semisolid materials as per their physiological characteristics' rather than molecular composition is termed as gel. [(6,7)] According to U.S.P., Gel can be defined as a semisolid system consists of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated liquid. Gel consist of two phase system in which inorganic particle are not dissolved but merely dispersed throughout the continuous phase , randomly coiled in the flexible chains.[(8)]

It is essential to know the Anatomy, Physiology, and physicochemical properties of

the skin to utilize the procedure of percutaneous absorption successfully. The skin the largest organ system of body having 1.7 to2m^2 surface area.[(9)]It consist of different tissues performing various specific activity. The thickness of skin about 0.5 to 4.0 mm having weigh.4.5 to5.0 kg. It is not just covering the body but .also protect the body .It performs the various junctions such as regulation of body temperature, protection, sensation, Excretion, immunity, reservoir of blood vitamin D synthesis. [(10)] The [medical] specialty that deals with

diagnosis, and treatment of skin disorder known as dermatology [10]

The skin consists of two layer of. (1) Epidermis (2) Dermis. The epidermis is structurally a thick keratinized stratified squamous epithelium consisting of four distinct cell types and four or five distinct layers. The cells covering the epidermis include- keratinocytes, melanocytes, Merkel cells and Langerhans'cell.The chief role of keratinocytes is to produce keratin, the fibrous protein that helps give the epidermis its protective properties. [11-14]

Layers of the Epidermis:-

Stratum Basale(Basal layer), Stratum Spinosum(Prickly layer), Stratum Granulosum(Granular layer), Stratum Lucidum(Clear layer), Stratum Corneum(Horny layer).[11-14]

Dermis:-

Dermis is second major skin region, is strong, flexible connective tissue layer. It composed of dense connective tissue and contains number of structures. Large cells belonging to the reticulo- endothelial system, fine elastic fibers, capillary blood vessels, Lymphatic. It is the most superficial layer of the corium is prolonged into minute papillae over which the epidermis is moulded. It contains sensory nerve ending, hair roots of hair follicle, sweat glands, sebaceous glands, Involuntary muscles fibers as in, scrotum, penis, nipple including Arrectorespilorum and Nails. [11-14]

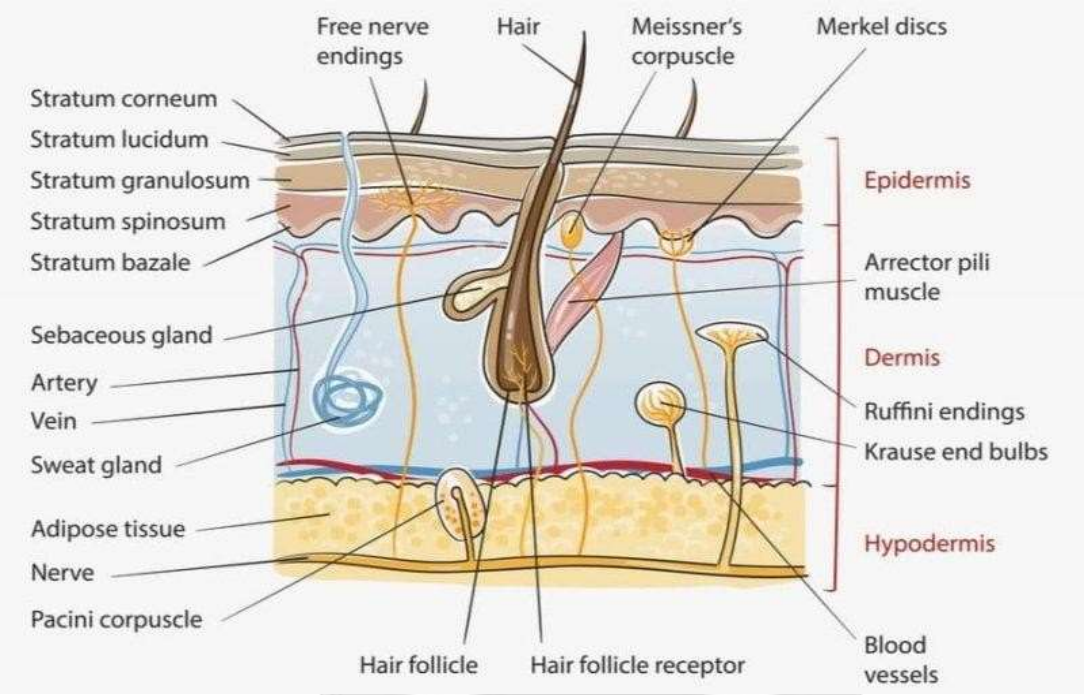

Figure 1.1:- The skin showing its main structure

Fungal infections:-

Fungal infection can be superficial or systemic. Superficial infections can be classified into the dermatomycoses and Candidiasis. Dermatomycoses are infections of the skin, hair and nails, most commonly caused by trichophyton, microsporum and epidermophyton spp. which causes various types of ringworm or Tinea pedis, the feet and Tinea corporis. The superficial Candidiasis, the yeast like organism infects the mucous membrane of the mouth, vagina, or skin. Whereas systemic fungal infections the body as whole. Sometime it caused by inhalation, ingestion or inoculation of primary pathogens and sometime by opportunistic invasion of Commensals in patients with lowered host resistance.[15,16] Treatment of fungal infection includes

Fluconazole, Itraconazole, Miconazole , Clotrimazole, Ketconanazole, and Griseofulvin. Fluconazole is synthetic antifungal agent of imidazole group. Fungal infections can be treated by topical as well as by oral and parental. Anyhow oral use of medicine is not much important in treating topical fungal infections because it has systemic side effects'.

; TYPES OF FUNGAL DISEASE:-

- **Skin infection:** e.g. foot fungus (usually smelly but not life threatening, sometimes becomes serious),

. Ring worms

- **Mucosal diseases:** vaginal or oral (it compasses from irritation to painful which is very difficult; intolerable but rarely life threatening).
- Systemic infection: fungus in the blood and tissues(immunocompromised population, usually life threatening.

Figure1.3: Onychomycosis: Foot fungus

Various classes of drugs that target the plasma membrane fungal cell ,by inhibiting the biosynthesis of sterol, biosynthesis of DNA, and biosynthesis of β-glucan. These agents can kill fungi easily without affecting host cell because fungal membranes and sterol biosynthetic enzymes are totally different from us . Fungi synthesize β-glucan, while we don't, so drugs that target β-glucan biosynthesis .

Two main fungal-specific molecules are β- glucan and mannan, chains of sugars linked in Immune receptors bind to these particular order. Immune receptors bind to these

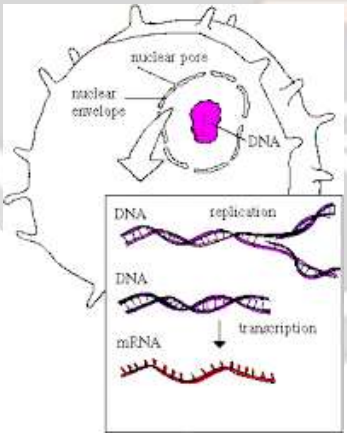

Figure1.2:Immune receptor

molecules and begin a choreographed immune response. A high- yielding immune response is lined: First engage more immune cells the site of infection, second is immune cells signal a seizure , and then these cells kill the fungus and provoke a long-lived response that protects against future infection. Recognition of β-glucan stimulates the antifungal of the fungus (leads to killing). Production of attractive and activating signaling molecules. Prompting of the modifying arm of the immune system to develop fungal-specific antibodies and T-cell.

Classification of antifungal drugs

(i).*Antibiotics*

A. *Polyenes*

Amphotericin B, Nystatin, Hamycin, Natamycin, B.*Heterocyclic benzofuran*

Griseofulvin

(ii)*Antimetabolite*

Flucytosine(5-FC)

(iii)*Azoles*

A.*Imidazole*(Topical)

Clotrimazole, Econazole, Miconazole (systemic) Ketoconazole.

B.*Triazoles*

Fluconazole, Itraconazole, voriconazole.

(iv) *Allylamine*

Terbinafine

(v)Other topical agents

Tolnaftate, Benzoic acid, Quiniodochlor, Ciclopirox olamine.

1.15 ; MECHANISM OF ACTION:-

- Triazoles drug targets the fungal-specific synthesis of membrane lipids.
- Fluconazole enters specially into fungal membranes and breakup their functions 5-Fluorocytosine targets fungal specific DNA replication

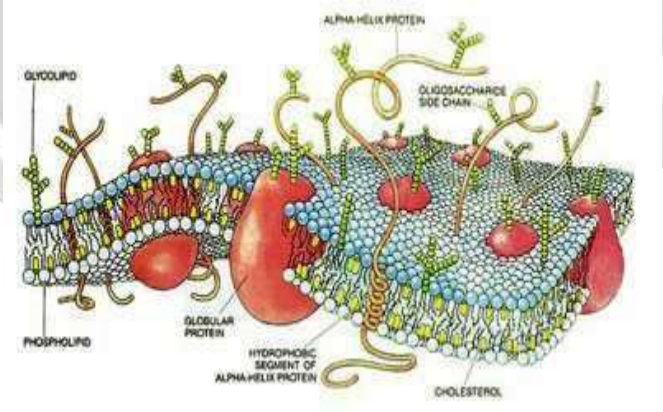

Figure1.3: Cell membrane

1.16 ; INTRODUCTION OF DRUG

Fluconazole is used as an antifungal drug preferentially; Fluconazole act aggressively against HIV and severe fungal infected, in peoples.

- Fluconazole is antifungal agent of Triazole class.

- It is new existing drug.
- It minimize the side effects of all other fungal drugs like, Itraconazole, Amphotericin B, Econazole, and Voriconazole.
- Even though it has some of the side-effects in the oral and I.V dosage forms.

Fluconazole is one of the most preferential drug prescribed by most of RMP because of its excellent pharmacokinetic and pharmacodynamic profile. More than 80 % of ingested drug is found in the circulation, and 60 to 70% is excreted in the urine. Only 10% of fluconazole is protein bound(12). Fluconazole also exhibits excellent tissue penetration. The serum levels of CSF and brain are good, and the other sites like nails, saliva,and vagina, are well within therapeutic ranges. The half-life is 25 to 30 h in the presence of normal renal function dose prescribed once-daily dosing. The normal dose should be reduced by 50% in patients who have a reduced creatinine clearance. Fluconazole serum levels are rarely necessary. In present time IV formulation exits in200 or 400 mg doses and tablets are available 50, 100, 150, and 200 mg .

Available dosage forms:

- Tablets
- Capsule
  - But the formulation of gel are rare.
  - Numerous dosage forms are used in the topical treatment of superficial fungal The gels, ointments, lacquers and others. The treatment of Tinea pedis and ringworm can easily be achieved with creams, liquids, gels and ointments.

Side effects:

When fluconazole overcomes side effects of other antifungal agents, it also has some side effects in the oral and parental dosage forms as pass through the1st pass metabolism through the liver and excretion through kidneys.

- Headache
- Diarrhea
- Nausea
- Dizziness
- Stomach pain
- Change in the way food tastes.
- Liver and Kidney damage.
- The most common side effects of fluconazole are headache, nausea and pain in the abdomen.
- A few people get diarrhea, most anti-HIV medications cause problems in the digestive system. Fluconazole could make those problems worse.
- Fluconazole can be hard on the liver.
- Fluconazole can also cause kidney damage.

Several side effects of tablet dosage form of fluconazole, the drug was formulated in the gel dosage form which was not yet marketed in India.

CLASSIFICATION OF GELS:-

Gels are classified as, colloidal phase, properties of solvents, physical properties and rheological nature.

(i).BASED ON COLLOIDAL PHASES:

They are classified into

(a) Inorganic (two phase system)

(b) Organic (single phase system

PREPARATION OF GELS:

Preparation of gels are normally under room temperature at the industrial scale. Before processing required special treatment by some polymers. Gels can be prepared by following method

A. Thermal changes

B. Flocculation

C. Chemical reaction

(A) Thermal changes:

Gelatin is produced when thermal changes applied to Solvated polymers (lipophilic colloids). Hot water is better solvent for most of hydrogen formers than cold water. When degree of hydration is decreases with reduced temperature gelatin is formed. (Cooling of a hydration is reduced and gelatin occurs). (Gel is produced when cooling of a concentrated hot solution will take place). E.g.: - Gelatin, agar sodium oleate, guar gummed and cellulose derivatives etc. Opposite to this, some substance like cellulose ether have their water solubility to hydrogen bonding with the water. disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Therefore this method cannot be applied for preparation gels.

(B) **Flocculation**:

The sufficient quantity of salt required to precipitate to produce gel state, but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitant. E.g.: Polystyrene in benzene, solution of ethyl cellulose can be gelled by rapid mixing with suitable amounts petroleum ether as non-solvent. The addition of salts to hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation method are Thixotropic in behavior. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to "salt out", the gelation and colloidal will not occur.

(C) Chemical reaction:

Here gel is produced when chemical interaction between the solute and solvent take place. E.g.: Aluminium hydroxide gel produced when increased concentration of reactants like interaction in aqueous solution of an aluminium salt and sodium carbonate. Some other examples that involve chemical reaction between glycidol ether (Glycidol), toluene diisocyanates, with Polyvinylalcchol, cyanoacrylates that cross-links the polymeric chain

GEL FORMING SUBSTANCES:-

Polymer which is necessary for the preparation of gels, provide them their the structural network.

Gel forming polymers are classified as follows:

(I) Natural polymer

a. Proteins

(i) Gelatin (ii). Collagen

b. Polysaccharides (1) Alginic acid (2) Agar (3) Tragacanth (4) Sodium or Potassium carrageenan (5) Pectin (6) Gellum Gum (7) Xanthin (8) Cassia tora (9) Guar Gum **(II). Semi synthetic polymers**

a. Cellulose derivatives (1)Hydroxyethyl cellulose (2)Methylcellulose (3) Hydroxypropyl methyl cellulose (4) Hydroxypropyl cellulose (5) Carboxymethyl cellulose

(III) Synthetic polymers a. Carbomer (1) Carbopol -941 (2) Carbopol -940 (3) Carbopol -934

b. Poloxamer
c. Polyvinyl alcohol
d. Polyacrylamide
e. Polyethylene and its co-polymers
(IV). Inorganic substances a. Bentonite
b. Aluminium hydroxide
(V) Surfactants a. Brij-96
b. Cetostearyl alcohol

Advantages of Gel formulations[31, 32] :

- As compared to other semisolid dosage form, gels are formulated easily.
- They adhere to the site of application effectively.
- They are biodegradable and biocompatible.
- Polar as well as nonpolar drugs can be delivered by the use of gel.
- They can be easily washed and are nontoxic.
- Certain stress conditions can be better tolerated by the gel.
- They form a protective covering over the site of application.
- There long term stability is comparatively better.

Disadvantages of Gel formulations[31, 32] :

- Evaporation of solvent from gel may cause drying of it.
- The solvent may be expelled out during storage**.**
- The medicament can be sealed in gel matrix due to unbreaking of covalent bonds present in gel matrix.
- The polymer used as gelling agent can be precipitated out.
- The gel may get destabilized due to flocculation.
- The polymer used for gelation can cause irritation.

Properties of Gel[33] :

- Gelling agent must be inert, safe and should be nonreacting to other ingredients which are used to prepare formulation.
- The jelly produced should be of rational solid like consistency throughout storing period that can be definitely wrecked down when subjected to shear forces.

- Gel should contain appropriate preservative to check the growth of microbes.
- The gel produced should not be waxy.

Materials and Methodology

Drug Profile:-

- **CATEGORY: - Antifungal** [17]
- **STRUCTURE** [17]**:-**

.

- **Fig** le
- **CHEMICAL NAME: -** 2-(2,4 difluorophenyl)-1,3-bis(1H-1,2,4-triazo-1-yl) propan- 2-ol.[17]
- **MOLECULAR FORMULA**. - **C13H12FN6O**.[17]
- **MOLECULAR WEIGHT**: - 306.3 g/mol.[17]
- **MELTING POINT:-**138˚ to 140˚C.[20]
- **DESCRIPTION: -** White or almost white crystalline powder.[17] .
- **WATER SOLUBILITY: -** slightly soluble in water [17]
- **Mechanism of action:-**
  Azoles are newer synthetic antifungal. They are orally effective and less toxic. They have broad spectrum antifungal activity. They inhibit Dermatophytes, Candida, Cryptococcus neoformans, H.Capsulatum, Deep mycosis. Azoles inhibit the synthesis of ergosterol of fungal cell membrane by inhibiting Lanosine 14α demethylase (cytochrome P450 enzyme).This enzyme catalyses the conversion of lansosterol to ergosterol **.**
- **BIOAVAILABILITY: -** 90% by oral route [19]
- **HALF LIFE: -** 25- 30 hrs [19]
- **VOLUME OF DISTRIBUTION: -** Fluconazole is widely distributed and apparent volume of distribution is close to that of total body water.[18]
- **TOXICITY:-** G.I. Disturbance. Hepatotoxicity and Teratogenicity at higher doses [18].
- **PROTEIN BINDING: - 12%** [18]
- **DOSE: -** 200mg to 400mg /day[17]

METHODOLOGY OF RESEARCH WORK[22,23,24]

Materials:-

- Fluconazole taken as a antifungal drug for preparation of topical gel with following drug excipients:-
- carbopol 934 as a synthetic polymer for dermatological products (0.5 to 5%) .
- Hydroxypropyl methyl cellulose and methyl cellulose as semisynthetic polymer

- Glycerol as a moistening agent.
- Triethanolamine for pH adjustment.
- Methylparaben and Propylparaben as preservatives
- For alteration of skin permeability ethyl alcohol or D.M.S.O. and EDTA as chelating agent.
- Distilled water (q.s)

Preformulation studies:-

Drug-Excipients Compatibility Studies:-

Preformulation studies progresses formulation development work . This Preformulation study includes drug-excipients

FT-IR infrared spectrum of pure drug was seen in between 600 to 3800 cm-1 when drug- excipients compatibility studies were carried out using FT-IR. The FT-IR study showed that there was no major change in the position of peak obtained in the drug change in the position of peak obtained in the drug alone and in a mixture of drug with excipients, which shows that there was no interaction between drug and excipients.

UV Spectrum analysis of Fluconazole:-

The UV Spectrum analysis of drug Fluconazole showed maximum absorption at wavelength 260 nm in alcohol. At given concentration range of 10 µg/ml to 50 µg/ml Standard curve obeyed Beer's law and when subjected to regression analysis, the value of regression coefficient was found to be 0.999, which showed linear relationship between concentration and absorbance.

Formulation of Gel

Preparation of gel base Carbopol934p (0.5, 1.0, 1.5 ,2.0 2.5%w/w) and purified water were taken in a beaker and allowed to soak for 24hour. To this required amount of drug (2gm) was dispersed in water and then carpobol940p was then neutralized with sufficient quantity of Triethanolamine. Glycerol as moistening agent, Methylparaben and Propyl parabens as preservatives were added slowly with continuous stirring until the homogenous gel was formed.

Table-1: formulation development of *Fluconazole* topical gel.

SN. No.	Ingredients	Formulations				
		F1	**F2**	**F3**	**F4**	**F5**
1	**Drug(gm)**	2.0	2.0	2.0	2.0	2.0
2	**Carbopol 934(gm)**	0.5	1.0	1.5	2.0	2.5
3	**Glycerol**	5	5	5	5	
4	**Methylparaben(mg)**	0.2	0.2	0.2	0.2	0.2
5	**Propyl paraben(mg)**	0.04	0.04	0.04	0.04	0.04
6	**EDTA(mg)**	0.03	0.03	0.03	0.03	0.03
7	**Triethanolamine**	Qs	Qs	Qs	Qs	Qs
8	**Water**	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100

EVALUATION OF FLUCONAZOLE GEL:-

(i) Percentage yield:

The empty container was Weighed in which the gel formulation was stored then again the container was weighed with gel formulation. Then subtracted the empty container weighed with the container with gel formulation then it gives the practical yield. It was calculated by the formula:-

$$\text{Percentage yield} = \frac{\text{Percentage yield}}{\text{Theoretical yield}} \times 100$$

(ii) Drug content:

Take100 ml of volumetric flask containing 20 ml of alcohol and weighed accurately10 gm of each gel formulation were transferred to it and stirred for 30 min. Make up the volume to 100 ml and filtered, and then 1 ml of this above solution was further diluted with 10 ml alcohol and again 1 ml of this above solution was diluted with 10 ml alcohol. The absorbance of the solution was measured with the help of spectrophotometer at 260 nm.

Drug content was calculated by the following formula.

$$\text{Drug content} = \frac{\text{Absorbance}}{\text{Slope}} \times \text{Dilution factor} \times \frac{1}{1000}$$

(iii) Dermination of pH:

With digital pH meter the pH of various gel formulations was determined. 100 ml distilled water was taken in250ml of volumetric flask and one gram of gel was dissolved in it and stored for two hours. The pH of each formulation was measured in three times and average values are calculated. for safe and efficacious treatment of the skin infections pH of the topical gel formulation should be between 3 to 9.

(iv) Spreadability:-

It can be defined as measurement of area of skin or affected part to which gel readily spreads on application. Spreading value of gel denotes the therapeutic potency of a formulation. When gel is placed in between the slides under the direction of certain load and thus time in seconds(s) taken by two slides to slip off known as Spreadability. For better Spreadability the time taken for the separation of two slides should be lesser. It is calculated by using the formula: $S = M. L / T$ where, M = wt. tied to upper slide

Spreadability:- By measuring diameter of 1 gm gel between horizontal plates (20×20 cm2) after 1 minute the Spreadability of the gel formulation can be determined.

(v) Viscosity study:-

Brookfield Viscometer was used to measure the viscosity of the prepared gel. The gels were rotated at the speed of 0.3, 0.6 and 1.5 rotations/min. The corresponding dial reading was noted at each speed/rotation. The viscosity of the gel was determined by multiplying the with factor given in the Brookfield Viscometer catalogues and dial reading.

Brookfield viscometer DVII model with a T-Bar spindle in combination with a helipath stand was used to determined the viscosity of gel.

a) Selection of spindle:

The viscosity of all the gels was measured by using Spindle T 95.

b) Sample container size:

A 100ml beaker was taken and filled it 50gm of gel then measured the viscosity.

c) Spindle immersion:

Taking care that spindle should not touch bottom of the jar when the T-bar spindle (T95) was lowered perpendicular in the centre

d) Measurement of viscosity:

The T-bar spindle (T95) was used for determining the viscosity of the gels. The factors Which affect the viscosity was maintained during the process like temperature, pressure and sample size etc. The viscosities at number of points along the path when helipath T- bar spindle was moved up and down giving. The torque

reading was always greater than 10%.For viscosity of gels the average of three readings taken in one minute was noted.

(vi) In vitro diffusion study:-

of Taking an Albino mice, of weighing 20 – 25 gm of 8 – 10 week old and their abdominal skin was shaved using hand razor and clean the skin with hot water cotton swab. on this skin surface 5 gm of gel was applied uniformly. The skin was mounted between the stratum corneum facing the donor compartment and the compartments of the Frantz diffusion cell. With the help of 100 ml phosphate buffer of pH 6.8 Reservoir compartment was filled. The study was carried out at 37

± 1°C and speed was adjusted until the vortex touches the skin and it carried out for 4½ h. 5 ml of sample was withdrawn from reservoir compartment at 30 min interval and absorbance was measured with the help of spectrophotometer at 260 nm. To maintain constant volume each time the reservoir compartment was refilled with the 5 ml volume of phosphate buffer pH 6.8 solution.

Figure 1.5: Franz diffusion cell with skin mounted between compartments

(vii) Skin irritation study:

This study was carried out on healthy Wister rats. The animals were divided into two group's i.e. control, Gel formulations F1. The back skin of area 5 cm2 was shaved before one day of starting the study. The study was carried out for 4 days. At the end of study, the animals were observed for any skin irritation like erythema or edema and score were given as per the irritation..

Score	Description
0	No irritation
0.5	Faint, barely perceptible erythema or slight dryness
1	Faint but definite erythema, no eruption or broken skin or no erythema but, definite dryness and may have epidermal fissuring.
1.5	Descriptive erythema or indistinct erythema with specific dryness, may have epidermal fissuring.
2.0	Moderate erythema: may have few papules or erythema in the cracks
2.5	Moderate erythema with barely perceptible edema.

3.0	Severe erythema (beet redness) may have generalized papules or moderate to severe erythema with slight edema (edges well defines by raising).
3.5	Moderate to severe erythema with moderate edema (confined to patch area).
4.0	Generalized vesicles or Escher formation or moderate to severe erythema and/or edema extending beyond the patched area.

Table2 : Scores for skin irritation

■ It is considered to have no irritation, if the formulation produces score of 2 or less.

(viii) Anti-fungal studies:-

Weighed 16.25 gm of sabouraud dextrose agar(SDA) was transferred in a 500 ml of conical flask and 250 ml of purified water and minute heat is applied to dissolve it completely. Sterilized it for 15 min at 121°C at 15 lb pressure in autoclave for about 20 min. The fungal strain(Candida albicans) was dispersed in the medium after cooling it at room temperature and then this medium was poured into the three Petridis and allowed it cool it for sometime until it forms solidifies at room temperature and with the help of sterile steel bore of 6 mm the three cups are bored in each Petridis and calculated concentration of the gel formulation(F1) , standard drug (Fluconazole), and placebo gel were placed in the Petri plates and bores then incubated for 72 h at 37°C in incubators. Then the zone of inhibition was observed and calculated the radius of the zone of inhibition.

(ix) Stability studies:-

Stability testing of drug product being as a part of drug discovery and ends with the commercial product, to assess the drug and formulation stability studies were done. The stability study was carried out for the most compensatory formulation. The most satisfying formulation was locked in a glass vial and kept at 30 ± 2°C and 40± 2°C at RH 65± 5 and 75± 5 RH for 2 months. , the samples were analyzed for the drug content and in vitro diffusion study at the end of 1 and 2 months

STANDARD GRAPH OF FLUCONAZOLE

SR.NO.	Concentration(in µg/ml)	Absorbance at 260nm±S.D
1	0	00
2	10	0.212±0.015
3	20	0.421±0.008
4	30	0.610±0.016
5	40	0.801±0.017
6	50	1.01±0.018
7	60	1.2±0.019

Table3: Standard graph of fluconazole

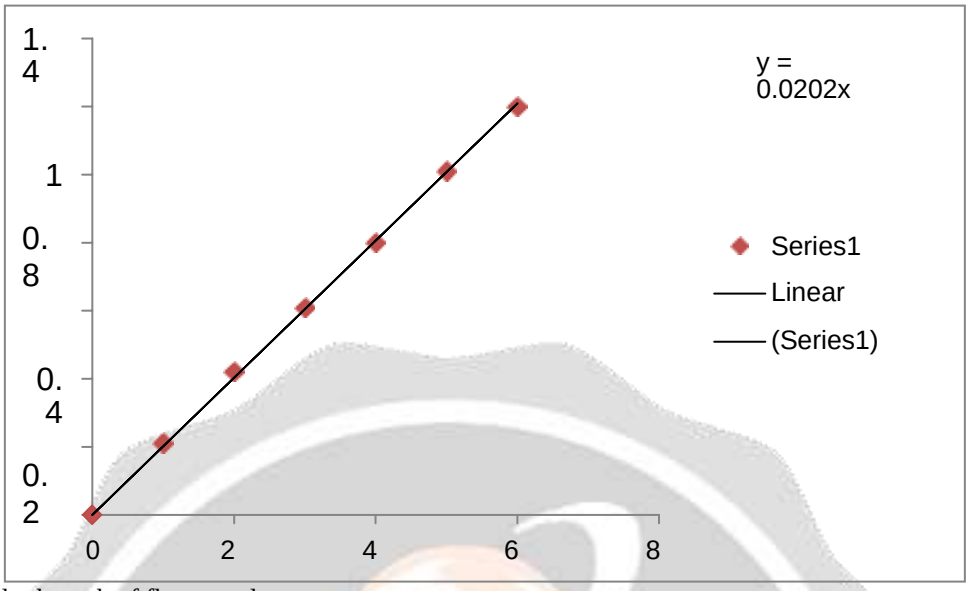

Figure1.6: Standard graph of fluconazole

CONCLUSION

→Fluconazole is an imidazole derivative, used for the topical as well as systemic fungal infections. The bioavailability of fluconazole is 90%. In this current study, an aim was made to formulate and evaluate topical gel of fluconazole for systematic delivery of drug across the Integumentary system.

→A suitable method of analysis of drug by UV spectrophotometry. Fluconazole showed a wavelength of 260 nm in alcohol maximum absorption. The value of correlation coefficient was found to be r2 = 0.999, which showed linear relationship between concentration and absorbance. Thus, it can be concluded that, it can be concluded that, Beer's law was obeyed.

→ Preformulation study for drug-excipients compatibility by FT-IR showed no interaction between drug and selected excipients.

→ Various formulation (F1, F2, F3, F4, F5) were developed by using suitable polymer (carbopol 934p) and penetration enhancer.

→ Developed formulations of fluconazole were evaluated for the physiochemical parameters such as drug content, viscosity, Spreadability, in vitro diffusion.

→Formulations F1 was better viscosity as compare to other Formulations

→ Skin irritation study indicated that no irritation have been produced by gel formulation F1.

→ Anti fungal studies also showed the good results of formulation F1.

→ Viscosity studies of various formulations revealed that formulation F1 was better compare to others.

→ Formulation, F1 did not produced skin irritation, good Rheological properties and good results of antifungal studies, From among all the developed formulation it shows better drug diffusion for a period of 4h. Therefore, it was selected as the best formulation.

→ The release rate of drug from F1 formulation is best fitted to Higuchi matrix model.

→The most satisfactory formulation-F1 did show any significant change in drug content, In vitro drug diffusion studies pattern after stability studies at 30 ±2°C and at 65 ± 5 RH for 2 months. Thus, the aim of the current work of formulation and evaluation of gel containing fluconazole has been performed with success.

REFERENCES:-

(1) Gupta A, Mishra AK, Singh AK, Gupta V, Bansal P, Formulation and Evaluation of topical gel of Diclofenac sodium using different polymers. Drug invention today 2010; 2(5) 250-253.

(2) Shah VP, Maibach HI, Topical drug bioavailability, bioequivalence, and penetration, 1, Springer, USA, 1993.

(3) Lieberman HA, Rieger MM, Banker GS, Pharmaceutical dosage form ; Disperse system,2, Marcel Dekker , new York 2005, (399-421).

(4) Shivdhare UD, Jain KB, Mathur VB, Bhusari KD, Roy AA, formulation development and evaluation of Diclofenac gel using water soluble polyacrylamide polymer. Digest 1 Nanomet and Biostruct, 2009 ; 4 (2) 285-290.

(5) Golinkin HS, Process for fracturing well formulation using aqueous gels 1979; US patent no. US 4137182 .

(6) Bhasa SA, Khalid SA, Duraival S, Bhowmi KD, Kumar KD, Recent trends in usage of polymer in formulation of dermatological gels, Indian journals of research in pharmacy & biochemistry, (1)2.2013,161-168.

(7) Thakur V, Prashar B,Arora S, Formulation in vitro Evaluation of gel for topical delivery of antifungal agent Fluconazole using different penetration enhancer's dug invention today, 4(8)2012, 414-419.

(8) Goyal S, Sharma P, Ramchandani U, Shrivastav SK, and Dubey PK; Novel anti- inflammatory topical gels. International journal of pharmaceutical and biological archives: 2011;2(4)1087-1094.

(9) Waugh Anne and Grant Allison, Ross and Wilson, Human Anatomy and Physiology in health and illness Tenth edition 2006; 354-358.

(10) Tortora, J Gerard and Grabowski Sandra Reynolds; Principles of Anatomy and Physiology seventh edition; 127-130.

(11) Harshmohan .Tex book of pathology 4th Edition (754-756)

(12) N.MARIEB. ELAINE. Human anatomy & physiology Edison community college Holyoke community college emeritus 4th edition 1947 (145-146)

(13) Prof. Bansal Rajpoot, Dr.Gupta Bansal, Dr. Bansal Mohit, Dr. Desal Keya. Essential of human anatomy & physiology vol-1. Birla Publication Pvt.Ltd. (167-168)

(14) Muthayya ; Human physiology 3rd Edition 2002. Jaypee Brothers medical Publishers (P) Ltd (195-196)

(15) Rang HP, Dale M.M. Ritter J.M, Moore P.K, pharmacology 5th Edition Churchill Livingstone Edinburgh London New York, oxford, Philadelphia, St.Lewis Sydney Toronto 2003. (666-669).

(16) National formulary of India 2011 Indian pharmacopeia commission ministry of family welfare government of India Antifungal 3L –(155)

(17) Indian pharmacopoeia 2014 vol-1 (only solubility 186)2 Vol-II (1767- 1768) government of India. Ministry of health & family welfare published by.
The Indian pharmacopeia commission Ghaziabad.

(18) MARTINDALE, The extra pharmacopeia edited by James EF Reynolds, deputy editor Kaththleen parfitt, Assistant editor, Annev parsons , Sean C Sweetman .Published by direction of council Royal pharmaceutical society or great Britain & prepared in society`s of publications dept. 1996.

(19) Tripathi KD, Essentiacal of medical pharmacology. 5th Edition .Jaypee brothers medical published Pvt. Ltd. New Delhi (P-721).

(20) http//www.chembook.com.>chem.properrty ENCS 37400293

(21) N.K.K. Shreedharan et al./ Journal of pharmacy research 2014,8 (11) 1608-1614. Formulation & Evaluation of anti-inflammatory gel from leaves extract of vitex negunda Linn.

(22) B.Niyaz, Basha et.al/ International journal of drug deportment & Research Oct- Dec 2011/vol. 3 issue 4. Formulation & Evaluation of gel containing Fluconazole – antifungal agent.

(23) Loveleen preet kaur et. al./ Asian journal of biomedical & pharmaceutical sciences March 2013. Topical gel: A recent approach for novel drug delivery.

(24) DOOA A, HELAL et al/ International journal of pharmacy and pharmaceutical sciences, Vol 4, suppl 5, 2012. Formulation & Evaluation of Fluconazole topical gel.