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FORMULATION AND EVALUATION OF KETOCONAZOLE LOADED EMULGEL FOR ENHANCED TOPICAL ANTIFUNGAL DELIVERY

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ABSTRACT

Topical drug delivery systems offer advantages such as localized drug targeting, avoidance of first-pass metabolism, and improved patient compliance. Among these, emulgels have emerged as a promising platform for the delivery of hydrophobic drugs due to their combined benefits of emulsions and gels. This study focuses on the formulation and evaluation of a ketoconazole emulgel intended for effective topical treatment of fungal infections including tinea, candidiasis, pityriasis versicolor, dandruff, and seborrheic dermatitis. Eight different formulations (F1–F8) were developed using Carbopol 934, hydroxypropyl methylcellulose (HPMC), and sodium alginate as gelling agents, with light liquid paraffin as the oil phase, Tween 80 as an emulsifier, propylene glycol as a co-surfactant, and methyl and propyl parabens as preservatives. The pH was adjusted to 6.0–6.5 using triethanolamine. All formulations were evaluated for solubility, drug content, viscosity, spreadability, pH, FTIR compatibility, in vitro drug release, entrapment efficiency, and antifungal activity. Results showed that the formulations exhibited good solubility in methanol and phosphate buffer (pH 5.5), uniform drug content, satisfactory rheological properties, and physical stability. FTIR analysis confirmed no interaction between the drug and excipients. Among the eight formulations, F4 was found to be the most effective, showing a drug content of 94.64%, entrapment efficiency of 94%, and a sustained in vitro drug release of 85.02% over 6 hours following Korsmeyer–Peppas kinetics with non-Fickian diffusion. The antifungal study demonstrated that F4 had a significantly larger zone of inhibition compared to marketed formulations, indicating superior therapeutic efficacy. In conclusion, the optimized ketoconazole emulgel formulation (F4) was found to be a stable, effective, and promising alternative for topical delivery of ketoconazole, providing controlled drug release, improved skin penetration, and enhanced antifungal activity over conventional formulations.

KEYWORDS: Emulgel, Topical formulation, Ketoconazole, Controlled drug delivery system.

INTRODUCTION

1.1 NOVEL DRUG DELIVERY SYSTEM[1]

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all.[1] On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non- specific toxicity, immunogenicity, bio recognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), which are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bio conjugate chemistry, and molecular biology. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development.[1] Controlled and Novel Drug Delivery which was only a

dream or at best a possibility is now a reality. During the last decade and half pharmaceutical and other scientist have carried out extensive and intensive investigations in this field of drug research.

1.2 TOPICAL DRUG DELIVERY SYSTEM[2]

Topical drug delivery (TDD) is a method of drug administration where a topical formulation is applied on skin that allowing the drug to be delivered across the skin upon application, to produce a localized effect primarily to treat skin disorders like eczema. The topical drugs can be classified into corticosteroids, antibiotics, antiseptics, and anti-fungal. The mechanism of topical delivery involves the diffusion and metabolism of drugs with in the skin. Historically, the topical route was the one of the earliest methods of drug delivery in humans dating back to ancient Egyptian and Babylonian civilization around 3000 BC, where ointments and lotions were used on the skin. The delivery of topical drugs needs passing through multiple skin layers and undergoing pharmacokinetics, and factor like dermal diseases can reduce the bioavailability of the topical drugs. wide use of topical drugs leads to the advancement in topical drug deliver, aim to enhance the delivery of topical medications to the skin by using chemical and physical agents. For chemical agents, (carriers like liposomes and other nanotechnologies) are used to enhance the absorption of topical drugs. On the other hand, physical agents, like (micro-needles) to improve absorption. Besides using carriers, other factors such as pH, lipophilicity, and drug molecule size influence the effectiveness of topical formulation.

ADVANTAGES

Targeted treatment.
Localized effect.
Reduced systemic side effects.
Convenience and ease of use.
Non-invasive Route.
Potential for controlled release.
Suitability for dermatological conditions.
Suitable for specific populations.
Reduced hospital congestion.
Fewer risks of abuse
Easy to administer.
Fewer risks of gastrointestinal difficulties.

DISADVANTAGES

Possibility of local skin irritation at the site of application.
Contact dermatitis due to some drug may occur.
Some drugs with poor permeability are difficult to penetrate via the skin.
Drugs with larger particle sizes are difficult to penetrate.
Possibility of allergenic reactions.

1.3 PHYSIOLOGY OF SKIN[3]

The skin is the largest organ of the human body, accounting for about 15% of the total body weight. It has a wide variety of functions. One of the major functions of the skin is to protect the body from water loss, maintains thermoregulation and mechanical, chemical, microbial, and physical influences. The protective properties are primarily provided by the outermost layer, the epidermis.[3]

The skin of an average adult human covers a surface area of an early and receives about one-third of the blood circulating through the body. Microscopically skin is composed of three main histological layers: epidermis, dermis and subcutaneous tissues. The skin consists of distinct layers of tissue. Non- viable epidermis (stratum corneum), viable epidermis, viable dermis, and sub cutaneous connective tissue.

The (outer laye)r, the epidermis consists of specific constellation of cells known as keratinocytes. Keratinocytes synthesize keratin, a protein with a protective role. The dermis is (middle layer), made up of the fibrillar structural protein known as collagen. The dermis lies on the subcutaneous tissue, or panniculus, which contains small lobes of fat cells known as lipocytes.

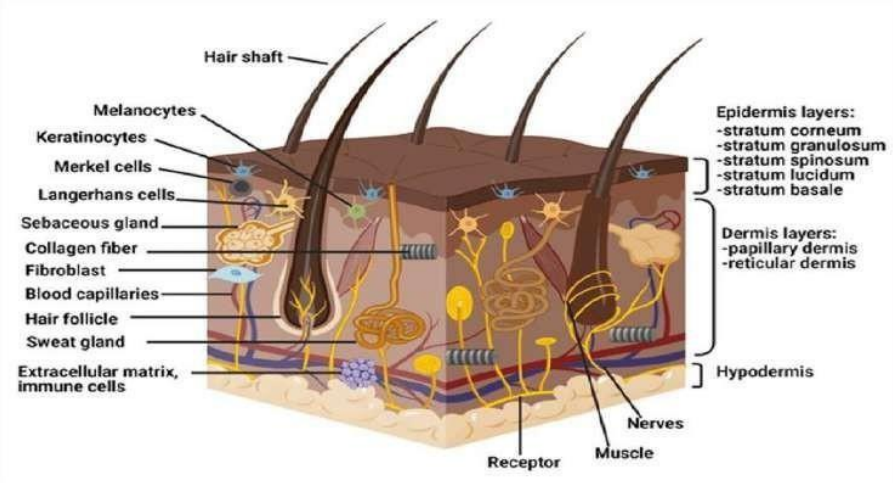


Fig. 1.1: Structure of Human Skin.

1.3.1 LAYERS OF SKIN

*The epidermis, is the outermost layer of skin, provides a water proof barrier and creates our skin tone.
*The dermis, present beneath the epidermis, contains tough connective tissue, hair follicles and sweat glands.
*The deeper subcutaneous tissue (hypodermis) is made of a connective tissue.

1.3.2 EPIDERMIS

It is derived from the greek word "epi" meaning "over" or "upon", is the outermost layer of the skin. The epidermis has five regions and can range in thickness from 0.5mm (eyelid) to 1.5mm on the palms and soles. It forms a water proof, protective wrap over the body serves as a barrier to infection and is made up of stratified squamous epithelium with an underlying basal lamina.

1.3.3 DERMIS

The dermis is the layer of skin beneath the epidermis. The dermis consists of epithelial tissue and cushions the body from stress and strain. The dermis is tightly connected to the epidermis by a basement membrane and contain many nerve endings that provide the sense of touch and heat. The dermis consist of tough connective tissue, the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. The blood vessels in the dermis provide nourishment and waste removal from its own cells as well as from the Stratum basale of the epidermis.

1.3.4 HYPODERMIS

The hypodermis also known as subcutaneous tissue located below the dermis is not considered as part of the skin. Its purpose is to attach the skin to underlying bone and muscles and to supplying it with blood vessels and nerves to the skin. It is composed of loose connective tissue, adipose tissue and elastin. The main cell types found in the hypodermis are fibro blasts, macrophages and adipocytes with adipose tissue, subcutaneous tissue up about 50% of the body fat. Fating the hypodermis serves as padding and insulation for the body.

1.4 SKIN PENETRATION PATHWAYS[3]

Routes of Skin Penetration

The skin, being a multifaceted organ, offers several routes for drug penetration:

Transcellular Route

*In this route, the drug molecule passes directly through the cells of the stratum corneum and subsequently the underlying epidermal cells.
*It involves the movement of the both to molecule in and out of the cells and through the intercellular lipid domains.
*This route can be challenging for drug penetration due to the hydrophobic nature of the cell membranes and the lipophilic environment surroundings.

Intercellular Route

In this route the drug molecule bypasses the cells and moves through the lipid-rich domains located between the cells of the stratum corneum.

*Given that these regions are lipophilic, lipophilic drugs often find this route more permeable. However, the tortuous path can hinder drug movement.

Transappendageal (or Shunt) Route

*This route involves drug movement through skin appendages like hair follicles, sweat glands, and sebaceous glands.
*While these structures occupy a minimal area of the skin, they can be essential for the penetration of certain drugs, especially macro-molecules or for iontophoretic delivery.

Subcutaneous Route:

*Though not typically utilized in TDDS, this route involves drug delivery into the subcutaneous tissue layers, usually via injections. It bypasses the barrier properties of the skin altogether

1.5 EMULGEL[4]

Emulsion + Gel Emulgels 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. The Gels component mucoadhessive property which prolongs the contact period of the medication over the skin. Both o/w and w/o type of emulsion are used in topical preparation serving as water washable preparation or emollients for dry skin respectively. If the emulsion exhibits less thixotropic nature(i.e. less viscous on shearing), the process of penetration becomes easier. In order to improve emulsion stability and its ability to penetrate stratum corneum jellying the emulsion in a gel base and the resulting formulation is known as Emulgels. Compared to cream the gel formulations included the emulgel offer advantage of ease of application and removal and provide better stability as compare to traditional cream and ointments. From the four classes of BCS classification of drugs class II drugs show poor solubility and high permeability. It is obvious that for class II drugs having low ability to dissolve is a more important limitation to their overall rate and extent of absorption then their ability to permeate through the membrane. Therefore, when one is concerned with topical delivery of poorly water-soluble drug Emulgels may serve as better option. Emulsified gel has proven a stable one and better vehicle for hydrophobic or poorly water-soluble drugs

Advantages[5,6,7]

1. As topical agent: Unlike many topical dermatological formulation such as creams and ointments, emulgel addressees the disadvantage of less spreading coefficient, sticky nature and needs rubbing during application. These limitations are

overcome in gel formulation but despite of various advantage gels have major limitation in delivery of hydrophobic drugs. Thus emulgels have proved a boon in delivery of hydrophobic drugs topically and providing them advantages of gel formulation.

2. Stability: Shows better stability than compared to other topical preparations like creams and powders. As creams show phase inversion, ointments show rancidity due to oily base and powders are hygroscopic in nature.
3. Better than other vesicular approaches: Supperior to niosomes, liposomes due to better loading capacity reduced leakage and due to small size in lesser entrapment efficiency,. Whereas gels due to their vast polymeric three dimensional structure show better loading capacity.
4. Easy production:Production of emulgels is easy and done in short steps and no specialized instruments are needed low cost is needed for its formulation.
5. Controlled release:Emulgels act as a dual control preparation and thus suitable for drugs with short half life.
6. No intensive sonication: unlike of vesicular molecules emulgel production does not needed sonication avoiding drug degradation and leakage.
7. Patient compliance: Emulgels improve patient compliance as they can be self applied and medication can be terminated whenever required.
8. Other benefits:Emulgels avoid first pass metabolism and provide site specific drug delivery.

Disadvantages[4]

Emulgels drug delivery show various advantages but also suffer from few disadvantage like:

Drugs with large particle size do not absorb through skin easily.

Some drugs show poor permeability through skin

Bubble formation may occur during formulation of emulgel.

Various ingredients of Emulgel formulation[5,6,8,9]

Aqueous material: This forms aqueous phase of the emulsion. Commonly water, alcohol are used.

Oils: They form the oily phase of the emulsion. Most commonly used oils are mineral oils either alone or in combination with soft and hard paraffin. Non biodegradable mineral oil and castor oils can be used which provide local laxative effects. Oils extracted from different types of plant with various medicinal values can be employed in emulgel formulation.

Emulsifiers: Emulsifiers are used to control stability and emulsification process. Emulsions are thermodynamically unstable system however stability can be increased by using appropriate emulsifying agent. Nonionic surfactants such as spans, tweens have HLB values greater than 8 and are used in the formulation of o/w emulsions whereas mineral oils such as liquid paraffin have HLB values less than 8 & therefore are employed in the formulation of water in oil emulsions. Joshi baibhav et al (2012) has prepared clarithromycin emugel using tween 80 and span 80 as emulsifying agents.

Gelling agent: These are used to increase consistency of dosage forms and provide gelled behaviour. It has been found with a inverse relationship existing between their concentration and drug released'. Carbopol based emulgelshows better drug release than HPMC based emugel. Various gelling agent used are Carbopol 934, HPMC 2910, HPMC K4M etc.

Permeation enhancers[6,10,11]

These agents increase the permeability of skin for drug penetration by various mechanisms like disruption of highly ordered structure of stratum corneum lipids or interacting with intracellular proteins or altering the portioning behaviour of drugs into the skin structures. Various penetration enhancers used in emulgel formulation are oleic acid, clove oil, lecithin, eucalyptus oil, menthol in various concentrations.

Types of emulgel[12,13]

Microemulsion

Micro emulsions are isotropic mixtures of a biphasic o/w systemic stabilized with a surfactant that is thermodynamically stable and optically clear. Droplets vary in size from 10 to 100nm and do not coalesce. It is made up of specific amounts of oil, co-surfactant, surfactant, and water. Micro emulsions may have unique properties, including extremely low interfacial tension, a broad interfacial region, and the ability to dissolve both aqueous and oil-soluble compounds. The ingredients in micro emulsion can help drug permeate faster by lowering the stratum corneum's diffusion barrier. However, because of their low viscosity, the use of micro-emulsions in the pharmaceutical industry is limited due to their low skin retention ability. To address this limitation, gelling agents like HPMC K100M, Carbopol 940, and guar gum are added to the micro emulsion to form micro emulsion-based gels with a appropriate viscosity for topical application.

Nanoemulgel

Nanoemulsion is transparent (translucent) oil-water dispersion's that are thermodynamically stable,it contains surfactant and co-surfactant molecules globule size range from 1nm to100 nm. When the emulsion is mixed with gel, the term Nanoemulgel is used. Many drugs have higher transdermal permeation compared to traditional formulations such as emulsions and gels. The Nanoemulsion possesses enhanced transdermal and dermal delivery properties in vivo as well as in vitro. Due to its high loading capacity and small globule size, the drug easily penetrates the skin and provides less therapeutic effect in a short period.

Macroemulsion gel
Emulgel with emulsion droplet particle sizes greater than 400nm. They are physically invisible, but, the individual droplets are visible under a microscope clearly. Macroemulsions are thermodynamically unstable, but surface-active agents can help to stabilize them.

MATERIALS USED
1.-Ketoconazole-Strides pharma
2.-Polaxomer 407-Strides Pharma
3.-Ethanol-Lab Chemicals,Melmaruvathur
4.-Glycerol-Lab Chemicals, Melmaruvathur
5.-Carbopol934-Lab Chemicals, Melmaruvathur
6.-Dimethyl sulfoxide-Lab Chemicals, Melmaruvathur
7.-Methyl paraben-Lab Chemicals, Melmaruvathur
8.-Propyl paraben-Lab Chemicals, Melmaruvathur
9.-Triethanolamine-Lab Chemicals, Melmaruvathur
10.-Liquid Paraffin-Lab Chemical, Melmaruvathur
11.-HPMC-Lab Chemical, Melmaruvathur

PREFORMULATION STUDIES
Physical Appearance[38]
The drug(ketoconazole) powder was examined for its organoleptic properties like colour and odour.
Solubility Studies Of Pure Ketoconazole 42

Qualitatively testing of solubility in various solvents. It was determined by taking 10 mg of drug sample in 10 ml of solvent excess drug in test tubes and subsequent shaking, according to IP.

Melting Point Determination[39]
Small amount of drug was loaded in a capillary tube where one of capillary tube was closed and kept in the melting point apparatus and temperature was noted when drug melts.

Determination of Wavelength of Maximum Absorbance (λ max)[40]
10 mg of drug(ketoconazole) was weighed accurately and transferred to 10ml of volumetric flask. added phosphate bufferpH 5.5 appropriate to dissolve the drug completely. The volume made up to 10 ml with solvent to obtain a stock solution in a concentration of 1000 µg/ml, transfer 1ml of above solution with stock kept to another 10 ml volumetric flask and diluted it up to the 10 ml with solvent. This result in a solution with a concentration of 100 µg/ml. Take 1ml of the 100 µg/ml solution and diluted upto 10 ml. The final solution concentration of this solution is 10 µg/ml. Measure the absorbance of the 10 µg/ml solution in a range of + 200 – 400 nm in U.V. Spectrophotometer. The at which the maximal absorbance is noted within this range is the λmax for ketocanazole.

Preparation of pH 5.5 Buffer (Phosphate Buffer)
Phosphate buffer of pH 5.5 was prepared by dissolving 1.354 g of sodium dihydrogen phosphate monohydrate and 0.034 g of disodium hydrogen phosphate dihydrate in about 80 mL of distilled water. The solution was made up to 100 mL with distilled water, and the pH was adjusted to 5.5 using a calibrated pH meter.

Preparation of Stock solution f Ketoconazole in phosphate buffer 5.541
10 mg of ketoconazole was dissolved in small volume of methanol then make up to 100 ml with phosphate buffer 5.5 to get 100 µg/ml.

Preperation of Standard Calibration Curve of ketoconozole in phosphate buffer pH 5.5.

From the above stock solution take 0.5, 1, 1.5, 2, 2.5 ml of the solution in 10 ml volumetric flask and made up to 10 ml with phosphate buffer to get concentration 5, 10, 15, 20, 25 µg/ml. Use phosphate buffer as blank, scann in uv- visible spectophotometer at wavelength of 258nm.

Drug–Excipient Compatibility Study
The possibilities of drug-excipient (lipid and surfactant) interactions were investigated by FT-IR spectrum study. The FT-IR spectrum of pure drug and combination of drug with excipient were recorded using Shimadzu FT-IR spectrophotometer. The spectrum was recorded in the wavelength region of 4000 to 400 cm-1. The IR Spectra of the test sample were obtained by Pressed Pellet Technique using Potassium bromide.

Fourier-Transform Infrared spectroscopy (FTIR) Study[43]
The FTIR spectra of the pure drug, excipients, and formulated emulgel were recorded using an FTIR spectrophotometer by the KBr pellet method in the range of 4000–400 cm^{-1}. Samples were finely ground, mixed with dry KBr, and compressed into a transparent pellet before scanning.

The obtained spectra were analyzed to identify characteristic peaks and to evaluate any possible drug–excipient interactions.

FORMULATION DEVELOPMENT[56,57,58]
PREPARATION OF GEL USING GELLING AGENT
The gel was prepared by dispersing a carbapol 934 (gelling agent) in purified water q.s with constant stirring at a moderate speed using mechanical stirrer, the pH was then adjusted to 6- 6.5 using tri ethanolamine (TEA).

PREPARATION OF EMULSION
Oil phase preparation
Liquid parrafin was dispersed in beaker with oil base ingredients and stirred continously usimg magnetic stirrer.

Aqueous phase preparation
Aqueous phase of emulsion is prepared by dispersing tween 80 in purified water. Ketoconazole was dissolved in ethanol in separate beaker. Simultaneously, in another beaker methyl paraben and propyl paraben are added in

propylene glycol. Add these two solutions in aqueous phase by continuous stirring.

Mixing of phases

Both the oily and aqueous phases were separately heated at 70°C-80°C, then the oily phase was added to the aqueous phase with continuous stirring until it was cooled to room temperature. The emulsion was obtained, which is stored in well closed air tight container.

INCORPORATION OF KETOCONAZOLE EMULSION INTO GEL BASE

The prepared emulsion is incorporated into gel base (1:1) in a drop wise manner with continuous stirring.

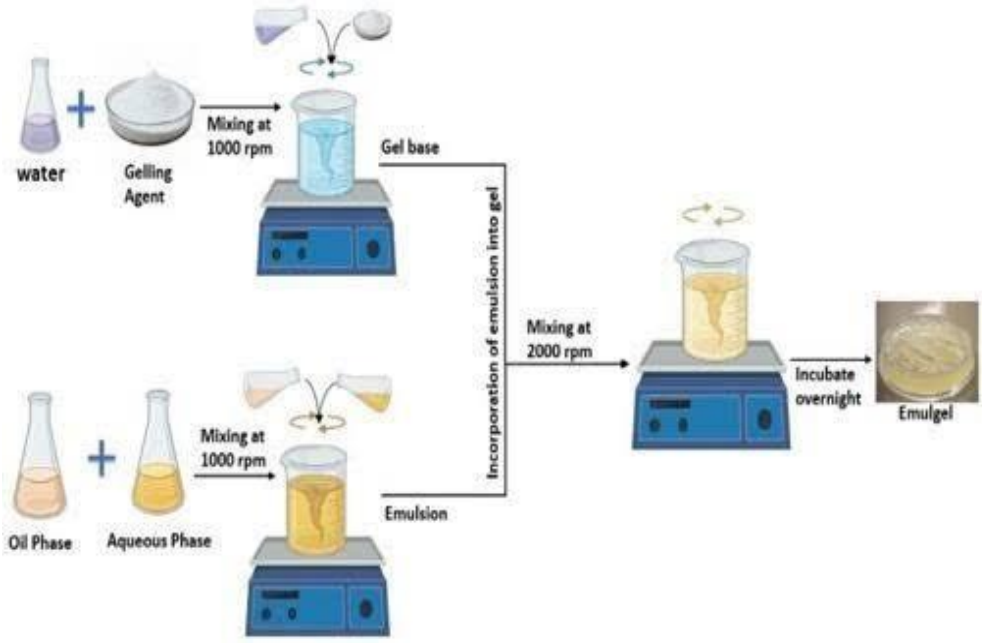


Figure 8.1: formulation of emulgel.

Table 8.3: Formulation chart for the Ketoconazole emulgel preparation.

INGRDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
DRUG(mg)	200	200	200	200	200	200	200	200
CARBOPOL 934(mg)	500	750	750	750	-	-	-	-
HPMC(mg)	-	-	500	750	500	750	-	-
SODIUM ALGINATE(mg)	-	-	-	-	500	750	500	750
POLOXAMER 407(mg)	500	500	500	500	500	500	500	500
PROPYLENE GLYCOL(ml)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
DMSO(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
ETHANOL(ml)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
TWEEN 80(ml)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
METHYL PARABEN(mg)	10	10	10	10	10	10	10	10
LIQUID PARAFFIN(ml)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
TRIETHANOLAMINE(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
D.WATER(ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Sunset yellow FCF(mg)	qs	qs	qs	qs	qs	qs	qs	qs

CHARACTERIZATION OF KETOCONAZOLE EMULGEL

Physical Appearance[44]

This involves observing the prepared emulgel after it has set into the container to analyse its general appearance and check for the presence of any aggregates.

Homogenicity

All formulated emulgels are tested for homogenecity. Visually inspected homogenecity after the gels have been set in the container.

Colour Assesment and Transperancy

Transperency: Emulgel formulations are assesed for colour, transparency and the absence of particles.

Viscosity[46]

The viscosity of the prepared emulgel is measured by using a Brookfield Viscometer. The gel is rotated at 20 and 30 rpm with spindle no.64 the corresponding reading is recorded.

Spreadability[47]
This is determined by using the following technique: 1g of emulgel was placed within a circle of 1 cm diameter pre marked on a glass plate over which a second glass plate is placed. A weight of 50 g was allowed to rest on the upper glass plate for 5min. The increase in the diameter due to spreading of the gels is then noted.
Spreadability (S) = (M × L) / T

Clarity Test[47]
The clarity of the prepared emulgel formulations was evaluated by visual inspection against a black and white background under adequate light, as reported in literature. The formulations were observed for the presence of particulate matter, turbidity, or phase separation. Clear and transparent appearance without any visible particles was considered as an indication of good clarity.

pH Determination[45]
Digital pH meter is used to determine the pH of emulgel. The pH meter was calibrated before using with buffered solution pH 4.0, 7.4, 10.0. One gram of gel was dissolved in 25 mL of distilled water and the electrode was then immersed into the above solution for 30 minutes until the constant reading was obtained.

Entrapment Efficiency[50]
The emulgel (1g) was placed in a test tube and add 10ml of Isotonic phosphate buffer of pH 5.5. This aqueous solution was sonicated in a sonicator bath. The drug containing emulgel were separated from the dispersion by centrifugation at 15000 rpm for 30 min. The supernatant (1 ml) was taken and diluted with phosphate buffer (in 10 ml volumetric flask). And again, from stock solution, 1 ml was withdrawn and transferred to a 10 ml volumetric flask and made up to the mark with buffer. The drug concentration in the resulting solution was assayed using the UV- visible spectroscopy method. The percentage of drug encapsulation was calculated using the following formula
Entrapment Efficiency = [(Ct – Cr) / Ct] × 100 Where, EE= Entrapment Efficiency, Ct = Concentration of total drug,
Cr = Concentration of un entrapped drug

Drug Content[48]
A 10 mg sample of the formulation was taken and placed in a 10ml volumetric flask. Methanol was added to the flask, and the mixture was thoroughly shaken to guarantee proper dissolution. The volume was then made up to mark with methanol. The volumetric flask has been allowed to stand for 2 hours and then shaken within a shaker to ensure thorough mixing.

The solution was then filtered via filter paper to remove any particulate matter, and the filtered mixture was me asure d for absorbanc e using a spe c t rophotomete r at 258 nm.

Drug Content (%) = (Absorbance of Sample / Absorbance of Standard) × (Concentration of Standard / Concentration of Sample) × 100

In-vitro Diffusion Study[49,51]
An in vitro drug release study is performed by using a Franz diffusion cell assembly. Which consists of two compartments, a receptor chambers containing a Phosphate Buffer Saline (PBS) of pH 5.5 and another donor compartment containing emulgel. A cellophane membrane was previously soaked for 24h. The cellophane membrane was placed in contact with PBS filled in the receptor compartment to avoid disruption in the ongoing process; it was ensured that no air bubbles were seen between the cellophane membrane and the liquid surface of PBS. The temperature was maintained at 37 °C at 50rpm using a magnetic stirrer. 1.5ml of the sample was withdrawn from the receptor chamber side tube at the time interval of 1h, 2h, 3h, 4h, 5h, 6h, equilibrated with a new or fresh dissolution medium to maintain a sink state. Suitable dilution was carried out and was spectroscopically analyzed at 258 nm using UV-visible spectroscopy.

Release Kinetics of the Best Formulation
To study the in vitro release kinetics of the optimized formulation, data obtained from dissolution study were plotted in various kinetics models. Different kinetic models such as zero order (cumulative amount of drug released vs. time), first order (log cumulative percentage of drug remaining vs. time), Higuchi model (cumulative percentage of drug released vs. square root of time), Korsmeyer- Peppas model (Log Cumulative percent drug release versus log time) and Hixson Crowell model(cube root of log cumulative percentage of drug remaining vs. log time) were applied to interpret the drug release kinetics from the formulations. Based on the highest regression values for correlation coefficients for formulations, the best fit model was decided.

Zero order equation
The zero order release can be obtained by plotting cumulative % percentage drug released vs Time (hr)

$$C = Ko\ t$$

Where,
Ko = Zero order constant
t = time in hr Application:

It is used to describe the drug dissolution of several types of modified release Pharmaceutical dosage forms, as in the case of some transdermal systems, as well as tablets with low soluble drugs in coated forms, osmotic systems, etc.

First order reaction
The graph was plotted with log % cumulative drug remaining vs. time (h)

$$Log\ C = Log\ C0 – Kt / 2.303$$

Where,
C0 = initial concentration of drug,

K=First order
t = time (hr)

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drugs in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi kinetics
It was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then sustained to different geometrics and porous systems. This model is based on the hypothesis that Initial drug concentration in the is much higher than drug solubility.

Drug diffusion takes place only in one dimension (edge effect must be negligible).

Drug particles are much smaller than system thickness.

Swelling and dissolution are negligible.

Drug diffusivity is constant and Perfect sink conditions are always attained in the release environment.

The graph was plotted with % cumulative drug release vs. square root of time.

$$Q = Kt1/2$$

Where,
K = constant reflecting design variable system (differential rate constant) t = time (hr)
The drug release rate is inversely proportional to the square root of time

Application
This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and tablets with water soluble drugs.

Hixson and Crowell erosion equation
To evaluate the drug release with changes in the surface area and the diameter of the particles, the data were plotted using the Hixson and Crowell rate equation. The graph was plotted by cube root of % drug remaining vs. time in hr.

$$0Q\ 1/3 –t\ Q\ 1/3\ H=CK\ t$$

Where,
Q0 = Initial amount of drug
Qt = Amount of drug released in time t
KHC = Rate constant for Hixson Crowell equation

Korsmeyer- peppas equation
Korsmeyer et al.(1983) derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model.

To evaluate the mechanism of drug release, t was further plotted in korsmeyerpeppas equation as log cumulative % of drug released vs log time

$$Mt/ M\alpha = Ktn$$

Where,
Mt / Mα = Fraction of rug released at time t
T = Release time
K = kinetics constant (instructing structural and geometric characteristic of the formulation)
N = Diffusional exponent indicative of the mechanism of drug release

Anti-fungal studies[52,53]
Mould is obtained from the retared bread. Agar (SDA) is added to 40 ml of distilled water in conical flask and stoppered with a cotton plug and autoclaved for 15 min at 15lbs of pressure. After cooling it at room temperature, pour 20 ml into two sterile petri plates between two flames swirl the plates to remove air bubbles, and let it solidify at room temperature near the sterile area. Addition of Mould through a cotton swab and streaked in all directions into the solidified agar, bore four wells from the sterile borer to add the ketoconazole emulgel formulation. Incubate at 25-30 °C for 72hrs for inhibition of fungi and observe the Zone of Inhibition and measure the diameter in mm; the greater the zone of inhibition, the more susceptible is the formulation.

Scanning Electron Microscopy (SEM)[55]
The surface morphology of ketoconazole emulgel was studied by Scanning Electron Microscopy (SEM). The shape of the formulation and the sizes of the vesicles were determined by SEM. A drop of emulgel was placed on the specimen stub which was coated with carbon and then with gold vapour appeared using a vacuum evaporator. The samples were examined under a scanning electron microscope for vesicular shape and then photographed.

Determination of zeta potential[54,63]
The zeta potential of the ketoconazole emulgel formulation was analyzed at 25°C using Zeta sizer. Emulgel was diluted 100 times with doubled-distilled water and voltage was set at 1.4 V and electrodes were placed in dispersion for the measurement of zeta potential. Each sample was run 3 times and analysis was continued at 25 °C with a scattering angle of 173°C.

Stability studies[56]
The formulated ketoconazole emulgel were kept at room temperature. After 30 days Physical Appearance, Homogenecity, pH, Clarity, Viscosity, Spreadability, Entrapment Efficiency, Drug Content was noted.

METHODOLOGY

PREFORMULATION STUDIES

Pre-forrmulation studies on the obtained sample of drug were performed for identification and compatibility studies.

PHYSICAL APPEARANCE

The drug (ketoconazole) powder was examined for its organoleptic properties like colour and odour and found to be white in colour and practically odour less.

SOLUBILITY ESTIMATION

Table 9.1: Solubility profile of Ketoconazole.

S.No.	Medium	Solubility Profile	Solublity terms
1.	Water	Insoluble	>10000 parts
2.	Methanol	freely Soluble	1-10 parts
3.	Ethanol	Soluble	10-30 parts
4.	0.1N Hcl	sparingly Soluble	30-100 parts
5.	Phosphate buffer 5.5	Slightly soluble	100-1000 parts

Inference

Ketoconazole is a poorly water-soluble antifungal drug, classified under BCS Class II. Its solubility in aqueous medium is very low; hence, organic solvents methanol, ethanol or buffered systems are generally required to enhance solubility. Use of phosphate buffer pH 5.5 improves wettability and dispersion, making it suitable for analytical and formulation studies.

DETERMINATION OF MELTING POINT

Table 9.2: Melting point of Ketoconazole.

S.No.	Melting Point(℃)	Average
1.	151	151℃
2.	150	
3.	151	

Inference

The observed melting point of ketoconazole falls within the reported range (≈146–152 °C), confirming its identity and purity, as no significant deviation or broadening was noted.

DETERMINATION OF WAVELENGTH OF MAXIMUM ABSORBANCE (λmax)

The maximum absorbance of Ketoconazole was found to be 258 nm.

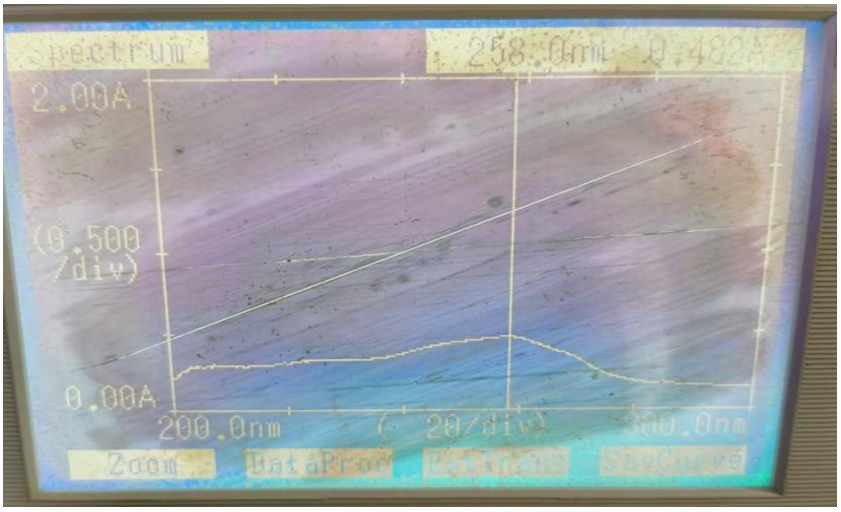


Fig. 9.1: λmax of ketoconazole.

CALIBRATION CURVE FOR KETOCONAZOLE

The absorbance of the drug in concentration ranging from 5-25µg/ml was measured at a wavelength of 258nm against blank.

Table 9.3: Calibration data of Ketoconazole.

S.No	Concentration(µg/ml)	Absorbance
1.	5	0.229
2.	10	0.482
3.	15	0.728
4.	20	0.964
5.	25	1.205

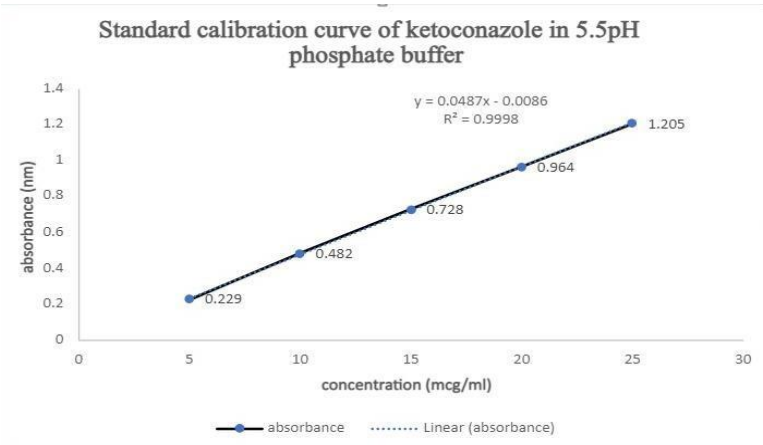


Fig 9.2: Standard curve of ketoconazole.

Inference

It was found that the solutions show linearity (R2 = 0.9998) at a concentration of 5- 25 µg/ml and obeys Beer Lambert's law.

PHYSICAL CAMPATIBILITYSTUDY

9.4. Physical compatibility study of drug and excipients

S.No.	Drug and Excipients	Description and Condition						
		Initial	At room temperature (in days)			At 40ºC± 2ºand75% RH ± 5% (in days)		
			10	20	30	10	20	30
1	Ketoconazole	White powder	NC	NC	NC	NC	NC	NC
2	Polaxomer	White powder	NC	NC	NC	NC	NC	NC
3	Tween80	Oily liquid	NC	NC	NC	NC	NC	NC
4	Sodium aliginate	White powder	NC	NC	NC	NC	NC	NC
5	Ketoconazole+polaxomer	White powder	NC	NC	NC	NC	NC	NC
6	Ketoconazole+tween80	White creamy solid	NC	NC	NC	NC	NC	NC
7	Ketoconazole + Sodium alginate	Whitish powder	NC	NC	NC	NC	NC	NC
8	Ketoconazole+ Poloxamer+ Tween 80+ Sodium alginate	Light orange gel	NC	NC	NC	NC	NC	NC

*NC-No Change

Inference

Therefore the drug and excipients are physically compatible with each other.

FTIR SPECTRUM OF KETOCONAZOLE

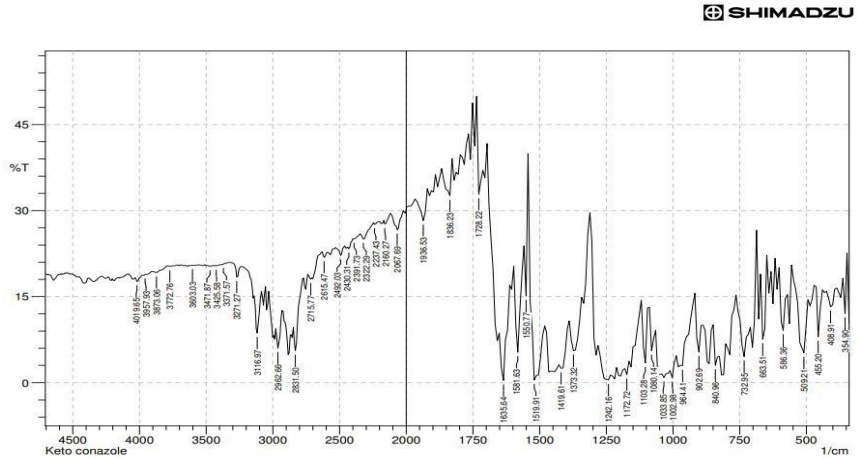


Figure 9.3: ftir spectrum of ketoconazole pure drug.

Table No. 9.5: FTIR spectral interpretation of ketoconazole.

Wave number (cm-1)	Types of vibrations
1581.63(cm-1)	C=N Stretching
1242.16(cm-1)	C-O Stretching
1635.64 (cm-1)	C=C Stretching
1728.22 (cm-1)	C=O Stretching
1103.28 (cm-1)	C-C Stretching
1080.41(cm-1)	C-N Stretching

FTIR SPECTRUM OF DRUG AND CARBOPOL934

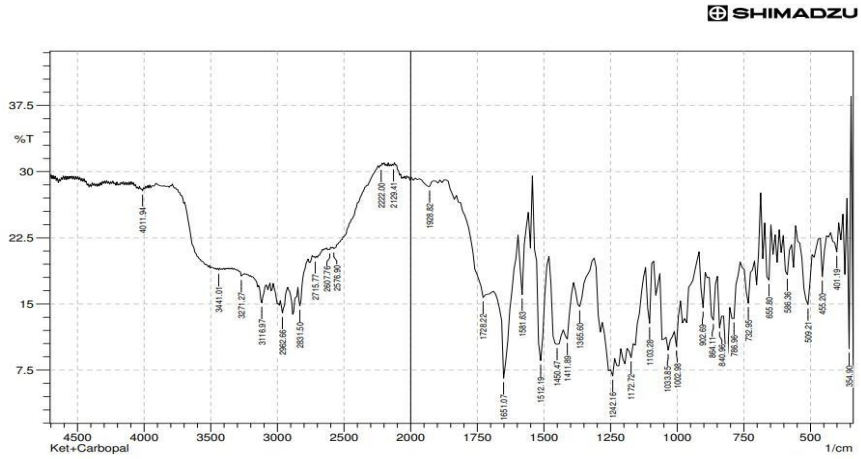


Figure 9.4: FTIR image of ketoconozole and carbopol 934.

Table No. 9.6: FTIR spectral interpretation of ketoconazole and carbopol 934.

Wave number (cm-1)	Types of vibrations
1651.07 (cm-1)	C=O Stretching
3441.01 (cm-1)	O-H Stretching
1172.72 (cm-1)	C-C Stretching
2715.77(cm-1)	C-H Stretching

9.2.3 FTIR SPECTRUM OF DRUG AND POLOXOMER 407

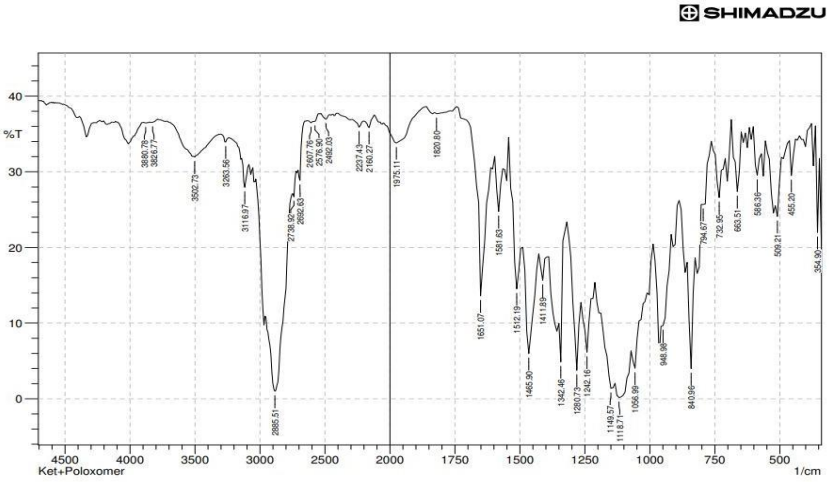


Figure 9.5: FTIR image of ketoconozole and poloxomer407.

Table No. 9.7: FTIR spectral interpretation of ketoconazole and poloxomer407.

Wave number (cm-1)	Types of vibrations
1118.71 (cm-1)	C-O Stretching
3502.73 (cm-1)	O-H Stretching
1149.57 (cm-1)	C-C Stretching
3263.56 (cm-1)	C-H Stretching

INFERENCE

The peak observed in the FT-IR spectrum of ketoconazole with carbapol and poloxomer showed no shift and no disappearance of the characteristic peak of drug. This suggest that there is no interaction between the drug and the gelling agents.

FORMULATION OF KETOCONAOZLE LOADED EMULGEL

Figure 9.6: Ketoconaozle loaded emulgel.

CHARACTERIZATION OF EMULGEL FORMULATION

PHYSICAL APPEARANCE

The physical appearance of the prepared gels were tested by visual observations after the gel had been set in the container.

Table 9.8: Physical appearance of Ketoconazole Emulgel.

FORMULATION CODE	COLOUR
F1	LIGHT ORANGE
F2	DARK REDDISH ORANGE
F3	DARK REDDISH ORANGE
F4	LIGHT ORANGE
F5	LIGHT ORANGE
F6	LIGHT ORANGE
F7	DARK REDDISH ORANGE
F8	DARK REDDISH ORANGE

Inferance

All the prepared formulations gives different types of orange.

HOMOGENICITY

All formulated gels were tested for homogeneity by visual inspection after the gels have been set in the container.

Table 9.9: Homogenicity of Ketoconazole Emulgel.

FORMULATION CODE	APPEARENCE
F1	HOMOGENOUS
F2	HOMOGENOUS
F3	HOMOGENOUS
F4	HOMOGENOUS
F5	HOMOGENOUS
F6	HOMOGENOUS
F7	HOMOGENOUS
F8	HOMOGENOUS

Inferance

All the prepared formulations are homogeneous in nature

CLARITY OR TRANSPERANCY

The clarity and transparency of each formulation was visually observed.

Table 9.10: Clarity of Ketoconazole Emulgel.

FORMULATION CODE	CLARITY
F1	CLEAR
F2	OPAQUE
F3	OPAQUE
F4	TRANSPERANT
F5	TRANSPERANT
F6	TRANSPERANT
F7	OPAQUE
F8	OPAQUE

Inferance

All the prepared formulations results clear in nature.

VISCOSITY

The viscosity of the gel formulations was determined at 20 to 30rpm by using Brookfield viscometer.

Table 9.11: Viscosity of Ketoconazole Emulgel.

FORMULATION CODE	VISCOSITY(centipoise)
F1	5201
F2	6300
F3	6800
F4	5529
F5	4110
F6	6780
F7	4100
F8	5260

Inference

All the formulation exhibits good consistency, which was dependent on the gelling agent.

SPREADABILITY

This method is done manually using glass plates.

Table 9.12. Spreadability of Ketoconazole Emulgel.

FORMULATION CODE	SPREADABILITY (cm)
F1	4.5
F2	4.7
F3	4.7
F4	5.1
F5	4.6
F6	4.9
F7	4.8
F8	5.0

Inference
All gel formulations shows good spreadability within a range of 4.5 to 5.1cm.

pH DETERMINATION
The pH of each formulation was measured using a calibrated pH meter.

Table 9.13: pH of Ketoconazole Emulgel.

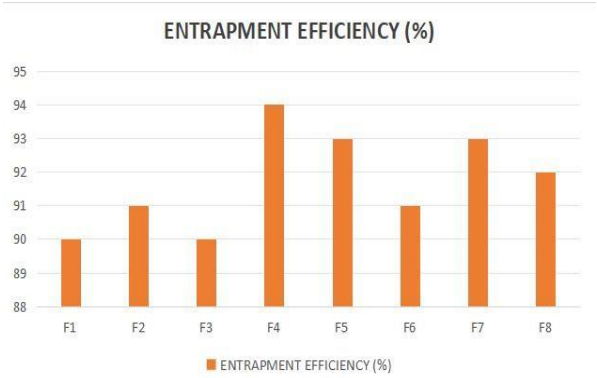
FORMULATION CODE	pH
F1	5.81
F2	5.90
F3	6.10
F4	6.12
F5	5.51
F6	5.70
F7	5.91
F8	6.20

Inference
The pH of all formulations was found to best satisfactory within a range 5.70-6.20. Therefore, it will not cause any irritation on administration.

ENTRAPMENT EFFICIENCY
Entrapment Efficiency was proceeded using centrifuge and analysed using UV-Spectrophotometer.

Table 9.14: Entrapment Efficiency of Ketoconazole Emulgel.

FORMULATION CODE	ENTRAPMENT EFFICIENCY (%)
F1	90
F2	91
F3	90
F4	94
F5	93
F6	91
F7	93
F8	92



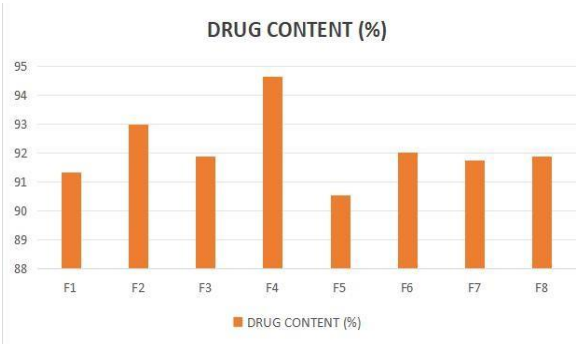
Graph 9.1: Graph of % Entrapment Efficiency.

Inference
The % Entrapment Efficiency was found to be in the range of 90.05% to 94.07%. A higher entrapment efficiency indicates effective drug loading within the emulsion system, which ensures stability and sustained release.

DRUG CONTENT
Drug content is one of the important evaluation parameter for any type of dosage form which is determined by UV spectrophotometer.

Table 9.15: Drug Content of Ketoconazole EmulGel.

FORMULATION CODE	DRUG CONTENT (%)
F1	91.34
F2	92.99
F3	91.89
F4	94.64
F5	90.52
F6	92.03
F7	91.75
F8	91.89



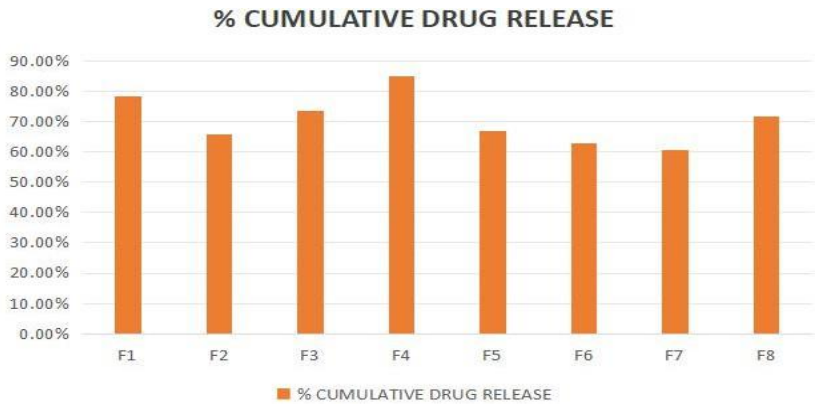
Graph 9.2: Graph of % drug content.

Inference
The % drug content of all formulations was in the range of 90.52-94.64% indicating uniform distribution of drugs in all formulation.

IN-VITRO DRUG RELEASE
An in-vitro drug release study was performed using Franz diffusion cell assembly.

Table 9.16: Datas of in-vitro drug release.

FORMULATION CODE	% CUMULATIVE DRUG RELEASE
F1	78.35%
F2	65.64%
F3	73.34%
F4	85.02%
F5	66.69%
F6	62.69%
F7	60.76%
F8	71.67%



Graph 9.3: Graph of cumulative % drug release.

Inference

The best emulgel formulation showed sustained drug release. The cumulative % drug release at 6 hrs for best formulation was found to be 85.02%.

10 RELEASE KINETICS OF KETOCONZOLE LOADED EMULGEL

Table No. 9.17: Release kinetics of ketoconazole loded emulgel.

Time (hours)	Log time	Square root of time	Cumulative % drug release	Cumulative % drug remaining	Log cumulative % drug release	Log cumulative % drug remainig	Cube root of % drug remaining
0	∞	0	0	100	∞	2	4.61
1	0	1	13.59	86.41	1.133219	1.936564	4.423
2	0.301	1.4142	27.47	72.53	1.438858	1.860517	4.173
3	0.477	1.732	46.15	53.85	1.664171	1.731185	3.777
4	0.602	2	69.09	30.91	1.839415	1.410099	3.138
5	0.698	2.236	79.12	20.88	1.898286	1.319730	2.755
6	0.778	2.440	85.02	14.98	1.929521	1.175511	2.466

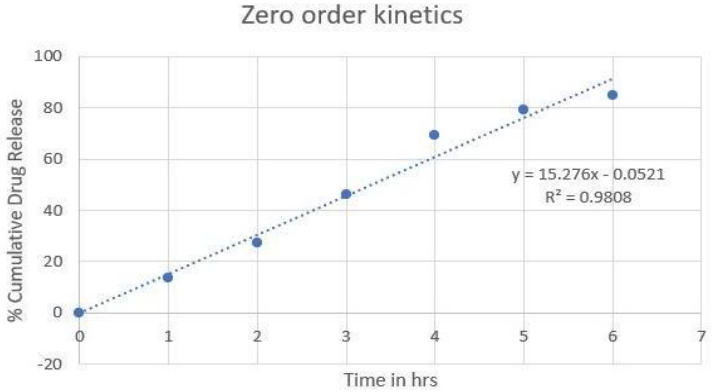


Figure 9.8: A plot for zero order kiinetics Ketoconazole emulgel.

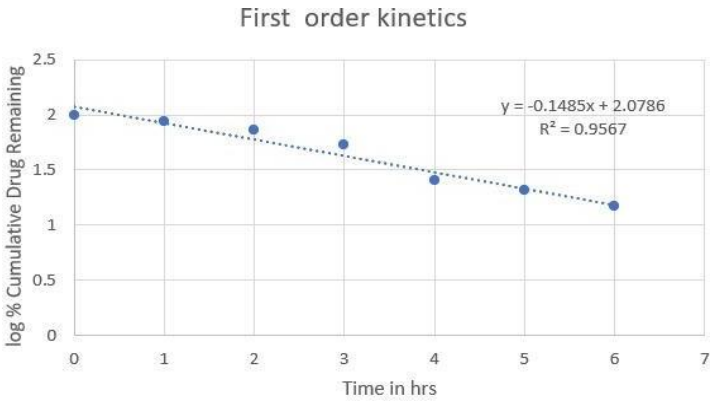


Figure 9.9: A plot for first order kinetics of Ketoconazole emulgel.

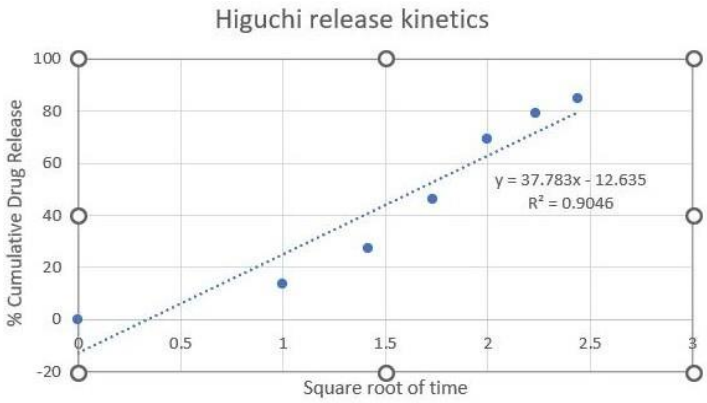


Figure 9.10 Higuchi release kinetics of Ketoconazole loaded emulgel.

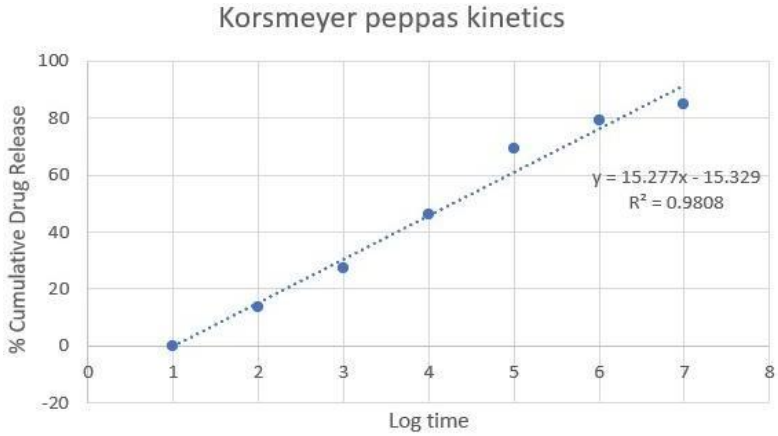


Figure No. 9.11: Korsmeyer- peppas kinetics of Ketoconazole loaded emulgel.

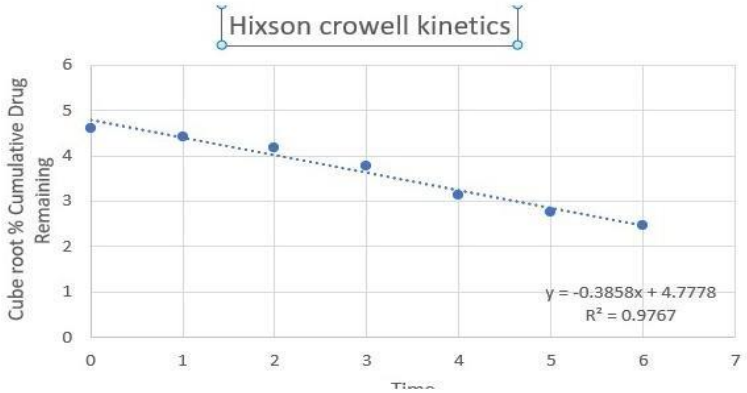


Figure No. 9.12: Hixson – crowell kinetics of Ketoconazole loaded emulgel.

The coefficient of determination (R2) was taken as criteria for choosing the most appropriate model. The R 2 values of various models are given in table no

Table No. 9.18: Kinetics Model and its R2 value.

S.No	Kinetics models	Coefficient of determination (R2) of optimized formulation
1	Zero order	0.9808
2	First order	0.9567
3	Higuchi	0.9046
4	Korsmeyer and peppas	0.9882
5	Hixson Crowell	0.9767

The data from in vitro release of optimized formulation was fit into various kinetic models.

Good linearity was observed with the Korsmeyer and peppas (R2=0.9882). Hence the result indicating that the release mechanism is controlled by both diffusion and possibly erosion or swelling of the gel matrix

ANTI-FUNGAL STUDIES FOR BEST FORMULATION

The micro-organism used for anti-fungal studies is MOULD which is taken from the retard bread.

Zone of inhibition for optimized emulgel after 24hours is 2.5cm.

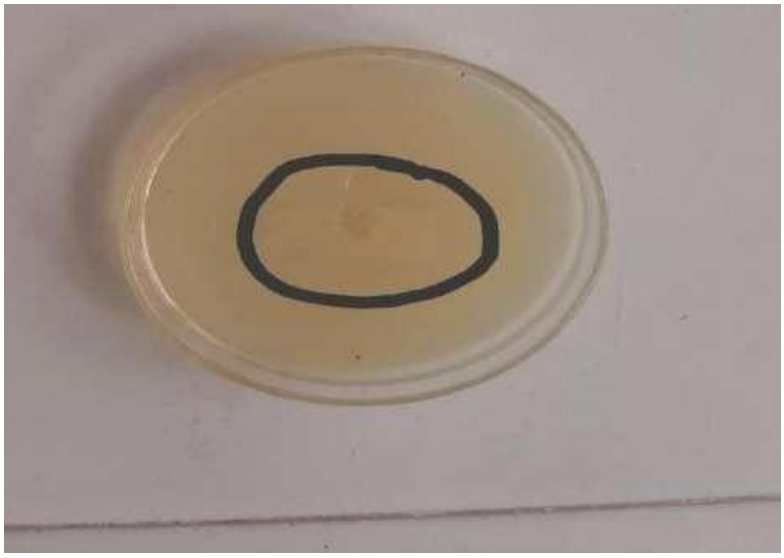


Fig. 9.13: Image 1 Antifungal study of 2% ketoconazole.

Fig. 9.14: Image 2 Antifungal study of 2% ketoconazole.

Inference
The optimized formulation shows a good Antifungal Activity.

SCANNING ELECTRON MICROSCOPY OF BEST FORMULATION

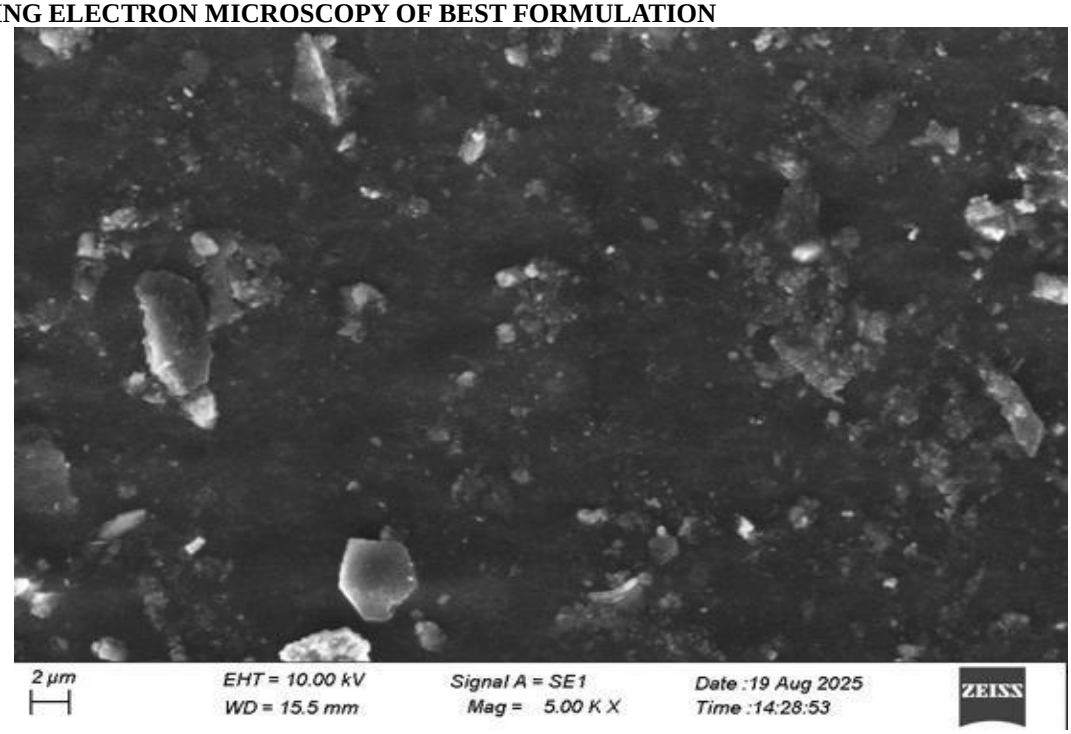


Fig. 9.15: SEM IMAGE1 of ketoconazole emulgel.

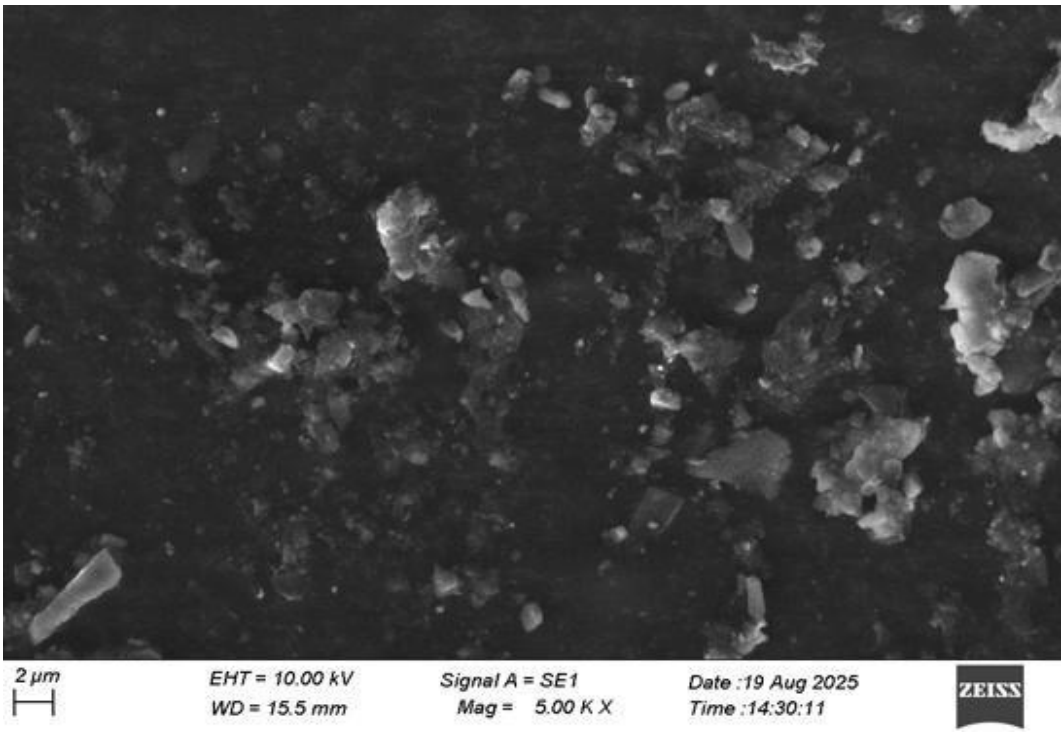


Fig. 9.16: SEM IMAGE 2 of Ketoconazole emulgel Inference.

This results shows that the Ketoconazole loaded emulgel have a spherical shape with smooth surface and discrete without any aggregation or agglomeration.

DETERMINATION OF ZETA POTENTIAL OF BEST FORMULATION

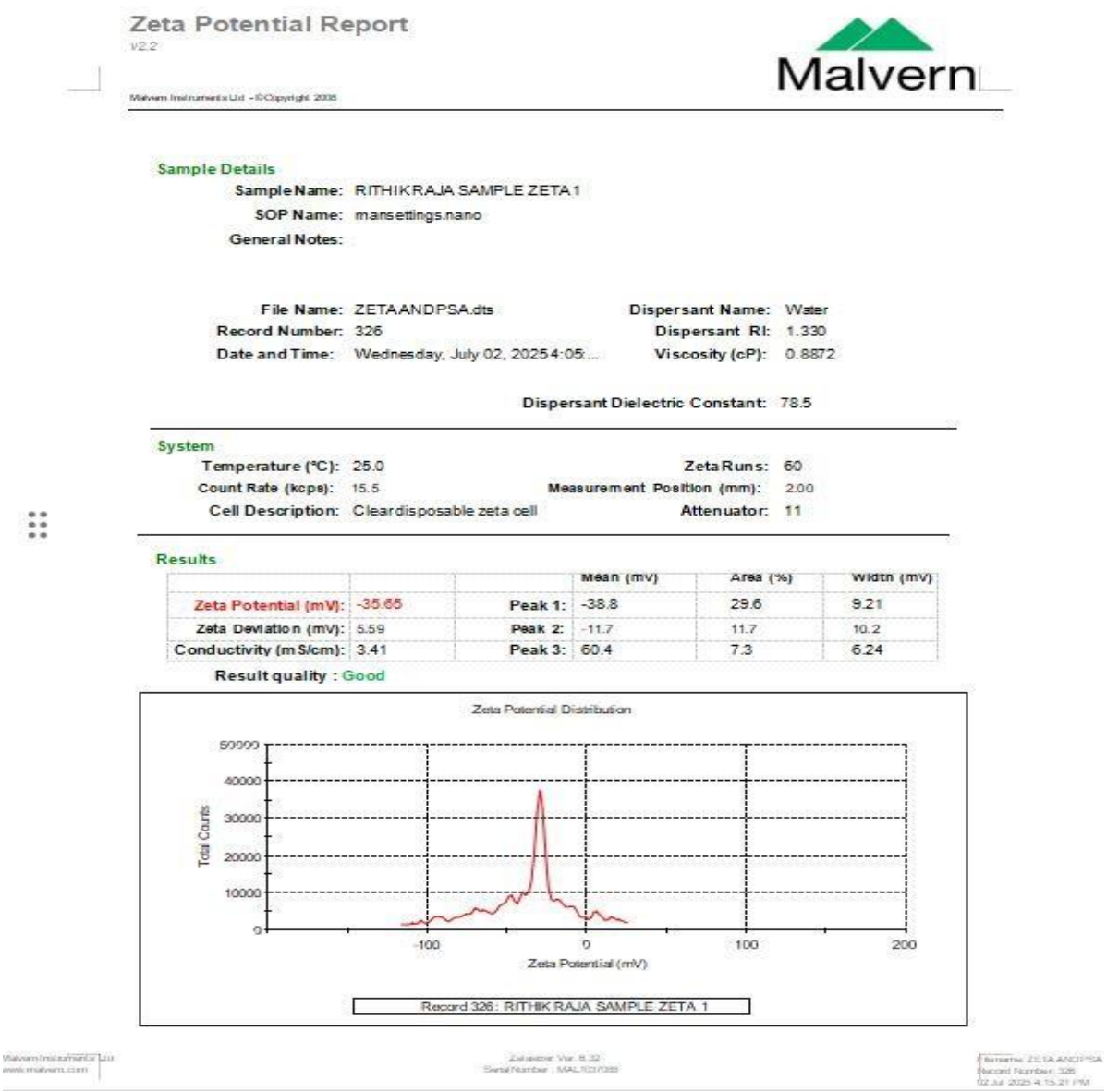


Figure 9.17: Zeta Potential of Ketoconazole emulgel.

Inference

The Zeta potential for the optimized formulation F4 was found to be-35.65 mV and it shows that the formulation is stable.

STABILITY STUDIES OF BEST FORMULATION

The formulated Ketoconazole emulgel(f4) were kept at room temperature and it was subjected to stability studies as per ICH guidelines.

Table 9.19: Datas for stability studies.

Parameter	Condition: At room Temperature	
	Initial	After 1 Month
Visual Appearance	LIGHT ORANGE	LIGHT ORANGE
Homogenicity	Homogenous	Homogenous
pH	6.12	6.10
Clarity or Transperancy	TRANSPERANT	TRANSPERANT
Viscosity	5529	5520
Spreadability	5.1cm	5.cm
Entrapment Efficiency(%)	94.07%	94%
Drug Ccontent (% w/v)	94.64%	94%

Inference

No significant changes in physical appearance, Homogenecity, Clarity, Viscosity, Spreadability, Entrapment Efficiency, drug content when observed at room temperature.

SUMMARY AND CONCLUSION

The purpose of this research was to prepare ketoconazole loaded emulgel for sustained release of drug and incorporate it into topical gel delivery system to reduce the side effects by site specific targeting.

The Physical compatibility of ketoconazole with excipients was studied. The drug and excipients were physically compatible with each other.

The Chemical compatibility study of Ketoconazole with excipients was carried out using FTIR Spectrometer. It revealed no interaction between the drug and excipients.

Among all these eight formulation, Formulation (F4) which is prepared using HPMC, polaxomer 407 and carbapol 934 exhibits high

- Percentage entrapment efficiency (94.07 %)
- Drug content (94.64%)
- In-vitro drug release (85.02 %)

Taking into consideration the high efficiency in systemic circulation delivery together with lack of physical and chemical instability and excellent safety profile, Polaxomer 407 and carbapol 934 could be considered as very promising candidates as absorption and penetration enhancer for ketoconazole transdermally.

Future Scope

In-vivo Study

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