

"Hydrogel Containing Fluconazole: Preparation and Assessment for Antifungal Properties"

Mr. Ritesh Raj*, Dr. Shailesh Jain, Dr. Dhanraj Patidar, Mr. Ajay Kumar, Miss. Pooja Yadav, Mr. Sumit Lodhi.

SAM College of Pharmacy, SAM Global University, Raisen, Madhya Pradesh, India.

Date of Submission: 15-03-2025

Date of Acceptance: 25-03-2025

ABSTRACT

A fungal infection is any sickness or condition produced by a fungal organism. They can infect your lungs or other parts of your body. Superficial fungal infections affect your nails, skin, and mucous membranes (such as your mouth, throat, or vagina). A hydrogel is a biphasic material composed of permeable and porous solids, with at least 10% of the weight or volume of the interstitial fluid consisting totally or largely of water. Fluconazole is an antifungal agent used to treat a variety of fungal infections. This comprises candidiasis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, dermatophytosis, and tinea versicolor. An in-vitro drug release study was carried out using Franz's diffusion cell (dolphin) and egg membrane. An egg membrane was stored in a phosphate buffer (pH 6.8) for 24 hrs before use.

Keywords: Blastomycosis, Coccidioidomycosis, Cryptococcosis, Histoplasmosis, Dermatophytosis, Fluconazole.

I. INTRODUCTION

Drugs have been delivered to the human body in several methods during the last few decades, including oral, sublingual, rectal, parental, topical, and inhalation. Topical delivery refers to the direct application of a drug-containing formulation to the skin to treat cutaneous diseases (such as acne) or the cutaneous symptoms of a general disease (such as psoriasis), hence limiting the drug's internal or pharmacological effects on the skin surface. Although foams, sprays, medicated powders, solutions, and even medicated adhesive systems are in use, semi-solid formulations in all their forms dominate the topical delivery method.

1.1 Fungal infections

A fungal infection is any sickness or

condition produced by a fungal organism. They can infect your lungs or other parts of your body, although they usually target your skin, hair, nails, or mucous membranes. Fungal infections are more likely to affect those with impaired immune systems. Antifungal medications are commonly used to treat fungal infections.

- **Superficial fungal infections**

Superficial fungal infections affect your nails, skin, and mucous membranes (such as your mouth, throat, or vagina). The following are examples of superficial fungal infections.

Ringworm (dermatophytosis). Ringworm is caused by a type of fungi called Dermatophytes, which consume cells from the skin, hair, and nails. Tinea infections can affect several parts of the body, including the hands (tinea manuum), scalp (tinea capitis), feet (tinea pedis/athlete's foot), groin and inner thighs (tinea cruris/jock itch), facial hair and surrounding skin (tinea barbae), and other regions.

Onychomycosis Onychomycosis is a fungal condition that affects fingernails and toenails. This may lead to cracked and discoloured nails. Diabetization. Candida albicans is the most common cause of Candida infections of the skin and mucous membranes, often known as mucocutaneous candidiasis.

Deeporinvasive fungal infections include:

Histoplasmosis. Histoplasma, the fungus that causes histoplasmosis, can infect your lungs, brain, and other organs. It is most typically seen in the Ohio and Mississippi River valleys.

Coccidioidomycosis (Valley Fever). Coccidioidomycosis is caused by the fungus Coccidioides and can infect your lungs and, on rare occasions, spread to other regions of your body. It is particularly prevalent in California and Arizona.



1.3 Hydrogel

A hydrogel is a biphasic material composed of permeable and porous solids, with at least 10% of the weight or volume of the interstitial fluid consisting totally or largely of water. The porous, permeable solid in hydrogels is a three-dimensional network of natural or synthetic

polymers that are insoluble in water and have absorbed a large volume of biological or water-based fluids. These characteristics lend themselves to a wide range of applications, notably in biology. While most hydrogels are synthetic, some are naturally occurring. The term 'hydrogel' was first used in 1894.



Sheets for cooking are hydrogel.



Fig. Peptide hydrogel formation shown by the inverted vial method.

Hydrogels are classified into various types based on their composition, structure, and properties.

Here are some common types of hydrogels:

Natural Hydrogels:

1. Gelatin hydrogel
2. Collagen hydrogel
3. Hyaluronic acid hydrogel
4. Alginate hydrogel
5. Chitosan hydrogel

Synthetic Hydrogels:

1. Polyacrylamide (PAAm) hydrogel
2. Polyethylene oxide (PEO) hydrogel
3. Polyvinylpyrrolidone (PVP) hydrogel
4. Polyacrylic acid (PAA) hydrogel
5. Polyethylene glycol (PEG) hydrogel

Hybrid Hydrogels:

1. Natural-synthetic hybrid hydrogels
2. Interpenetrating network (IPN) hydrogels
3. Semi-interpenetrating network (SIPN) hydrogels

Stimuli-Responsive Hydrogels:

1. pH-responsive hydrogels
2. Temperature-responsive hydrogels
3. Light-responsive hydrogels
4. Electric field-responsive hydrogels

Biodegradable Hydrogels:

1. Poly(lactic-co-glycolic acid) (PLGA) hydrogel

2. Poly(lactic acid) (PLA) hydrogel

3. Poly(caprolactone) (PCL) hydrogel

Injectable Hydrogels:

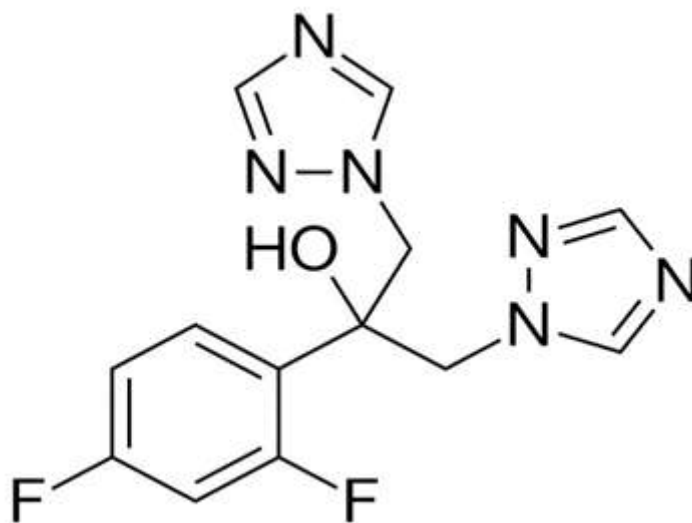
1. In situ-forming hydrogels
2. Thermoresponsive hydrogels
3. Photo-cross linkable hydrogels

1.4 Fluconazole

Fluconazole is an antifungal agent used to treat a variety of fungal infections. This comprises candidiasis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, dermatophytosis, and tinea versicolor. It is also used to prevent candidiasis in high-risk groups, such as those who have had organ transplants, have low birth weight infants, or have low blood neutrophil levels. It is administered either orally or intravenously.

Common adverse effects include vomiting, diarrhoea, dermatitis, and elevated liver enzymes. Serious adverse effects may include liver damage, QT prolongation, and seizures. During pregnancy, it may increase the chance of miscarriage, and high dosages may cause birth abnormalities. Fluconazole belongs to theazole antifungal class of medications. It is thought to act by altering the fungal cellular membrane.

Fluconazole was invented in 1981 and commercialised in 1988. It is on the WHO's list of essential medicines. Fluconazole is available as a generic medicine. In 2021, it was the 165th most often prescribed drug in the United States, with over 3 million prescriptions.



1.5 Topical delivery

Includes two basic types of products:

- External topicals are disseminated into cutaneous tissues to treat the afflicted region.
- Internal topicals that are applied to the mucous membrane orally, vaginally or on anorectal tissues for local activity.

Topical medicines are most commonly utilised for localised effects at the point of application due to medication penetration into the underlying layers of skin or mucous membranes. Although some unintentional medication absorption may occur, it is often in subtherapeutic amounts and of small significance.

Advantages of Topical Drug Delivery Systems

- Avoidance of first-pass metabolism.
- Convenient and easy to apply.
- Avoid the risks and inconveniences of intravenous therapy and the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time, etc.
- Achievement of efficacy with a lower total daily dosage of the drug by continuous drug input.
- Avoids fluctuation in drug levels inter- and inpatient variations.
- Ability to easily terminate the medications when needed.
- A relatively large area of application in comparison with the buccal/nasal cavity.
- Ability to deliver drugs more selectively to a specific site.
- Avoidance of gastrointestinal incompatibility.

- Providing utilisation of drugs with short biological half-life and narrow therapeutic window.
- Improving physiological and pharmacological response.
- Improve patient compliance.
- Provides suitability for self-medication.

Disadvantages of Topical Drug Delivery Systems

Skin irritation or

contact dermatitis may occur due to the drug and/or excipients.

- Poor permeability of some drugs through the skin.
- Possibility of allergic reactions.
- Can be used only for drugs that require very small plasma concentration for action.
- Enzymes in the epidermis may denature the drugs.
- Drugs of larger particle size are not easy to absorb through the skin.

Permeation through skin

Most topical preparations are meant to be applied to the skin. So, basic knowledge of skin and its physiology, function and biochemistry is very important for designing topicals. The skin is the heaviest single organ of the body, combined with the mucosal lining of the respiratory, digestive and urogenital tracts to form a capsule, which separates the internal body structures from the external environment. The pH of the skin varies from 4 to 5.6. Sweat and fatty acids secreted from sebum influence the pH of the skin surface. It is suggested that the acidity of the skin helps in limiting or preventing the growth of pathogens and other organisms.

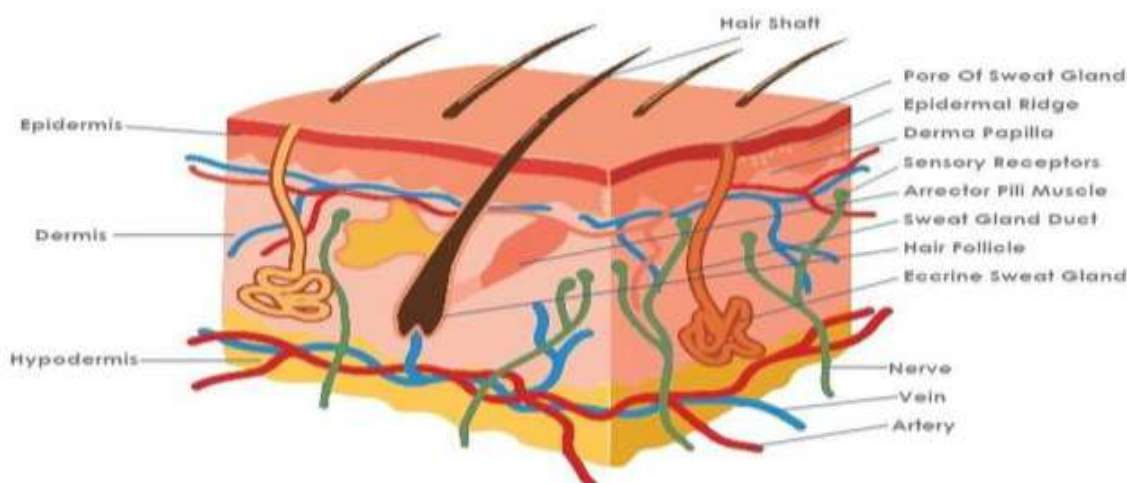


Figure-Cross-section of human skin

II. LITERATURE REVIEW

Singh et al. 2023 hydrogel has been extensively explored as a novel vehicle for novel drug delivery systems for the prolonged or delayed action in subcutaneous, ocular, topical, transdermal and parenteral infusions of drugs. They are developed to facilitate the solubility, bioavailability & stability of drugs having a wider range of applications (Grampurohit et al. 2009). Hydrogel is a quaternary compound made out of an Oil portion, a Water portion, a surfactant & co-surfactant ().

Anoop Kumaret al. (2014) said hydrogel has been regarded as a more effective topical vehicle than its conventional skin applications like cream and gel. Being a transparent and thermodynamically stable system, the hydrogel is formed spontaneously with relative ease of manufacture. Such a system has better scale-up potential, demonstrating their industrial feasibility as well. These nano-structured vehicles exhibited better solubilisation of the drug and higher skin permeation of the drug in comparison to conventional formulations when applied on the skin.

Enhanced drug solubilisation, increased flux across the skin, and a decrease in diffusion coefficient are major attributes of the hydrogel system owing to the internal phase existing as nanosized droplet, ultralow interfacial tension with enhanced surface free energy. The present review focuses on different characterisation methods available to establish phase behaviour, type of microemulsion, microstructure details, rheological properties, etc. The effect of formulation components of the microemulsion and trends in the selection of new excipients constituting the oil phase, surfactant and surfactant have been highlighted herein and future orientations. Hydrogel-based systems find significant improvement in topical delivery of antifungal, antiviral, anti-inflammatory, antioxidant, local anaesthetics, etc.

B. Niyaz Basha et al. (2011) Fluconazole is an imidazole derivative used for the treatment of local and systemic fungal infections. The oral use of fluconazole is not recommended as it has many side effects. Commercially, fluconazole topical gel preparation is not available in the market. Thus, this formulation is made for better patient compliance to reduce the dose of the drug and avoid the side effects of liver damage and kidney damage. The gel was formulated by changing the polymer ratio. FT-IR study confirmed the purity of

the drug and revealed no interaction between the drug and excipients. Gel formulations were characterised

for drug content, pH determination, viscosity measurement, in-vitro diffusion, antifungal

Activity and skin irritation. Among the five formulations, F1 was selected as the best formulation as its %CDR after 4½h was 97.846%, and the release rate of the drug from the formulation is best fitted to the Higuchi model. The viscosity of the F1 formulation was within the limits, and the F1 formulation did not show any skin irritation. Gel formulation F1 was found to be stable at 30

$\pm 2^\circ\text{C}$ and $65 \pm 5\text{RH}$. It was found that at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\text{RH}$, the gel formulation was not stable, and the %CDR was decreased. Efficient delivery of the drug to skin application was found to be highly beneficial in localising the drug to the desired site in the skin and reduced side effects associated with conventional treatment.

Juan Pablo et al. (2015) The incidence of invasive fungal infections has increased globally as a result of several factors. Conventional (sodium deoxycholate) has been used as standard therapy for the treatment of invasive fungal infections; however, it is associated with adverse drug reactions, including acute kidney injury (AKI). New formulations have aimed to improve the safety profile of the conventional formulation. Objectives: This review aimed to assess the effects of deoxycholate versus liposomal on kidney function. Search methods: We searched Cochrane Kidney and Transplant's Specialised Register to 10 March 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. Selection criteria: We included randomised controlled trials (RCTs) that compared sodium deoxycholate with liposomal. Data collection and analysis: Two authors independently assessed studies for eligibility and conducted a risk of bias evaluation. Main results: We included

12 studies (2298 participants) are in this review. Of these, 10 were meta-analysed (2172 participants). Liposomal was found to be significantly safer than conventional in terms of serum creatinine increase (RR 0.49, 95% CI 0.40 to 0.59).

Dubtebdy Sejgar Baget al. (2020) Hydrogels are well-known soft materials that are used to develop soft and wet technology. A solid cross-linked polymer remains in a solvent-entrapped swollen state, and this swollen mass is called a hydrogel. Hydrogel material having high water absorption and

retention capacity are specifically called superabsorbent hydrogels. Such hydrogels are widely used in baby diapers, sanitary towels and agricultural applications. Many hydrogels exhibit the phenomenon of sudden and reversible phase transitions under the influence of external stimuli such as temperature, pressure, electric and magnetic field, light intensity, pH and ionic strength of the medium and chemical triggers: these are called smart hydrogels (also stimuli-responsive or intelligent hydrogels). Smart hydrogels have been tailored to challenging technological applications such as artificial muscles and organs, drug delivery systems, smart sensors and actuators. The synthesis of functional smart hydrogels having an extraordinary activity like sensing, healing, actuation, and another function to fulfil the present technological demand for functional soft materials is a challenging task. Syntheses of fast stimuli-responsive and also strong and stretchable hydrogels are two other aspects to consider in the development of smart hydrogels. The present chapter surveys all aspects of hydrogel materials, including their synthesis, characterization, property evaluations, and recent trends in their technological applications.

Vidya Sabale and Sejal Vora (2012) The mechanism of drug release from microemulsion-based hydrogel was observed to follow zero-order kinetics. The studied optimized microemulsion-based hydrogel showed good stability over 3 months. The average globule size of optimized microemulsion (F5) was found to be 18.98 nm, zeta potential was found to be -5.56 mv, and permeability of drug from microemulsion within 8 h was observed 84%. The antifungal activity of microemulsion-based hydrogel was found to be comparable with marketed cream.

Yosif Almoshari et al. (2012) Active pharmaceutical ingredients (API) or drugs are normally not delivered as pure chemical substances (for the prevention or the treatment of any diseases). APIs are still generally administered in prepared formulations, also known as dosage forms. Topical administration is widely used to deliver therapeutic agents locally because it is convenient and cost-effective. Since earlier civilizations, several types of topical semi-solid dosage forms have been commonly used in healthcare to treat various skin diseases. A topical drug delivery system is designed primarily to treat local diseases

by applying therapeutic agents to surface level parts of the body such as the skin, eyes, nose, and vaginal cavity. Nowadays, novel semi-solids can be used safely in pediatrics, geriatrics, and pregnant women without the possibility of causing any allergic reactions. The novel hydrogels are being used in a wider range of applications. At first, numerous hydrogel research studies were carried out by simply adding various APIs in pure form or dissolved in various solvents to the prepared hydrogel base. However, numerous research articles on novel hydrogels have been published in the last five to ten years. It is expected that novel hydrogels will be capable of controlling the APIs' release pattern. Novel hydrogels are made up of novel formulations such as nanoparticles, nanoemulsions, microemulsions, liposomes, and self-nano-emulsifying drugs.

Delivery systems, cubosomes, and so on. This review focuses on some novel formulations incorporated in the hydrogel prepared with natural and synthetic polymers.

OBJECTIVE

Preparation and evaluation of hydrogel containing Flucanazole for Antifungal Properties

RESEARCH ENVISAGED AND PLAN OF WORK

PLAN OF WORK

- 1) Selection of drug
- 2) Literature review
- 3) Preformulation study
 - Identification study
 - Solubility study
- 4) Formulation development and optimization
- 5) Characterization of optimized formulation
- 6) In vitro study
- 7) Stability study
- 8) Data Compilation
- 9) Result-s-s & discussion
- 10) References

III. EXPERIMENTAL WORK

Preparation of hydrogel for fungal infection:

In this present work, the hydrogel was prepared with Flucanazole

Method of preparation

Three primary constituents make up the hydrogel. Carbopol 940 and tween 80. Typically, it

consists of two phases: the oil phase, which is composed of oleic acid and tween 50, and the aqueous phase, which is composed of water and carbopol 940. In other words, the hydrogel is combined with the oil phase, which is composed of oleic acid and tween 80.

To prepare hydrogel, we first take carbopol and let it swell for four hours before continuing with the formulation process. I employed the medication as the active component, carbopol-940 as the gelling agent, and other excipients to make the hydrogel. I started by adding 15 millilitres of oleic acid and 9.5 millilitres of tween 80, stirring constantly at room temperature while spinning at 500 rpm. Ten milligrams of amphotericin B were then added after one hour of constant stirring. After another hour of waiting, add 4 millilitres of water, drop by drop, along with 50 milligrams of fluconazole. After that, they added the carbopol-940, which had swollen during the previous four hours. They left it on a magnetic stirrer for three to four more hours and left it for twenty-four hours to ensure that the gel formed properly and that the fluconazole was ready.

Viscosities were measured using a Brookfield viscometer at 100 rpm using spindle number 64. Viscosities were recorded at room temperature for all formulations.

4) SPREADIBILITY: Two equal-sized glass plates were taken, and about 1 gm of gel was placed into a circle of 1 cm diameter marked on graph paper, which was placed on a glass plate, over which a second glass plate was placed. A weight of 100 gm was allowed to rest on the upper glass plate, and an increase in diameter due to the spreading of the gels was noted. Spreadability was determined using the following formula. $S = ML/T$

5. DRUG RELEASE STUDY: An in-vitro drug release study was carried out using Franz's Diffusion cell (Dolphin) and egg membrane. An egg membrane was stored in a phosphate buffer (pH 6.8) for 24 hrs before use. The egg membrane was tied to one end of the donor compartment, the receptor compartment was filled with the phosphate buffer of 6.8 pH, and the temperature was maintained at $37 \pm 0.5^\circ\text{C}$ with constant stirring. 1 gm of gel was placed on a donor compartment. The 1 ml



EVALUATION PARAMETERS

1) PHYSICAL EVALUATION: Gels were visually checked for colour, odour, consistency and homogeneity.

2) pH MEASUREMENT: The pH of prepared gels was determined using a digital pH meter, which was calibrated before each use with a standard pH solution. Each formulation was found in an oral cavity pH range (6.8-7.2).

3) VISCOSITY: All eight formulated gels'

samples were collected from the receptor compartment at predetermined time intervals and replaced by an equal volume of phosphate buffer to maintain a sink condition throughout the experiment. The amounts of drugs in the sample were assayed by using a UV-Vis spectrophotometer (Shimadzu-1900) at 210 and 410 nm.

1. Preformulation studies

Preformulation studies are performed before the commencement of formulation development, and the major aim of the study is to

produce or develop stable, safe, and therapeutically efficacious dosage forms that are mainly related to the characterisation of the physico-chemical properties of the drug molecule.

2. Identification of drug

FT-IR spectroscopy method was used for the identification and evaluation of drugs and excipients. Drug KBR pellets were used to record the FT-IR spectrum with a Perkin-Elmer model.

Process-3:-Analysis

The content of fluconazole was estimated by the UV spectrophotometer technique, which is based on the measurement of absorbance at wavelength 275 nm in a phosphate buffer medium at pH.

7.4. The technique was validated for its accuracy and precision. The method obeyed Beer's law in the concentration range 0-25 µg/ml. In observation (n=6), the mean error (accuracy) and relative S.D. (precision) were found to be 0.6% & 1.2%, respectively.

3.1 In-vitro diffusion studies

The skin (abdomen) of Swiss albino male mice was taken for diffusion procedures. Mice (30-35g) were anaesthetised slightly by diethyl ether, and hairs were removed from the skin of the mice. They were sacrificed, and the abdominal skin of the mice was taken off. After removing the subcutaneous fat, the skin was washed and checked for its integrity. The skin was stored in a refrigerator at 4°C overnight and

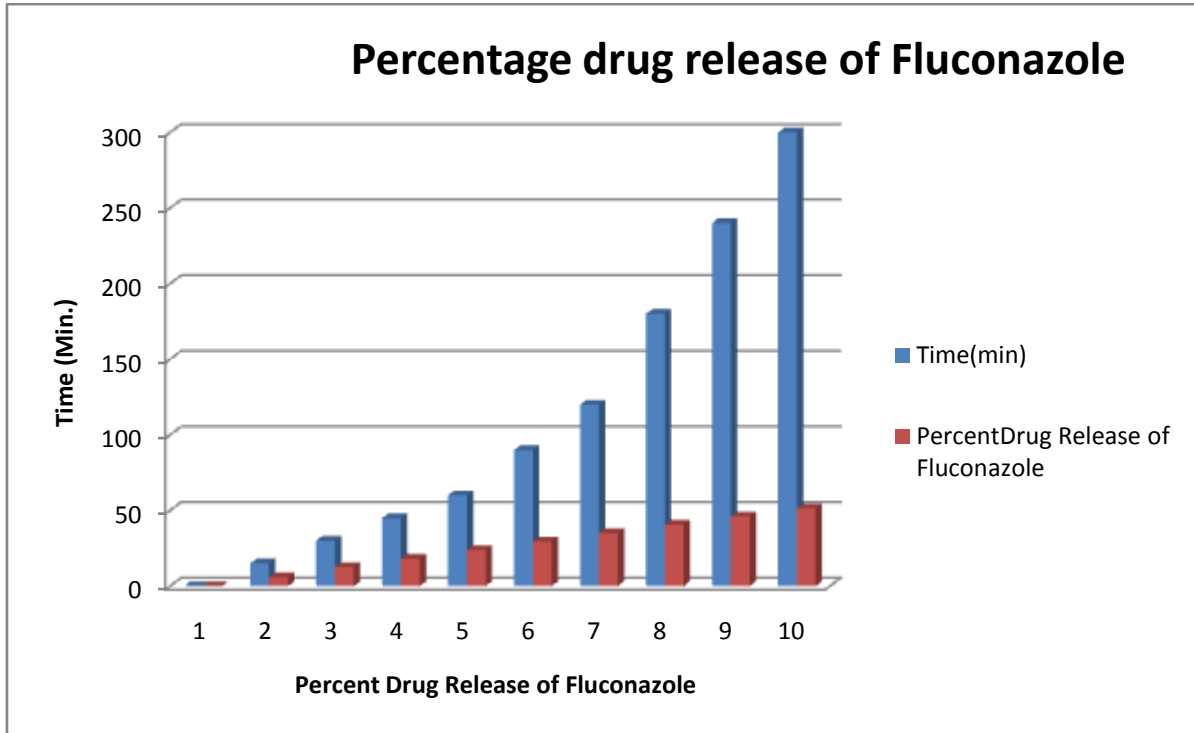
then used for the evaluation. The diffusion procedures were performed in a diffusion cell with a recirculating water bath with 12 diffusion cells. The skin was stretched and fixed between the donor and the receptor chamber of diffusion cells. The cell has an effective diffusion area of 2.8 cm² and a 7 ml volume of the cell. The receptor chamber was filled with a freshly prepared mixture of water-ethanol in the ratio of 4:1 v/v to solubilise the fluconazole. The solution of 20% ethanol was used to solubilise fluconazole. The receptor chambers were thermostated at 37°C, and the solution in the receptor chamber was stirred (continuously) at 300 rpm. The formulation (1.5g) containing fluconazole was kept in the donor chamber. At appropriate time intervals, 0.5 ml of the solution from the receptor chamber was removed for UV evaluations and replaced immediately with the same volume of fresh solution of ethanol (20%). The cumulative amount of drug diffused through mice skin was plotted against time (Salgado et al. 2010)

3.2 Skin irritation studies

A set of 8 rats was used for studying skin irritation tests. The emulsion was applied on the shaved skin of rats. The undesirable skin changes, i.e., changes in colour, scratches and change in morphology, were determined within 24 hours of application.

	Fluconazole
C. Albicans	++
C. dubliniensis	++
C. tropicalis	++
C. glabrata	+/+
C. Krusei	--
C. parapsilosis	++
C. Guiliermondii	+
C. Lisitaniae	++

Table: Spectrum of activity for antifungal drugs



S No.	Time(min)	PercentDrug Release of Fluconazole
1	0	0
2	15	5.71750285
3	30	12.56385405
4	45	18.1559293
5	60	23.89338654
6	90	29.4541049
7	120	35.03762828
8	180	40.54703535
9	240	46.07354618
10	300	51.37725199

effects.

IV. RESULTS AND DISCUSSION

Fluconazole was prepared using constituents such as Carbopol 940 and distilled water. Non-ionic surfactants were more convenient to use due to their less toxic and less skin- irritation

Formulations	Viscosity (CPS)*
ME-1	52.6±0.6
ME-1	75.36±0.8
ME-1	91.4±0.4
ME-1	103.5±0.5
ME-1	118.2±0.2

Table 10: Viscosity measurements.

Mechanical stress study

The following table demonstrates the mechanical stress study of different formulations developed. The highest % phase separation was recorded as 10 after exploring 60 minutes of centrifugation time. The minimum % phase separation was noted as two after 10 exploring 10 minutes of centrifugation time.

V. CONCLUSION

It was possible to manufacture fluconazole using a variety of excipient kinds and ratios. According to the current study, there may be several benefits, including improved transdermal layer action, improved drug solubility, high thermodynamic stability, and simplicity of fabrication. Aside from that, for patients who are unable to take the medication orally, fluconazole may be the most practical and effective topical formulation.

The New Drug Administration System (NDDS), which improves the novel strategy for frequent administration of loaded and fluconazole, is the subject of this study.

It would be a fantastic beginning for allopathic medications to improve millions of people's lives. Additionally, the cost of producing it in large quantities would be acceptable. It will lower the frequency of the same dose.

REFERENCE

- [1]. Prorost C. Transparent oil-water gels. *A review. Int J Cosmet Sci.* 1986;8(3):233-247.
- [2]. 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.
- [3]. Provost C. Transparent oil-water gels. *A review. Int J Cosmet Sci* 1986;8(7):233-247.
- [4]. Rashmi MS. Topical gel. *A review* 2008;6(3):244-249.
- [5]. Shivhare UD, Jain KB, Mathur VB, Bhusari KP, Roy AA. Formulation development and evaluation of diclofenac sodium gel using water soluble polyacrylamide polymer. *Digest J Nanomet and Biostruct.* 2009;4(2):285-290.
- [6]. Vasileiou E, Apsemidou A, Vyzantiadis TA, Tragiannidis A. Invasive candidiasis and candidemia in pediatric and neonatal patients: A review of current guidelines. *Curr Med Mycol.* 2018 Sep;4(3):28-33.
- [7]. Jansook P, Fülöp Z, Ritthidej GC. loaded solid lipid nanoparticles (SLNs) and nanostructured lipid carrier (NLCs): physicochemical and solid-solution state characterizations. *Drug Dev Ind Pharm.* 2019 Apr;45(4):560-567.
- [8]. Ullmann AJ, Sanz MA, Tramarin A, Barnes R A, Wu W, Gerlach BA, Krobot KJ, Gerth WC., Longitudinal Evaluation of Antifungal Drugs (LEADI) Investigators. Prospective study of formulations in immunocompromised patients in 4 European countries. *Clin Infect Dis.* 2006 Aug 15;43(4):e29-38.
- [9]. Hamill RJ. formulations: a comparative review of efficacy and toxicity. *Drugs.* 2013 Jun;73(9):919-34.
- [10]. Al Balushi A, Khamis F, Klaassen CHW, Gagneux JP, Van Hellemond JJ, Petersen E. Double Infection With *Leishmania tropica* and *L. major* in an HIV Patient Controlled With High Doses of. *Open Forum Infect Dis.* 2018 Dec;5(12):ofy323.
- [11]. Rybak JM, Fortwendel JR, Rogers PD. Emerging threat of triazole-resistant *Aspergillus fumigatus*. *J Antimicrob Chemother.* 2019 Apr 01;74(4):835-842
- [12]. Rang HP, Dale MM, Ritter JM, Moore PK. *Pharmacology.* 5th ed. Edinburgh, UK: Churchill Livingstone; 2005. p. 666
- [13]. Mitchell J. Transdermal drug delivery. *American academy of dermatology – 58th Annual Meeting, San Francisco, CA.* 2000
- [14]. Patel V, Kukadiya H, Mashru R, Surti N, Mandal S. Development of microemulsion for solubility enhancement of clopidogrel. *Iran J Pharm Res.* 2010;9:327–34.
- [15]. Yamane M, Williams A. Effect of terpenes and oleic acid on skin penetration enhancers. *Int J*

- Pharm. 1995;116:237–51.
- [16]. Touitou E, Godin B, Karl Y, Bujanover S, Becker Y. Oleic acid, a skin penetration enhancer, affects Langerhans cells and corneocytes. *J Control Release*. 2002;80:1–
- [17]. Kawakami K. Microemulsion formulation for enhanced absorption of poorly soluble drugs. *J Control Release*. 2002;81:75–82.
- [18]. Lawrence M, Gareth D. Microemulsion-based media as novel drug delivery systems. *Adv Drug Deliv Rev*. 2000;45:89–121.
- [19]. Singh V, Bushetti SS, Raju AS, Ahmad R, Singh M, Bisht A. Microemulsions as promising delivery systems: A Review. *Indian J Pharm Educ Res*. 2011;45:392–401.
- [20]. Fakhree M., Ahmadian S. *Drug Delivery*. Nova Science Publishers, Inc.; Hauppauge, NY, USA: 2011. Pharmaceutical dosage forms: Past, present, future; pp. 51–89.
- [21]. Afrin S., Gupta V. *Pharmaceutical Formulation*. StatPearls Publishing; Treasure Island, FL, USA: 2020.
- [22]. Noordin M.I. *Pain Relief-From Analgesics to Alternative Therapies*. IntechOpen; London, UK: 2017. Advanced delivery system dosage form for analgesic, their rationale, and specialty.
- [23]. Singh Malik D., Mital N., Kaur G. *Topical drug delivery systems: A patent review*. *Expert Opin. Ther. Pat*. 2016;26:213–228. doi:10.1517/13543776.2016.1131267.
- [24]. Sharma S., Singh S. Dermatological preparations, formulation and evaluation of various semi-solid dosage form. *Asian J. Pharm. Res. Dev*. 2014;2:10–25.
- [25]. Panwar A., Upadhyay N., Bairagi M., Gujar S., Darwhekar G., Jain D. Emulgel: A review. *Asian J. Pharm. Life Sci*. 2011;2231:4423.
- [26]. Ilić T., Pantelić I., Savić S. The implications of regulatory framework for topical semisolid drug products: From critical quality and performance attributes towards establishing bioequivalence. *Pharmaceutics*. 2021;13:710. doi:10.3390/pharmaceutics13050710.
- [27]. Bora A., Deshmukh S., Swain K. Recent advances in semisolid dosage form. *Int. J. Pharm. Sci. Res*. 2014;5:3594–3608.
- [28]. Sharadha M., Gowda D., Gupta V., Akhila A. An overview on topical drug delivery system—updated review. *Int. J. Res. Pharm. Sci*. 2020;11:368–385. doi:10.26452/ijrps.v11i1.1831.
- [29]. Yu Y.-Q., Yang X., Wu X.-F., Fan Y.-B. Enhancing permeation of drug molecules across the skin via delivery in nanocarriers: Novel strategies for effective transdermal applications. *Front. Bioeng. Biotechnol*. 2021;9:646554. doi:10.3389/fbioe.2021.646554.
- [30]. Ajay Kumar, Rahul Sharma, & Jagdish Chandra Rathi. (2021). Development and Evaluation of Gastro-Retentive Floating Beads of Simvastatin. *World Journal of Pharmaceutical Research*, 10, 1337–1344.
- [31]. Abhay Kushwaha, Shailesh Jain, Ajay Kumar, Ritesh Raj, Phool Singh Yaduwanshi, & Dhanraj Patidar. (2025). An Overall Review of Different Derivatives That Activate Glucokinase Enzyme Having Multiple Actions to Treat Type 2 Diabetes. *International Journal of Pharmaceutical Research and Applications*, 10(1), 358–367. <https://doi.org/10.35629/4494-1001358367>.
- [32]. Shantanu Namdev, Shailesh Jain, Dhanraj Patidar, Ajay Kumar, & Ritesh Raj. (2025). Recent Advances in Pharmaceutical Formulations for the Treatment of Various Diseases: a Review. *International Journal of Pharmaceutical Research and Applications*, 10(1), 389–394. <https://doi.org/10.35629/4494-1001389394>.
- [33]. Shivam Kumar Shukl, Shubham Kumar, Dhanraj Patidar, Shailesh Jain, Ajay Kumar, & Ritesh Raj. (2025). Improvement of Aqueous solubility of Poorly Water-Soluble Drug (Ibuprofen) Using Mixed Solvency Technique. *International Journal of Pharmaceutical Research and Applications*, 10(1), 407–416. <https://doi.org/10.35629/4494-1001407416>.
- [34].