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Formulation and Evaluation of Topical Antifungal Gel Containing Itraconazole by Cold Mechanical Method

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ABSTRACT
The present study involves the formulation and evaluation of a topical antifungal gel containing Itraconazole using the cold mechanical method. Itraconazole, a broad-spectrum antifungal agent, was incorporated into a gel base to enhance skin penetration and patient compliance. The gel was made with carbopol as a gelling agent and tested for pH, spreadability, drug content, and antifungal activity. The results indicated that the gel was stable, effective, and suitable for topical use against fungal infections.

Keywords: Itraconazole, Antifungal gel, Cold mechanical method, Topical drug delivery, Skin fungal infections, Carbopol.

I. INTRODUCTION:

1.1 Topical Drug Delivery System:

Topical drug delivery refers to the application of drug formulations to the skin or mucous membranes for localized therapeutic effects. It is frequently used to treat skin conditions such fungal infections, acne, and psoriasis. Gels, creams, ointments, and lotions are common dose forms. This route offers advantages like ease of use, localized action, reduced systemic side effects, and avoidance of first-pass metabolism. Topical delivery has gained importance in recent years because of the skin's accessibility and big surface area.

- **Common Types of Topical Drug Delivery Systems.**

Several topical dose forms are employed based on the drug's characteristics and therapeutic goals:
Creams and Ointments: Creams are water-based emulsions, whereas ointments are oil-based. Both offer good spreadability and skin contact, however ointments are more occlusive.
Gels: Semisolid systems with a polymeric network that provide cooling and efficient drug release. They are appropriate for regional application to the skin or mucous membranes.
Lotionsare liquid emulsions applied on wide areas of the skin to provide a calming effect. They are less oily and ideal for repeated use.
Clear solutions containing dissolved medications are commonly utilized for fast absorption or antibacterial purposes.
Transdermal Patches: Adhesive patches provide regulated systemic drug distribution through the skin.
Nanoparticles and liposomes are advanced carriers that improve drug stability, penetration, and controlled release.
Microneedles are minimally invasive technologies that promote transdermal absorption via micropores, allowing for precise distribution.The appropriate system is chosen based on the drug's properties, the treatment site, and the desired pharmacological impact.

1.2 Benefits of Topical Drug Delivery System.

Topical medication delivery have plenty of benefits, including:

1. Bypasses the first-pass metabolism.
2. Suitable for local treatment with lower systemic toxicity.
3. Easy to use and patient-friendly.
4. Prevents gastrointestinal incompatibility and enables site-specific medication delivery.
5. Suitable for medicines with limited half-lives or tight therapeutic windows.
6. Improves local bioavailability and Increases patient cooperation and comfort.

1.3 Cons of Topical Drug Delivery System

1. Despite its benefits, the topical approach has limitations:
2. Risk of local skin irritation or allergic responses.
3. Limited to medications that require low systemic concentrations.

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4. Poor permeability for medicines with large molecular weight or low lipophilicity
5. Contact dermatitis caused by drugs or their excipients.
6. Difficulty delivering medications with high particle sizes.

1.4 Skin

The skin is the largest organ in the human body, covering over 20 square feet. It acts as a barrier against environmental factors like microbes, toxins, and variations in temperature. In addition to protection, the skin controls body temperature and allows for sensory experience. Skin health is affected by genetics, nutrition, lifestyle, sun exposure, hygiene, and medical problems. Maintaining skin integrity with adequate care is critical for general health and effective topical medicine delivery.

1.5 Structure of Skin

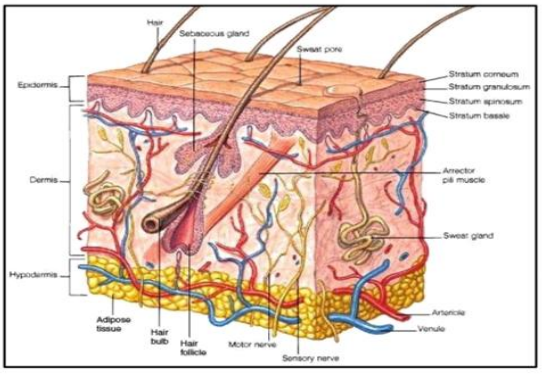

Fig 1. Structure of Skin

The skin is the body's greatest organ, composed of water, protein, fat, and minerals. Your skin protects your body from pathogens and controls its temperature. Nerves in the skin allow you to feel feelings such as hot and cold. The integumentary system includes your skin, hair, nails, oil and sweat glands. An average human skin surface has 40-70 hair follicles and 200-300 sweat ducts per 2 cm of skin. The pH of the skin is between 4-4.5.

- **The skin consists of three layers of tissue.**

1. The epidermis is the top layer.
2. Dermis is the middle layer.
3. The hypodermis is the bottom, fatty layer.

- **Here are the main functions of the skin:**

1. Protection
2. Sensation.
3. Thermal regulation
4. Excretion
5. Absorption.
6. Vitamin D Synthesis
7. Immune defence.

Overall, the skin serves multiple functions, including protection, sensation, temperature regulation, excretion, absorption, immune defence, and vitamin D synthesis.

- **Gels**

Gels are semisolid systems in which a liquid phase is trapped within a polymer matrix, forming a network via physical or chemical crosslinking. Gels are widely used in pharmaceuticals for topical, oral, and ophthalmic applications because they allow for localized drug delivery, controlled release, and improved patient compliance.

- **Pharmaceutical gels typically contain three key components:**

1. The active pharmaceutical ingredient (API) is the therapeutic agent.
2. Gel-forming agents, such as hydrogels, emulgels, and organogels, provide structural support.
3. Excipients are preservatives, stabilizers, pH modifiers, and penetration enhancers that improve stability and efficacy.

- **Benefits of Gels:**

1. Enhanced drug absorption.: Promotes penetration through the skin or mucous membranes.
2. Controlled release: Enables sustained and targeted therapeutic action.
3. Patient compliance has improved due to the ease of application and increased comfort.
4. Localized delivery: Reduces systemic side effects while increasing efficacy.

- **Applications**

1. Gels can be applied topically to treat inflammation, fungal infections, and pain.
2. Oral: Improves the solubility and bioavailability of poorly soluble drugs, allowing for controlled release.
3. Ophthalmic: Allows for longer ocular contact time and sustained drug release in eye formulations.

- **Properties of gels**

1. Safe and inert gelling agents suitable for pharmaceutical/cosmetic use.

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2. Stable semisolid consistency with shear-thinning behavior for easy application.
3. Compatible with preservatives to prevent microbial growth.
4. Sterility is essential for ophthalmic gels.
5. Should not react with other formulation components.

- Gels are categorised according to their physical characteristics, rheological characteristics, colloidal phases, and solvent type.

1. Colloidal Phase-Based:
• Inorganic (system with two phases).
• Single-phase system (organic).

2. Depending on the solvent type:
- Hydrogels are made of water. Aerogels and organic gels (non-aqueous solvents).

3. Considering the rheological characteristics:
• Gels that are plastic or pseudo-plastic. Thixotropic gels are one example.
4. Elastic and rigid gels are based on their physical characteristics.

II. MATERIALS AND METHODS:

Sr No	Name of Equipment	Purpose
1	Mechanical Stirrer	Stirring purpose
2	Electronic balance	Weighing purpose
3	Digital pH meter	pH study
4	UV Spectroscopy	Determination of Absorption maxima
5	Autoclave	Sterilization of Culture Media
6	BOD Incubator	For Fungal growth

List of Equipments

DRUG & EXCIPIENTS PROFILE:

➢ **Itraconazole**

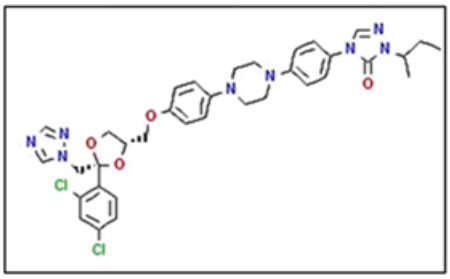

Fig. Structure of Itraconazole

1. IUPAC NAME: (+) -1-[(RS)-sec-butyl] -4-[p-[4-[p-[[(2R,4S) -rel-2-(2,4-dichlorophenyl) -2-(1H-1,2,4-triazol-1-ylmethyl) -1,3-dioxolan-4-yl]methoxy]phenyl] -1-piperazinyl]phenyl] -A2-1,2,4-triazolin-5-one
2. Molecular Formula C15H3Cl2N8O4 has a molecular weight of 705.64 g/mol and the following appearance. White Amorphous Powder.
3. Solubility Alcohol, DMSO, DMF, and methylene chloride
4. Therapeutic Category This antifungal has a melting point of 166.2 °C and is used to treat fungal infections in toenails, fingernails, and the lungs, which can spread throughout the body.

- **EXCIPIENT PROFILE**

➢ **HPMC**

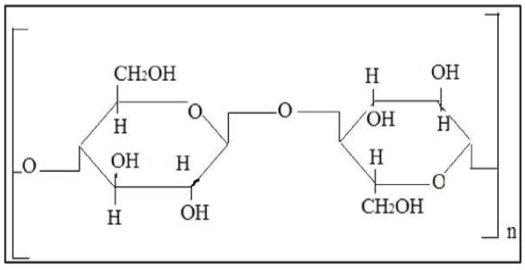

Fig. Structure of HPMC

1. IUPAC name: 2-({6-[(6-{[4,5-dihydroxy-2-(hydroxymethyl)-6-methoxyoxan-3-yl) oxy). -4,5-dihydroxy-2-(hydroxymethyl) oxan-3-yl) oxy] -4,5-dihydroxy-2 (hydroxymethyl)oxan-3-yl) oxy) -6-(hydroxymethyl) oxane-3,4,5-triol

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2. Molecular Formula: C56H108O30 has a molecular weight of 1261.4387.
3. Appearance: White, yellowish-white, or greyish-white powders or granules.
4. Solubility: Water viscosity: 35.0-65.0 cps.
5. Melting temperature ranges from 225-230 °C.
6. Uses: Thickner, binder, texture enhancer, and emulsion stabilizer.

➢ **Carbopol**

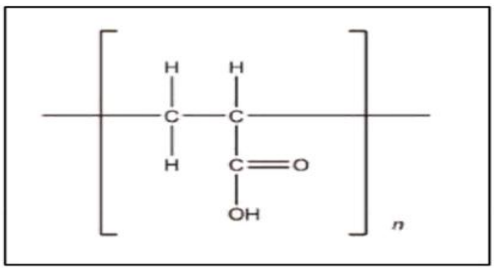

Fig Structure of Carbopol

1. IUPAC name: prop-2-enoic acid.
2. Molecular formula c42h80o8 has a molecular weight of 713.1 g/mol.
3. Appearance white loses power.
4. Solubility highly water and polar solvent are soluble.
5. Melting point: 392-401 °f.
6. Viscosity: 6.0–7.0 cps.
7. Uses: thickeners for lotions, creams, and gels.

➢ **Triethanolamine**

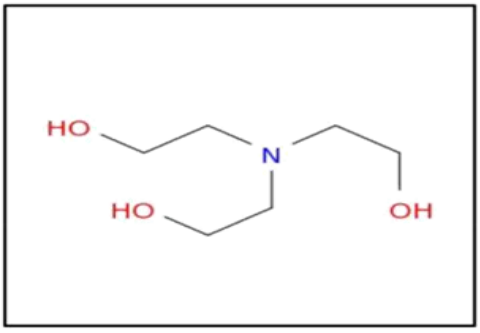

Fig Structure of Triethanolamine

1. IUPAC Name: 2-[bis(2-hydroxyethyl)amino]. ethanol (molecular formula) C6H15NO3 has a molecular weight of 149.188 grams per mole.
2. APPEARANCE Colourless, viscous, hygroscopic liquid.
3. SOLUBILITY Water, aceone, ethanol, and diethyl ether
4. Melting point: 21.60 °C; viscosity: 590.5 cps.
5. Used as a neutralizer, emulsifier, or stabilizer.

➢ **Methyl Paraben**

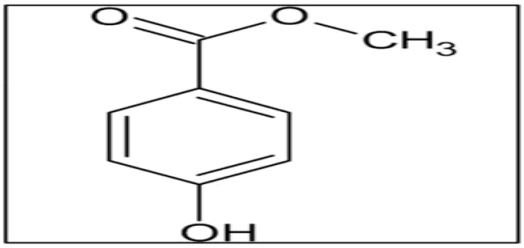

Fig. Structure of Methyl Paraben

1. IUPAC Name: Methyl-4-Hydroxy Benzoate Molecular Formula C8H8O3 has a molecular weight of 152.15 g/mol.
2. APPEARANCE White Crystalline Powder.
3. SOLUBILITY Souble in water, benzene, DMSO, and glycerol
4. MELTING POINT: 125-128 °C.
5. VISCOSITY: 15–20,500 cps.
6. USES: Antimicrobial preservative in cosmetics and food.

➢ **Propylene Glycol**

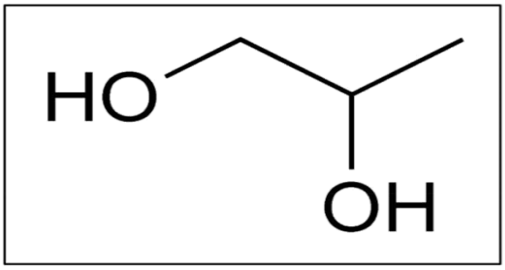

Fig. Structure of Propylene Glycol

1. IUPAC name: Propane-1,2-diol Molecular formula CHO MOLECULAR WEIGHT: 76.09 g/mol.
2. Appearance colourless liquid.
3. Solubility soluble in water, ethanol, ether, and acetone.
4. Melting point: -59°c.
5. Viscosity: 9.91cps.
6. Uses: preserve moisture in medicines, cosmetics, and food products.

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EXPERIMENTAL WORK

- **Formulation Table**

Sr no	Ingredient	Quantity	Uses
1	Itraconazole	0.5 mg	Antifungal Drug
2	H2O	50 ml	Solvent
3	Carbopol	0.3 g	Polymer
4	HPMC	0.5 g	Polymer
5	Methyl Paraben	0.05 g	Preservative
6	Propylene glycol	2 ml	Humectant
7	Triethanolamine	0.2 ml	Neutralizer

Selection of Drugs

Some drugs, such as Itraconazole, Fluconazole, Econazole, and Clotrimazole, were tested for antimicrobial properties based on a literature review. Itraconazole was chosen after reviewing the literature. This compound has antimicrobial properties and is more effective as a drug in the preparation of topical gels.

Selection of Polymers

The most applied polymer on skin belong to various classes, for example to cellulose derivatives, chitosan, carrageenan, polyacrylates, polyvinyl alcohol and silicones. We selected two polymers, HPMC and Carbopol, based on a literature survey.

Formulation of Topical Gel

Collect all the required apparatus and wash them with the help of water and dry it.

- **Method:**

The cold mechanical approach was used to make the gels.

Step 1: Weighing out the necessary quantity of natural and synthetic polymer, it was then gradually sprinkled over the cleansed water's surface for two hours. A mechanical stirrer was then used to constantly agitate it until the polymer had absorbed the water.

Step 2: To neutralise the gel and preserve its pH, triethanolamine was added while being constantly stirred. The gel was then treated with the proper quantity of methyl paraben as a preservative and propylene glycol, which serves as a penetration booster.

Step 3: Itraconazole was added to the gel at last, stirring constantly until the medicine was evenly distributed throughout the gel.

Fig. Itraconazole Gel

- **Evaluation tests for gel**

1. Homogeneity: The physical characteristics of gels, including colour, transparency, and phase separation, were examined visually. They are examined to see whether aggregates are present.

2. Grittiness: Under a microscope, particulate debris was discovered in the formulations.

3. Skin irritation test: Ten participants, both male and female, in good health, took part in the test. An area of 2 em was covered with 100 mg of gel, and any lesions, irritation, or redness were noted.

4. To find the pH, weigh 50 grammes of gel formulation and pour it into a 10-milliliter beaker. To measure, use a digital pH meter. To treat skin infections, the topical gel formulation's pH should be in the range of 3 to 9.

5. Spreadability: The gel formulation's spreadability was assessed by measuring the diameter of 1 gm gel between horizontal plates (20-20 cm2) after 1 minute. The standardized weight tied to the upper plate was 125 gm.

S=M. L/T M- Weight attached to the upper slide.

L-Length moved across the glass.

T-Time Taken

6.Antifungal study: The formulated and marketed gels were tested for antifungal activity against Candida albicans strains using the nutrient agar cup method. Nutrient agar Cups were aseptically

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prepared and inoculated with the tested fungal suspension strain by spreading it on the agar surface. Wells were made in the cups with a sterile borer and filled with the prepared gels using a sterile syringe. The zone of inhibition in each cup was measured, and the radius was calculated and compared to the control using an antibiotic zone reader.

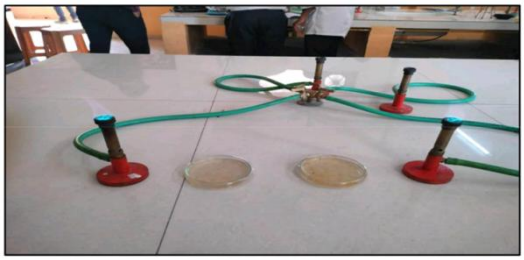

Fig. Antifungal study

7. In vitro diffusion study: 5 gm of gel was applied uniformly to the skin and cellophane membrane. The cellophane membrane was positioned between the compartments of the Frantz diffusion cell. The reservoir compartment was filled with 100 milliliters of pH 6.8 phosphate buffer. The speed was adjusted until the vortex touched the skin, which lasted 4 hours. At 30-minute intervals, 5 ml of the sample was removed from the reservoir compartment and its absorbance was measured spectrophotometrically at 260 nm. To keep the reservoir compartment at a constant volume, 5 ml of phosphate buffer pH 6.8 solution was added each time.

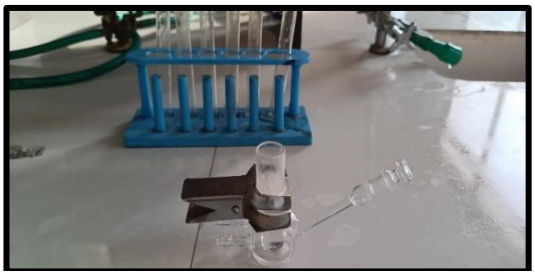

Fig. In vitro diffusion study

III. RESULTS AND DISCUSSION: -

1. Visual examination: The formulation was visually inspected for color, homogeneity, and grittiness. The preparation was observed to be clear and white. The formulation showed good homogeneity with absence of lumps and grittiness.
2. Skin irritation: Formulation passed skin irritation test when applied to the skin.

3. PH and Spreadability-

Evaluation Parameter	pH	Spreadability
Marketed formulation	6.8 - 7.1	2.5 - 3
Project Formulation	6.9	2.8

Table. Determination Of pH and Spreadability

The pH of the formulated gel was 6.9, which is within the ideal range for skin application. Its spreadability value was 2.8 cm/sec, demonstrating smooth and uniform spreading properties.

The zone of inhibition was determined by measuring the minimum dimension of no fungal growth around both marketed and formulated gels. The results show that the formulated gel has an equivalent antifungal effect to the marketed gel.

1. Antifungal activity:

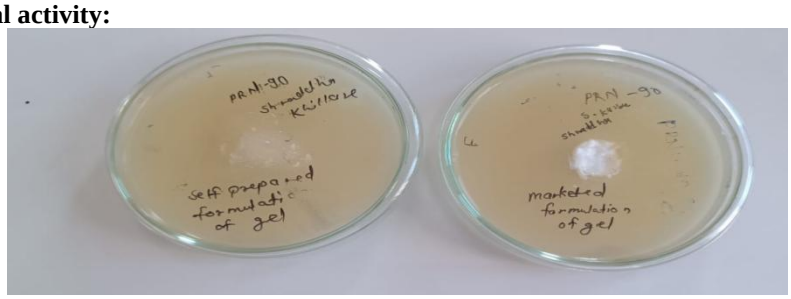

Fig. Antifungal Activity

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2. In Vitro Diffusion Study

Time (min)	% Drug release of Project Formulation	% Drug release of Marketed Formulation
0	0	0
30	9.5	8.9
60	28.69	26.77
90	35.04	34.02
120	49.75	48.71
150	57.63	56.32
180	70.10	68.87
210	83.87	82.44
240	97.67	96.77

Table. In vitro Diffusion Chart

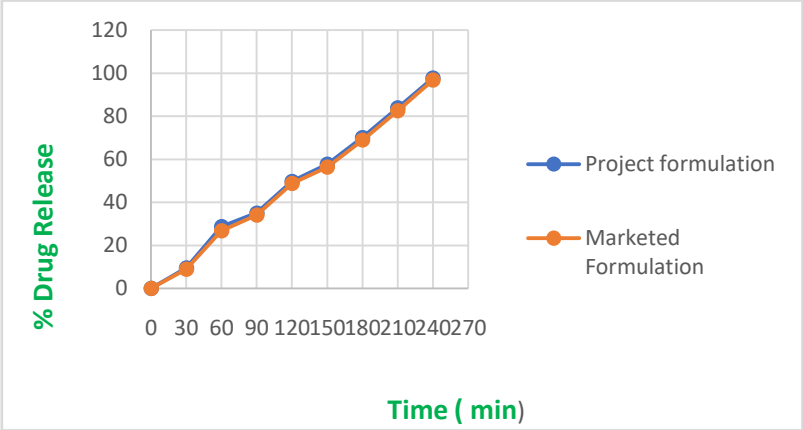

Fig. In vitro Diffusion for Project Formulation and Marketed Formulation

The marketed formulation releases 96.77% of the drug over 4 hours, while the project formulation releases 97.67% over the same time period, indicating a marginal improvement in the project formulation's release profile.

IV. CONCLUSION

The project formulation of Itraconazole topical gel concludes with the following: The formulation of Itraconazole topical gel was successfully developed, with the goal of providing an effective and convenient treatment option for superficial fungal infections. The project was divided into several stages, which included selecting appropriate excipients, optimizing formulation variables, and assessing the gel's physicochemical properties, stability, and in vitro performance. The project formulation has nearly equal bioavailability and efficacy as the marketed formulation.

Throughout the formulation development process, various excipients were tested to ensure compatibility with Itraconazole and achieve desirable gel characteristics such as consistency. spreadability, and drug release. The optimized formulation demonstrated nearly equal physicochemical properties, including pH, viscosity, and appearance with marketed formulation.

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