

Formulation and Evaluation of Topical Gel Containing Fluconazole Vitamin C

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ABSTRACT

Topical drug delivery systems have gained considerable attention in recent years due to their ability to deliver therapeutic agents directly to the site of action, thereby minimizing systemic side effects and improving patient compliance. Among various dermatological disorders, fungal infections remain highly prevalent and often require prolonged treatment. Fluconazole, a widely used triazole antifungal agent, exhibits broad-spectrum activity by inhibiting fungal cytochrome P450-dependent enzymes, thereby disrupting ergosterol synthesis and compromising fungal cell membrane integrity. However, its effectiveness in topical formulations is often limited by poor permeability through the stratum corneum and reduced retention at the site of infection.

To overcome these limitations, the incorporation of adjunct therapeutic agents such as Vitamin C and zinc compounds has been explored. Vitamin C (ascorbic acid) is a potent antioxidant that plays a critical role in neutralizing reactive oxygen species, promoting collagen synthesis, and enhancing tissue repair. Zinc compounds, on the other hand, exhibit significant antimicrobial, anti-inflammatory, and wound healing properties, along with the ability to enhance epithelialization and local immune response. The combination of fluconazole with Vitamin C and zinc in a gel-based formulation offers a synergistic therapeutic approach by targeting fungal infection, oxidative stress, and tissue damage simultaneously.

The present review comprehensively discusses the formulation aspects of such a topical gel, including selection of suitable polymers (Carbopol, HPMC, Sodium CMC), penetration enhancers (propylene glycol, ethanol), and stabilizing agents. Various methods of preparation, including polymer hydration, drug incorporation, neutralization, and homogenization, are elaborated to ensure

formulation uniformity and stability. In addition, detailed evaluation parameters such as organoleptic properties, pH, viscosity, spreadability, drug content uniformity, in-vitro drug release using Franz diffusion cell, rheological behavior, and stability studies as per ICH guidelines are critically reviewed.

Furthermore, advanced drug delivery approaches such as niosomal gels, microsphere systems, solid lipid nanoparticles (SLN), and nanogels are highlighted for their ability to enhance drug penetration, provide controlled release, and improve therapeutic efficacy. The combined formulation demonstrates a multi-mechanistic mode of action involving antifungal activity, antioxidant defense, and accelerated wound healing, making it highly effective for the treatment of dermatophytosis, candidiasis, and other skin infections.

In conclusion, the integration of fluconazole, Vitamin C, and zinc into a topical gel system represents a promising and innovative strategy in dermatological therapy. Future research focusing on nanotechnology-based delivery systems and clinical evaluation is expected to further enhance the potential and applicability of such multifunctional formulations.

Keywords: Fluconazole; Vitamin C; Zinc compounds; Topical gel; Antifungal therapy; Drug delivery system; Nanogel; Skin infections; Wound healing; Franz diffusion cell; Rheology; Controlled drug release.

I. INTRODUCTION

1.1 TOPICAL DRUG DELIVERY SYSTEMS

Topical drug delivery systems are pharmaceutical preparations intended for application on the skin to achieve localized

therapeutic effects. These systems are advantageous because they provide site-specific drug delivery, reduce systemic side effects, and improve patient compliance [5].

In recent years, topical formulations have gained significant importance due to increased prevalence of skin disorders and the need for non-invasive drug delivery approaches. Among various topical dosage forms, gels are preferred due to their transparency, ease of application, and better drug release characteristics [13].

1.2 STRUCTURE AND FUNCTION OF SKIN

The skin is one of the most accessible and largest organs of the human body, covering an average surface area of about 1.5–2.0 m². It serves as a protective barrier against environmental factors such as pathogens, chemicals, and physical stress. Due to its large surface area and ease of application, the skin is considered an attractive route for topical and transdermal drug delivery systems [7].

Topical drug delivery involves the application of drugs directly onto the skin to achieve localized therapeutic effects. However, the effectiveness of this route depends on the ability of the drug to penetrate the outermost layer of the skin, known as the stratum corneum, which acts as a major barrier to drug absorption [5].

The permeability of drugs through the skin is influenced by several factors, including:

- Physicochemical properties of the drug (molecular weight, lipophilicity)
- Condition of the skin
- Type of formulation used
- Presence of penetration enhancers

Therefore, designing an effective topical formulation requires a thorough understanding of skin structure and drug transport mechanisms.



Fig.1.2 Structure of Skin layers

1.2.1 Structure of Skin and Barrier Function

The skin is composed of three major layers:

1.2.1.1 Epidermis

The epidermis is the outermost layer of the skin and primarily consists of keratinized stratified squamous epithelium. It is further divided into multiple sublayers:

- Stratum corneum
- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum basale

Among these, the stratum corneum is the most critical barrier for drug penetration. It consists of dead keratinized cells (corneocytes) embedded in a lipid matrix, often described as a “brick and mortar” structure. This layer restricts the entry of most drugs, especially hydrophilic molecules [7].

1.2.1.2 Dermis

The dermis lies beneath the epidermis and contains:

- Blood vessels
- Nerve endings
- Hair follicles
- Sweat glands

This layer provides structural support and plays a role in thermoregulation. Once a drug crosses the epidermis, it can easily diffuse through the dermis and reach systemic circulation [14].

1.2.1.3 Hypodermis (Subcutaneous Tissue)

The hypodermis is the innermost layer composed mainly of adipose tissue. It acts as:

- Energy storage
- Thermal insulation
- Shock absorber

Although it is not directly involved in drug absorption, it supports deeper penetration of drugs [5].

1.2.2 Barrier Function of Skin

The primary barrier to drug penetration is the stratum corneum. It prevents the entry of harmful substances and limits the permeation of drugs.

Drug permeation through the skin occurs via three main pathways:

1. Transcellular route – through cells
2. Intercellular route – between cells (most common)
3. Appendageal route – via hair follicles and sweat glands

To enhance drug delivery through the skin, formulation strategies such as the use of

penetration enhancers, nanoparticles, and optimized gel systems are employed [2].

1.2.3 Relevance to Gel Formulation

Understanding skin structure is essential for designing effective topical gels. The use of:

- Suitable polymers
- Penetration enhancers
- Optimized viscosity

helps in improving drug diffusion through the stratum corneum and enhances therapeutic efficacy.

1.3 PATHOPHYSIOLOGY OF FUNGAL SKIN INFECTIONS

Fungal infections are caused by dermatophytes, yeasts, and molds. These organisms invade keratinized tissues and thrive in warm and moist environments.

Common infections include:

- Dermatophytosis (ringworm)
- Candidiasis
- Athlete's foot

These infections can cause inflammation, itching, redness, and tissue damage. Effective treatment requires antifungal therapy along with agents that promote healing and reduce inflammation [3].

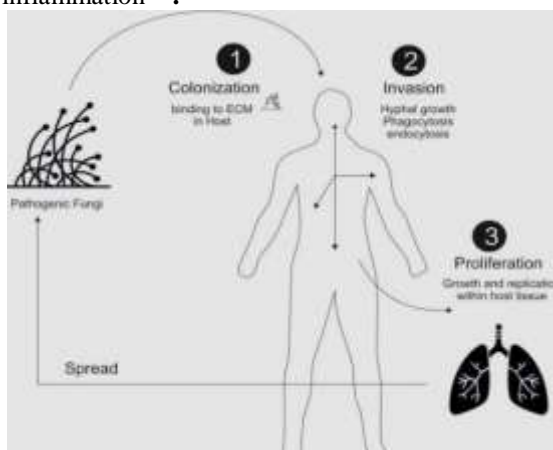


Fig.no.1.1 Pathogenesis of Fungal Infections

1.4 NEED FOR COMBINATION THERAPY

Single-drug therapy often fails to provide complete treatment due to:

- Drug resistance
- Slow healing
- Inflammation and oxidative damage

Therefore, combination therapy involving antifungal, antioxidant, and healing agents is required for effective treatment [11].

1.5 ROLE OF FLUCONAZOLE IN THERAPY

Fluconazole is a triazole antifungal drug that inhibits fungal sterol synthesis.

- Blocks lanosterol conversion to ergosterol
- Disrupts fungal membrane integrity
- Leads to fungal cell death [4]

However, its topical efficacy depends on formulation design due to limited penetration through the stratum corneum [7].

1.6 ROLE OF VITAMIN C IN DERMATOLOGY

Vitamin C plays a crucial role in maintaining skin health:

- Stimulates collagen synthesis
- Neutralizes free radicals
- Enhances wound healing
- Reduces inflammation

It also improves skin elasticity and prevents oxidative damage caused by infections and environmental stress [9].

1.7 ROLE OF ZINC IN SKIN REPAIR

Zinc is an essential trace element involved in multiple biological processes:

- Promotes epithelialization
- Enhances immune response
- Exhibits antimicrobial activity
- Reduces inflammation

Zinc also accelerates wound healing by supporting cell proliferation and tissue regeneration [12].

1.8 RATIONALE OF COMBINED GEL FORMULATION

The combination of fluconazole, Vitamin C, and zinc provides a multi-mechanistic therapeutic approach:

- Antifungal activity (Fluconazole)
- Antioxidant protection (Vitamin C)
- Wound healing and antimicrobial action (Zinc)

This synergistic combination improves drug efficacy, reduces healing time, and enhances patient outcomes.

II. DRUG PROFILE

2.1 FLUCONAZOLE

2.1.1 General Information

- Chemical Name: 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol
- Molecular Formula: C₁₃ H₁₂ F₂ N₆ O
- Molecular Weight: 306.27 g/mol

- Category: Triazole antifungal agent
- Dosage Form: Tablets, capsules, injections, topical gels

Fluconazole is a widely used antifungal drug belonging to the triazole class. It is effective against a broad range of fungal pathogens and is commonly used in dermatological and systemic infections ^[1].

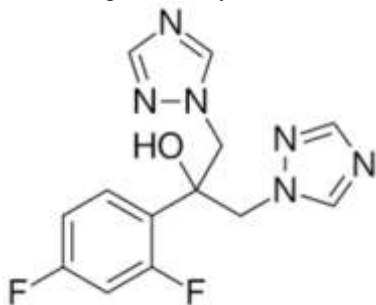


Fig.2.1 Chemical Structure of Fluconazole

2.1.2 Structure and Physicochemical Properties

- Appearance: White crystalline powder
- Solubility: Slightly soluble in water, freely soluble in alcohol
- Melting Point: 138–140°C
- pKa: ~1.76
- Log P: Moderate lipophilicity

These properties influence its permeability and formulation behavior in topical dosage forms ^[7].

2.1.3 Mechanism of Action

Fluconazole inhibits the fungal enzyme lanosterol 14- α -demethylase, which is responsible for converting lanosterol into ergosterol.

- Decreased ergosterol synthesis
- Increased membrane permeability
- Leakage of cellular contents
- Fungal cell death

This mechanism makes fluconazole highly effective against fungal infections ^[4].

2.1.4 Pharmacokinetics

- Limited penetration through stratum corneum
 - Requires penetration enhancers
 - Retention at site depends on formulation
- Topical formulations improve localized action and reduce systemic exposure ^[10].

2.1.5 Therapeutic Uses

- Dermatophytosis
- Candidiasis
- Ringworm
- Athlete's foot

2.1.6 Advantages

- Broad-spectrum antifungal activity
- Low toxicity
- Good stability

2.1.7 Limitations

- Poor skin penetration
- Requires optimized formulation
- Slow healing when used alone

2.2 VITAMIC C (ASCORBIC ACID)

2.2.1 General Information

- Chemical Name: L-ascorbic acid
- Molecular Formula: C₆ H₈ O₆
- Molecular Weight: 176.12 g/mol
- Category: Water-soluble vitamin (antioxidant)

Vitamin C is an essential nutrient widely used in dermatological formulations due to its antioxidant and skin-repairing properties ^[9].

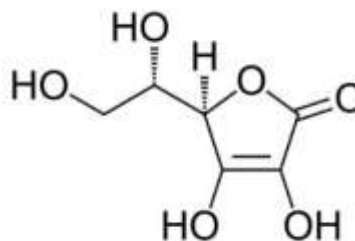


Fig.2.2 Chemical Structure of Vitamin C

2.2.2 Physicochemical Properties

- Appearance: White to pale yellow crystalline powder
 - Solubility: Highly soluble in water
 - pH: Acidic (pH ~2–3 in solution)
 - Stability: Easily oxidized in air and light
- Due to instability, it requires proper stabilization in formulations.

2.2.3 Mechanism of Action

Vitamin C acts through multiple mechanisms:

- Scavenges free radicals (antioxidant action)
- Stimulates collagen synthesis
- Reduces oxidative stress
- Enhances tissue repair

This improves skin healing and reduces inflammation ^[20].

2.2.4 Role in Topical Formulation

- Promotes wound healing
- Improves skin elasticity
- Protects against environmental damage

2.2.5 Advantages

- Strong antioxidant

- Enhances collagen production
- Improves skin regeneration

2.2.6 Limitations

- Highly unstable (oxidation sensitive)
- Requires stabilizers
- pH-sensitive

2.3 ZINC COMPOUNDS

2.3.1 General Information

- Common Forms: Zinc oxide, Zinc sulfate
- Category: Trace element / dermatological agent

Zinc is an essential micronutrient widely used in topical formulations for its healing and antimicrobial properties ^[12].

2.3.2 Physicochemical Properties (Zinc Oxide)

- Appearance: White amorphous powder
- Solubility: Insoluble in water
- Stability: Stable under normal conditions

2.3.3 Mechanism of Action

Zinc acts through multiple pathways:

- Antimicrobial action against bacteria and fungi
- Anti-inflammatory effect
- Promotes epithelial cell growth
- Enhances immune response

It also forms a protective barrier on the skin ^[21].

2.3.4 Role in Topical Formulation

- Accelerates wound healing
- Reduces irritation and inflammation
- Protects skin from infection

2.3.5 Advantages

- Safe and well-tolerated
- Promotes tissue regeneration
- Broad antimicrobial activity

2.3.6 Limitations

- Poor solubility
- May require dispersion techniques

2.4 COMPARATIVE ROLE IN COMBINED FORMULATION

Component	Primary Role	Additional Benefit
Fluconazole	Antifungal	Controls infection
Vitamin C	Antioxidant	Skin repair
Zinc	Antimicrobial	Wound healing

III. MATERIAL USED

The selection of appropriate materials is a critical step in the formulation of a stable and effective topical gel. Each component plays a specific role in determining the physicochemical properties, drug release behavior, and therapeutic efficacy of the formulation.

3.1 ACTIVE PHARMACEUTICAL INGREDIENTS

3.1.1 Fluconazole

Fluconazole is the primary antifungal agent incorporated into the gel. It is selected due to its broad-spectrum activity against dermatophytes and Candida species. However, due to its limited permeability through the stratum corneum, it requires the use of suitable polymers and penetration enhancers to improve its topical delivery ^[7].

3.1.2 Vitamin C (Ascorbic Acid)

Vitamin C is included as an antioxidant and skin-repairing agent. It helps in reducing oxidative stress at the site of infection and promotes collagen synthesis, thereby accelerating wound healing. Due to its instability, it must be protected from oxidation during formulation ^[9].

3.1.3 Zinc Compound

Zinc compounds are incorporated for their antimicrobial and anti-inflammatory properties. They also enhance epithelialization and provide a protective barrier on the skin, thereby improving the healing process ^[12].

3.2 GELLING AGENTS (POLYMERS)

Polymers are the backbone of gel formulation and play a crucial role in determining viscosity, consistency, and drug release.

3.2.1 Carbopol 934/940: Widely used synthetic polymer that provides high viscosity and clear gel formation. It exhibits excellent swelling properties and forms stable gels upon neutralization ^[6].

3.2.2 Hydroxypropyl Methylcellulose (HPMC): A semi-synthetic polymer that provides controlled drug release and improves gel stability.

3.2.3 Sodium Carboxymethyl Cellulose (Na – CMC): Used as a thickening and stabilizing agent to improve consistency.

The selection and concentration of polymers significantly influence the rheological properties and drug diffusion rate ^[15].

3.3 PENETRATION ENHANCERS

Penetration enhancers are used to increase drug permeation through the stratum corneum by altering its lipid structure.

- Propylene Glycol: Enhances drug solubility and permeability
- Ethanol: Disrupts lipid bilayers and improves drug diffusion

These agents improve the bioavailability of fluconazole in topical formulations^[2].

3.4 pH ADJUSTING AGENTS

- Triethanolamine (TEA): Used to neutralize Carbopol and convert the dispersion into a gel. It also helps in adjusting the pH of the formulation to match skin pH (5.5–6.5).

3.5 PRESERVATIVES

- Methyl Paraben / Propyl Paraben: Used to prevent microbial contamination and enhance shelf-life of the formulation.

3.6 SOLVENTS AND VEHICLES

- Distilled Water: Primary vehicle for gel formulation
- Ethanol / Propylene Glycol: Used as co-solvents

3.7 Stabilizers and Antioxidants

Since Vitamin C is prone to oxidation, stabilizers may be added to prevent degradation and maintain formulation integrity^[20].

3.8 ROLE OF EACH COMPONENT IN FORMULATION

Component	Function
Fluconazole	Antifungal activity
Vitamin C	Antioxidant & healing
Zinc	Antimicrobial & repair
Carbopol	Gelling agent
Propylene glycol	Penetration enhancer
TEA	pH adjustment
Parabens	Preservative

IV. METHOD OF PREPARATION

The preparation of topical gel involves a systematic process to ensure uniformity, stability, and desired physicochemical properties. The method must be carefully controlled to prevent degradation of active ingredients and ensure homogeneity.

4.1 PRINCIPLE AND PROCEDURE OF GEL FORMATION

Gel formation occurs when a polymer swells in the presence of a liquid medium and forms a three-dimensional network. Neutralization of Carbopol leads to ionization, resulting in increased viscosity and gel formation^[10].

4.1.1 Step-by-Step Procedure

4.1.1.1: Preparation of Polymer Dispersion

- Required quantity of polymer (e.g., Carbopol 934) is slowly added to distilled water with continuous stirring
- The dispersion is allowed to hydrate and swell for sufficient time (usually 1–2 hours)
- Care is taken to avoid lump formation

4.1.1.2: Preparation of Drug Solution

- Fluconazole is dissolved in a suitable solvent such as ethanol or propylene glycol
- This ensures proper solubilization and uniform distribution

4.1.1.3: Incorporation of Vitamin C and Zinc

- Vitamin C is dissolved separately in distilled water under controlled conditions to prevent oxidation
- Zinc compound is dispersed uniformly
- Both are then added to the drug solution

4.1.1.4: Mixing of Phases

- The drug solution is slowly added to the hydrated polymer dispersion with continuous stirring
- Uniform mixing ensures homogeneity of the formulation

4.1.1.5: Neutralization and Gel Formation

- Triethanolamine is added dropwise
- Neutralization leads to:
 - Increase in viscosity
 - Formation of clear gel

4.1.1.6: Homogenization

- The formulation is subjected to continuous stirring or mechanical homogenization
- Ensures uniform distribution of all ingredients

4.1.1.7: Deaeration

- Entrapped air bubbles are removed by allowing the gel to stand or by applying mild vacuum
- This improves clarity and stability

4.1.1.8: Filling and Storage

- The prepared gel is transferred into suitable containers (collapsible tubes or jars)
- Stored under controlled conditions to maintain stability.

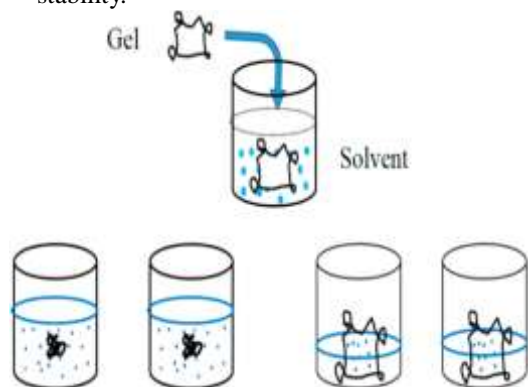


Fig.4.1 Gel formation

4.3 PRECAUTIONS DURING PREPARATION

- Avoid exposure of Vitamin C to light and air
- Maintain controlled temperature
- Ensure proper mixing to avoid phase separation
- Maintain pH within skin-compatible range

4.4 FACTORS AFFECTING GEL FORMATION

- Polymer concentration
- pH of formulation
- Type of solvent
- Mixing speed and time

These factors directly influence viscosity, spreadability, and drug release^[6].

4.5 IMPORTANCE OF PROPER FORMULATION TECHNIQUE

A well-designed preparation method ensures:

- Uniform drug distribution
- Improved stability
- Controlled drug release
- Enhanced therapeutic efficacy

V. EVALUATION PARAMETERS

5.1 ORGANOLEPTIC PROPERTIES

Includes:

- Color
- Odor
- Appearance
- Texture

A good gel should be clear, smooth, and free from grittiness.

5.2 pH DETERMINATION

- Measured using digital pH meter
- Ideal range: 5.5–6.5 (skin compatible)

Importance:

- Prevents skin irritation
- Maintains drug stability^[17]

5.3 Viscosity

- Measured using Brookfield viscometer

Significance:

- High viscosity → better retention
- Low viscosity → better spreadability

An ideal gel shows shear-thinning (pseudoplastic) behavior^[16].

5.4 SPREADABILITY

Measured using slip and drag method.

Formula: Spreadability = $M \times L / T$

Where:

M = weight tied to upper slide

L = length moved

T = time taken

5.5 DRUG CONTENT UNIFORMITY

- Ensures uniform distribution of drug
 - Determined using UV spectrophotometry
- Acceptable range: 95–105%^[15]

5.6 IN-VITRO DRUG RELEASE STUDY

- Conducted using Franz diffusion cell

Procedure:

- Membrane placed between donor & receptor compartment
- Sample withdrawn at intervals

Importance:

- Determines release kinetics
- Predicts in vivo performance

5.7 RHEOLOGICAL STUDY

- Determines flow behavior

5.7.1 Types

- Newtonian
- Non-Newtonian (ideal for gels)

Most gels show pseudoplastic flow, meaning viscosity decreases with shear stress → easy spreading^[16].

5.8 STABILITY STUDIES

Conducted as per ICH guidelines [18]:

- Temperature: 25°C & 40°C
- Humidity: 60–75%

Parameters checked:

- pH
- Drug content
- Appearance

VI. MECHANISM OF COMBINED ACTION

The combination works through multiple synergistic pathways:

6.1.1 Antifungal Mechanism (Fluconazole)

- Inhibits ergosterol synthesis
- Leads to fungal cell membrane damage
- Causes cell death^[4]

6.1.2 Antioxidant Mechanism (Vitamin C)

- Scavenges free radicals
- Reduces oxidative stress
- Promotes collagen synthesis

This accelerates tissue repair and regeneration^[9].

6.1.3 Zinc Mechanism

- Enhances immune response
- Promotes epithelialization
- Acts as antimicrobial agent

Zinc also reduces inflammation and supports wound healing^[12].

6.1.4 Synergistic Effect

Combined action results in:

- Faster fungal clearance
- Reduced inflammation
- Improved wound healing
- Better skin regeneration

Thus, the formulation provides multifunctional dermatological therapy.

VII. FUTURE PROSPECTS

The development of topical gel containing fluconazole, Vitamin C, and zinc presents a promising approach in dermatological therapy. However, further advancements can significantly enhance its therapeutic potential.

7.1.1 Development of Nano-based Drug Delivery Systems

Nanotechnology offers innovative solutions to improve drug delivery through the skin.

- Nanogels, nanoparticles, and nanoemulsions enhance drug penetration through the stratum corneum
- Provide controlled and sustained drug release
- Increase bioavailability and site-specific targeting

Nano-based formulations can overcome the limitations of conventional gels, particularly poor drug permeability.

7.1.2 Incorporation of Novel Carriers

Advanced carriers can improve stability and efficacy of active ingredients:

- Niosomes → enhance drug entrapment and penetration
- Liposomes → improve drug delivery and reduce toxicity
- Microsponge systems → provide controlled release

These systems protect sensitive components like Vitamin C from degradation and improve overall formulation performance.

7.1.3 Stability Enhancement Strategies

Vitamin C is highly unstable and prone to oxidation.

Future strategies may include:

- Use of encapsulation techniques
 - Addition of stabilizing agents and antioxidants
 - Use of air-tight and light-resistant packaging
- Improving stability will increase shelf-life and therapeutic effectiveness.

7.1.4 Combination with Herbal or Natural Extracts

The addition of herbal ingredients may further enhance therapeutic benefits:

- Aloe vera → soothing and moisturizing
- Neem → antimicrobial
- Turmeric → anti-inflammatory

Such combinations can provide synergistic effects and reduce side effects.

7.1.5 Clinical Evaluation and Trials

Most studies are limited to in-vitro and preclinical evaluation.

Future research should focus on:

- Clinical trials to confirm safety and efficacy
- Comparative studies with existing formulations
- Long-term safety assessment

This will help in establishing the formulation for commercial use.

7.1.6 Personalized and Targeted Therapy

Advancements in dermatology are moving towards personalized medicine.

- Formulations tailored according to skin type and condition
- Targeted delivery systems for specific infections

This approach can improve treatment outcomes and patient satisfaction.

7.1.7 Commercial and Industrial Scale-up

For large-scale production, the formulation must be optimized for:

- Manufacturing feasibility
- Cost-effectiveness
- Regulatory compliance (ICH, WHO guidelines)

Scaling up will ensure wider availability and practical application

VIII. CONCLUSION

The present review highlights the potential of a topical gel formulation containing fluconazole, Vitamin C, and zinc as an effective and multifunctional approach for the treatment of fungal skin infections. Fluconazole provides potent antifungal activity by inhibiting ergosterol synthesis, while Vitamin C contributes to antioxidant defense and collagen synthesis, and zinc enhances wound healing and exhibits antimicrobial effects. The combination of these agents results in a synergistic therapeutic effect that not only eliminates fungal infection but also promotes faster skin repair and reduces inflammation.

The formulation of such a gel requires careful selection of polymers, penetration enhancers, and stabilizing agents to ensure optimal physicochemical properties, stability, and drug release behavior. Evaluation parameters such as pH, viscosity, spreadability, drug content, in-vitro release, and stability studies play a crucial role in determining the quality and efficacy of the formulation.

Furthermore, advancements in drug delivery systems, particularly nanotechnology-based approaches, offer significant opportunities to overcome the limitations associated with conventional topical formulations. These include improved drug penetration, controlled release, and enhanced bioavailability.

In conclusion, the integration of antifungal, antioxidant, and wound healing agents into a single topical gel system represents a promising strategy in modern dermatological therapy. Future research focusing on advanced delivery systems, stability enhancement, and clinical validation is essential to fully explore the potential of this formulation and to translate it into a successful therapeutic product.

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