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FORMULATION AND EVALUATION OF ANTIFUNGAL HANDWASH

Prof. Kshitij S. Varma*[1], Siddhi S. Sonawane[2], Sapna K. Sonawane[2], Vedant V. Sonawane[2], Rushikesh S. Sonawane[2], Bhushan M. Shirsath[2] and Shubham S. Shirsath[2]

[1]Assistant Professor, Mahatma Gandhi Vidyamandir's Pharmacy College Panchavati Nashik-3.

[2]Student, Mahatma Gandhi Vidyamandir's Pharmacy College Panchavati Nashik-3.

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***Corresponding Author: Prof. Kshitij S. Varma**
Student, Mahatma Gandhi Vidyamandir's Pharmacy College Panchavati Nashik-3.
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ABSTRACT

Fungal infections of the skin are a common concern, especially in environments where hygiene is paramount. Traditional antifungal treatments often require prolonged contact with the skin, which may not always be practical in everyday situations. Antifungal handwash formulations represent an innovative approach to addressing this challenge by combining effective antifungal agents with the convenience and frequency of hand hygiene practices. This review explores the development and formulation of antifungal handwash products, discussing the selection of active pharmaceutical ingredients (APIs) such as clotrimazole, ketoconazole, miconazole, and econazole, and their efficacy in controlling common fungal pathogens. The role of excipients in ensuring skin compatibility, enhancing the stability and release of the active agents, and improving the user experience. Additionally, the review highlights key evaluation parameters, including antimicrobial efficacy, skin irritation potential, foamability, and release testing, which ensure the safety and effectiveness of these products. Finally, the potential benefits of incorporating antifungal handwash formulations into public health strategies for preventing fungal infections are discussed, along with the challenges in developing such products for widespread use. This article provides an in-depth understanding of antifungal handwash formulations, and their role in advancing topical antifungal therapies.

KEYWORDS: Antifungal Handwash, Fungal Skin infections, Fungal Pathogens.

INTRODUCTION

Fungal infections have become a significant global health concern due to their increased incidence and potential severity. These infections range from superficial skin conditions to invasive diseases, especially in immunocompromised individuals. The rise in fungal infections correlates with factors such as increased use of immunosuppressive therapies, the global spread of resistant fungal strains, and the high prevalence of co-morbidities in

the aging population.[1] Fungal pathogens, including *Candida*, *Aspergillus*, *Cryptococcus*, and *Mucorales* species, contribute substantially to morbidity and mortality worldwide. Traditional antifungal treatments have been effective to some extent, but resistance and adverse effects have spurred the need for newer, safer, and more effective options.

Scope of Antifungal Research and Development

The scope of antifungal research spans the discovery of novel agents, optimization of existing drugs, and exploration of combination therapies. Key areas include:

1. **Mechanisms of Action**: Understanding how antifungal drugs disrupt fungal cell walls, inhibit synthesis pathways, and prevent replication.
2. **Drug Resistance**: Investigating genetic mutations and biofilm formation that contribute to resistance, particularly in species like *Candida auris*.
3. **Drug Development**: Focus on newer antifungal classes, improved delivery systems, and targeting mechanisms that reduce toxicity and enhance efficacy.[2]
4. **Public Health Impact**: Addressing the implications of antifungal resistance and treatment limitations on vulnerable populations, such as patients with weakened immune systems.[3]

Challenges in Antifungal Therapy: The effectiveness of antifungal agents is often limited by several factors:

- **Drug Toxicity**: Many antifungals have narrow therapeutic windows.
- **Resistance**: Emerging strains resistant to first-line treatments are increasingly common.
- **Access to Medications**: Disparities in healthcare access limit the availability of effective treatments in some regions, particularly in low- and middle-income countries.

Need for Antifungal Drug Formulation: The development of effective antifungal formulations is critical in addressing the global rise in fungal infections, which range from mild superficial conditions to life-threatening systemic infections. Here's why novel and optimized antifungal drug formulations are essential:

1. Improving Drug Efficacy and Bioavailability

Many traditional antifungal drugs face issues with poor solubility and bioavailability, which limits their effectiveness. Innovative formulations, such as lipid-based nanoparticles, liposomes, and micellar systems, help improve the delivery of drugs to the site of infection, enhancing bioavailability and efficacy. For instance, liposomal amphotericin B has shown higher effectiveness and lower toxicity than conventional formulations.

2. Reducing Toxicity and Side Effects

Systemic antifungals, such as amphotericin B and azoles, are often associated with severe side effects, particularly nephrotoxicity and hepatotoxicity. Novel drug delivery systems aim to reduce these toxicities by targeting the drug directly to infected tissues, minimizing off-target effects, and enabling lower dosing. Lipid-based and targeted delivery formulations are currently under investigation to address these challenges.[4]

3. Combating Drug Resistance

Antifungal resistance is a growing concern, particularly with strains like *Candida auris* and *Aspergillus* species. Developing new formulations can improve the drug's ability to overcome resistance mechanisms, such as biofilm formation and efflux pump activity, by enabling more efficient drug penetration and prolonged action at the infection

site. Combination therapies, where multiple antifungal agents are formulated together, are also being explored to prevent resistance.

4. Enhancing Patient Compliance

Many antifungal treatments require prolonged or complex dosing regimens, which can lead to poor patient adherence. Novel formulations, like controlled-release and once-daily dosing forms, improve convenience and adherence. For example, sustained-release formulations of fluconazole can simplify treatment for conditions like onychomycosis, where therapy may last several months.

5. Targeting Specific Infections and Populations

Patients with certain conditions (e.g., diabetes, immunosuppression) or infections in specific body sites (e.g., oral candidiasis, onychomycosis) may benefit from topical or targeted formulations that directly address the local infection with minimal systemic exposure. Additionally, formulations such as oral dispersible tablets and localized gels cater to vulnerable populations, including pediatric and elderly patients, who may have difficulty with conventional tablets or intravenous treatments.

Fungal infection

1. Stimulates the arrival of monocytes at the site of infection.
2. Which subsequently mature into monocyte-derived dendritic cells (moDCs). Depending on local environmental host and pathogen factors, these moDCs can develop into either inflammatory DCs (inf-DCs; 3a) or immunomodulatory DCs (imo-DCs; 3b), which subsequently direct the immune response. Inf-DCs promote sterilizing immunity characterized by interferon gamma (IFNγ)- producing Th1 cells, interleukin (IL)-17-producing Th17 cells, and " classically activated " exudate macrophages (ExMs; 4a). Imo-DCs promote fungal persistence characterized by IL-10-producing Treg cells, IL-4-, IL-5, and IL-13-producing Th2 cells, and " alternatively-activated " exudate macrophages (4b).[5,6]

Classification of Fungal Infections

Fungal infections can be categorized into three main groups:

1. Superficial Mycoses:
2. Dermatomycoses: These infections affect the skin, hair, and nails and include conditions like athlete's foot (tinea pedis) and ringworm (tinea corporis). They are often caused by dermatophytes, a group of fungi that thrive in warm, moist environments.[7]
3. Candidiasis: This infection can affect mucous membranes (such as oral thrush and vaginal yeast infections) and skin. It is caused by Candida species, particularly Candida albicans. These infections are prevalent worldwide and can become endemic in certain areas.
4. Subcutaneous Mycoses: These infections typically arise from environmental sources, such as soil or plant materials, and are more commonly found in tropical and subtropical regions. They can remain dormant for years and may present as chronic infections that affect deeper layers of the skin and underlying tissues.[8]
5. Opportunistic Infections: These primarily affect immunocompromised individuals, such as those with HIV/AIDS, cancer patients, or those undergoing immunosuppressive therapy.

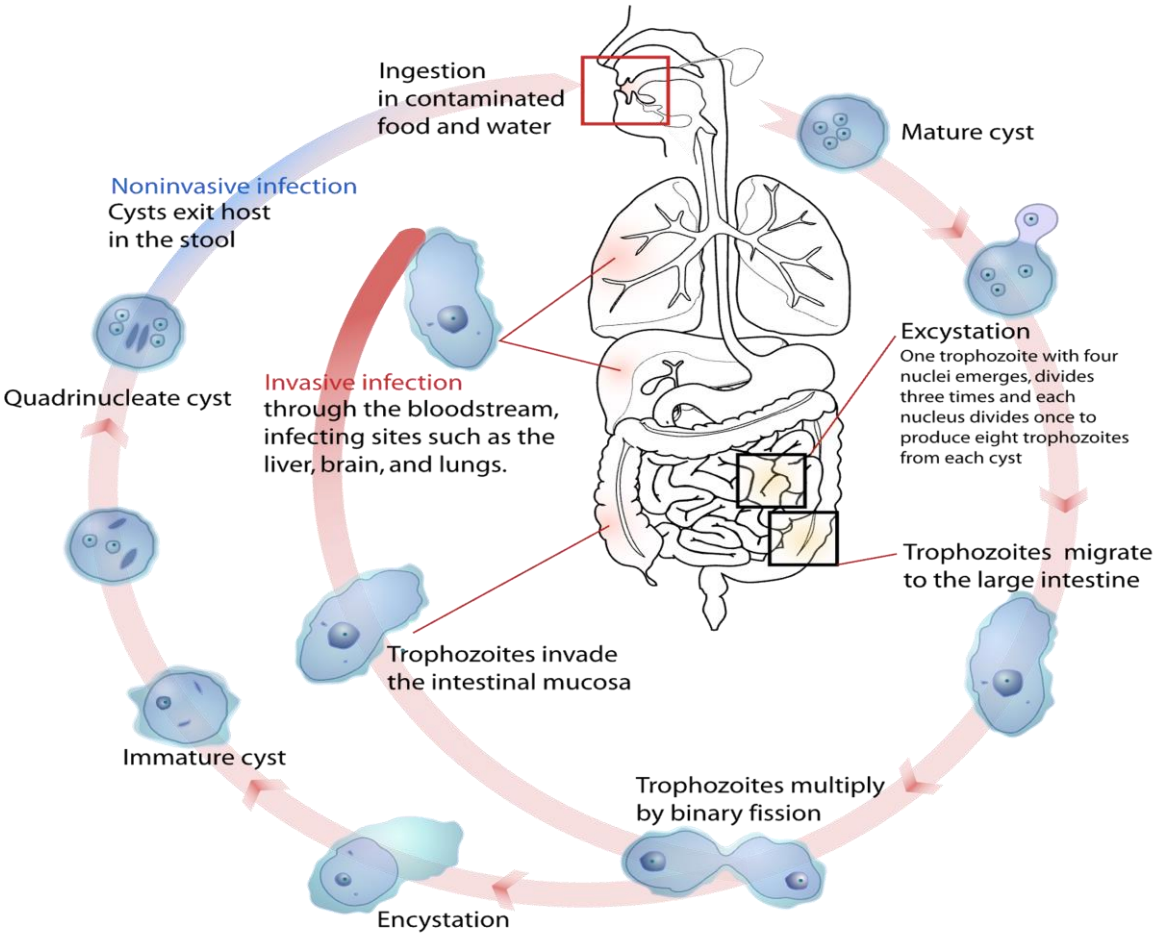

Fig. 1: Life Cycle of Fungal Infections.

Materials Methodology for Antifungal Handwash based Formulation

AIP Used for Handwash Formulation:

1. **Clotrimazole**

- **Pharmacopoeial Listing**: United States Pharmacopeia (USP), British Pharmacopoeia (BP), and European Pharmacopoeia (Ph. Eur.).
- **Properties**: Broad-spectrum antifungal activity effective against dermatophytes, yeasts, and molds.
- **Usage**: Commonly used in topical products, including creams and washes, for fungal skin infections. Suitable for incorporation in handwash formulations due to its efficacy and safety profile.

2. **Ketoconazole**

- **Pharmacopoeial Listing**: USP, BP, Ph. Eur.
- **Properties**: Effective against yeasts and dermatophytes. Known for its broad-spectrum antifungal activity and is often used in topical formulations.
- **Usage**: Suitable for inclusion in handwash formulations due to its ability to treat and prevent fungal skin infections.

3. **Miconazole**

- **Pharmacopoeial Listing**: USP, BP, Ph. Eur.
- **Properties**: Effective against dermatophytes and *Candida* species.
- **Usage**: Frequently used in topical applications like creams and gels. Miconazole's broad activity makes it useful for antifungal handwash formulations.

4. **Econazole**

- **Pharmacopoeial Listing**: USP, BP, Ph. Eur.
- **Properties**: Broad-spectrum antifungal, effective against a variety of fungal infections.
- **Usage**: Commonly formulated in topical solutions and creams, making it suitable for antifungal handwash products.

Excipients for Handwash Preparation

Active Antifungal Agents

Choose an antifungal agent that is effective against common fungi (e.g., *Candida albicans*, *Aspergillus* species) and safe for topical application. Examples include:

- **Clotrimazole**
- **Ketoconazole**
- **Miconazole**
- **Tea Tree Oil** (natural antifungal)
- **Thyme Oil** or **Eucalyptus Oil** (essential oils with antifungal properties)

Excipients for Handwash Formulation[9]

- **Surfactants**: Cocamidopropyl betaine, SLS, or sodium laureth sulfate for foam production and cleansing.
- **Thickening Agent**: Carbopol or xanthan gum to achieve desired viscosity.
- **Humectants**: Glycerin or propylene glycol to retain moisture on the skin.
- **pH Adjuster**: Citric acid or sodium hydroxide to balance pH.
- **Preservatives**: Parabens, phenoxyethanol, or other suitable preservatives to prevent microbial growth.
- **Color and Fragrance**: Food-grade colors and essential oils for an appealing look and scent.

2. Formulation Process For formulation

A. Preparation of Antifungal Handwash

1. **Handwash Base Preparation**
   - In a beaker, combine water and humectants (e.g., glycerin, propylene glycol).
   - Gradually add the chosen surfactants (cocamidopropyl betaine, SLS) while stirring, ensuring they dissolve completely.

2. **Incorporating Antifungal Agent**
   - Add the antifungal agent to the mixture, ensuring it is fully dissolved or dispersed. If necessary, use mild heating for oil-based antifungals to blend them effectively.

3. **Adding Thickeners and Adjusting Viscosity**
   - Gradually add a thickener (e.g., carbopol, xanthan gum) and stir until the desired viscosity is achieved.
   - Adjust the pH using citric acid or sodium hydroxide to reach an optimal range (pH 5.5-7) suitable for skin.

4. **Incorporating Fragrance and Color**
   - Add essential oils for fragrance and food-grade colorants, mixing thoroughly to ensure even distribution.

5. **Quality Control Testing**
   - Conduct quality control tests for pH, viscosity, and microbial load to ensure product safety and consistency.

6. **Packaging**
   - Transfer the formulated handwash into pump or squeeze bottles and label with product details and instructions.

Types of Handwash Formulation

1. **Gel Base Handwash**

Antifungal gels for handwashing are specialized hygiene products designed to not only clean the hands but also to prevent or treat fungal infections. These gels typically contain active antifungal ingredients that help eliminate or inhibit the growth of fungi, which can thrive on the skin, especially in warm, moist environments. [10] While handwashing is primarily associated with removing dirt, bacteria, and viruses, antifungal handwash gels add an extra layer of protection by targeting fungal pathogens that can cause common skin infections like athlete's foot, ringworm, or yeast infections.

The primary goal of an antifungal gel for handwashing is to cleanse the hands while providing antifungal protection. Unlike traditional hand soaps or sanitizers, which are generally focused on bacteria and viruses, antifungal handwashes are specifically designed to target fungal organisms, reducing the chances of developing or spreading fungal infections.

Key Features of Antifungal Handwash Gels[11]

- **Antifungal Ingredients**: Common ingredients such as tea tree oil, clotrimazole, ketoconazole, and miconazole can be found in antifungal handwash gels.
- **Moisturizing Agents**: Many antifungal handwashes are also enriched with moisturizers like aloe vera or glycerin to prevent skin dryness or irritation, which can result from frequent washing.
- **Convenient & Portable**: The gel formulation is often designed for quick and easy use, making it ideal for on-the-go sanitization. The gel texture also helps prevent the product from dripping, allowing for controlled application.

Preparation method for gel based formulation[12]

Ingredients required for formulation

1. **Active Antifungal Agents**: These can include agents like clotrimazole, miconazole, ketoconazole, or natural antifungal agents such as tea tree oil or neem extract.
2. **Gelling Agent**: Carbomer, hydroxyethyl cellulose (HEC), or xanthan gum can be used to create a gel consistency.
3. **Neutralizer**: Triethanolamine or sodium hydroxide, to adjust pH and stabilize the gel.
4. **Solvent/Base**: Purified water or alcohol (for better penetration and evaporation).
5. **Preservative**: A mild preservative to prevent microbial growth if the gel will be stored long-term.

Preparation Method[13]

A. Preparation of Gel Base

- Dissolve the gelling agent (e.g., carbomer) in water by stirring until fully hydrated. This can take time, so a magnetic stirrer or gentle heating may be needed.
- Once the gel has formed, add the neutralizer (e.g., triethanolamine) gradually while stirring. This adjusts the pH and activates the thickening properties, resulting in a clear gel.

B. Incorporation of Active Antifungal Agent

- Dissolve the antifungal agent in a compatible solvent if necessary. Some active ingredients, such as essential oils, may need solubilizers (like polysorbate) for even distribution.
- Slowly add the dissolved antifungal agent to the gel base while stirring continuously to ensure a homogeneous mixture.

C. Addition of Preservative and Optional Ingredients

- Add the preservative to prevent microbial contamination.
- Stir in any additional soothing or moisturizing agents, ensuring each ingredient is evenly distributed.

D. pH Adjustment and Final Mixing

- Check the pH of the formulation; an optimal range for skin application is typically between 5.5 and 7.
- Mix thoroughly until a smooth, uniform gel is achieved.

E. Packaging

- Transfer the gel into clean, sterilized containers.
- Label with instructions for use and storage condition.

Fig. 2: Herbal Gel Handwash.

Example of Marketed Formulation

Product Name	Active Ingredient(s)	Concentration	Key Additional Ingredients	Function
Defense Antifungal Gel Handwash	Tea Tree Oil, Eucalyptus Oil	1.5% each	Glycerin, Aloe Vera, Cocamidopropyl Betaine, Sodium Chloride, Water	Antifungal, antibacterial, soothing, moisturizing, gentle on hands
Lotrimin Antifungal Gel Handwash	Clotrimazole	1%	Glycerin, Sodium Laureth Sulfate, Water, Citric Acid, Sodium Chloride	Antifungal, prevents fungal growth, cleanses skin, moisturizing
Purely Northwest Antifungal Gel Handwash	Tea Tree Oil, Oregano Oil	1.5%, 0.5%	Aloe Vera, Glycerin, Castile Soap, Sodium Chloride, Water	Antifungal, soothing, moisturizing, gentle for sensitive skin
Dr. Bronner's Tea Tree Gel Handwash	Tea Tree Oil	1%	Organic Olive Oil, Coconut Oil, Glycerin, Hemp Oil, Water, Citric Acid	Antifungal, antibacterial, moisturizing, multipurpose cleanser for hands
Himalaya Antifungal Gel Handwash	Tea Tree Oil, Neem Extract	1.5%, 1%	Glycerin, Sodium Chloride, Turmeric Extract, Aloe Vera, Citric Acid	Antifungal, antibacterial, soothing, hydrating, gentle for daily use

Example of Marketed Formulation

2. Foam based Handwash

Antifungal hand wash foam is a specialized hygiene product designed to cleanse the hands while providing antifungal protection. These foaming hand washes are typically formulated with active antifungal ingredients and additional skin-care agents to address fungal infections, promote skin health, and enhance the overall user experience.

Ingredients

- **Surfactants**: Gentle surfactants like sodium lauryl sulfate (SLS), cocamidopropyl betaine, or decyl glucoside, which produce good foam and are skin-friendly.
- **Foaming Agent**: These are often surfactants like cocamidopropyl betaine or lauryl glucoside, which stabilize foam.
- **Skin Conditioning Agents**: Glycerin, aloe vera extract, or panthenol for hydration and skin-soothing properties.
- **Water (Purified)**: The main ingredient, acting as the solvent.
- **pH Adjuster**: Citric acid or sodium hydroxide to ensure a skin-friendly pH (typically between 5 and 7).
- **Optional Additives**:
  - **Antimicrobial Agents**: Benzalkonium chloride, chlorhexidine, or essential oils like tea tree oil.
  - **Preservative**: Phenoxyethanol or sodium benzoate to maintain shelf life.
  - **Fragrance or Essential Oils**: For scent, such as lavender or eucalyptus essential oil.
  - **Colorants**: Cosmetic-grade dyes for appearance.

Preparation Method

1. **Prepare the Base Solution**
   - In a clean mixing container, add purified water.
   - Gradually add the primary surfactants (e.g., SLS and cocamidopropyl betaine), stirring gently to avoid creating bubbles during these surfactants will provide the cleaning action.

2. **Add Foaming and Conditioning Agents**:
   - Add the foaming agent (e.g., cocamidopropyl betaine, if not used as a primary surfactant) to stabilize and increase foam production.
   - Stir in conditioning agents like glycerin or panthenol to moisturize and protect skin.

3. **Incorporate Active Ingredients and Additives**
   - If you're using an antimicrobial agent, dissolve it in a small amount of water first, if needed, and then add it to the solution.
   - Mix in any fragrance or essential oils, and add a preservative to extend shelf life.

4. **Adjust pH**
   - Test the pH of the solution; the target is around 5.5–7 for skin compatibility.
   - Use citric acid or sodium hydroxide to adjust the pH as necessary.

5. **Final Mixing and Packaging**
   - Mix the solution thoroughly but gently to avoid excess foaming.
   - Pour the solution into foam pump bottles, which will aerate the liquid into foam upon dispensing.

Ingredients	Concentration	Function
Water (Aqua)	q.s. (to 100%)	Solvent, diluent for other ingredients.
Clotrimazole/Miconazole /Ketoconazole	1-2%	Active antifungal agent for infection prevention.
Sodium Lauryl Sulfate (SLS)	10-12%	Primary surfactant for foaming and cleaning.
Cocamidopropyl Betaine	5-7%	Secondary surfactant, mild foam booster.
Glycerin	3-5%	Humectant, moisturizer to prevent skin dryness.
Aloe Vera Extract	2-3%	Soothing agent for the skin.
Panthenol (Pro-Vitamin B5)	0.5-1%	Skin conditioner, helps with skin hydration.
Citric Acid	0.1-0.5%	pH adjuster to balance the formulation.
Phenoxyethanol	0.8-1%	Preservative to prevent microbial contamination.
Fragrance	0.1-0.3%	Scenting agent, for a pleasant user experience.
Sodium Hydroxide	As needed	pH adjuster, used to raise pH if necessary.

Example of foam base Handwash

Evaluation Test

- **pH Testing**

The pH of a handwash formulation is critical for skin compatibility and stability of the antifungal agent. Typically, the pH should be in a skin-friendly range (5.5–7) to prevent skin irritation. A pH meter or pH indicator strips can be used. The handwash is diluted with distilled water and measured for pH.

- **Antifungal Efficacy (In Vitro Testing)**

The formulation's antifungal activity is tested against *Candida albicans* and *Aspergillus* species using the agar diffusion or broth dilution method. The formulation is applied directly or soaked onto sterile disks placed on agar plates inoculated with fungal strains. The zone of inhibition is measured after incubation to determine effectiveness.[14]

- **In Vitro Cytotoxicity Studies**

Cytotoxicity is evaluated using L929 fibroblast cells to assess potential toxic effects. Cells are exposed to the product or its components for 24–48 hours. Observations help determine the safety and biocompatibility of the formulations.

- **Foam Height and Stability**

Foam height and stability are key to user satisfaction and perceived cleaning efficacy. Using the cylinder shake method, the handwash is diluted, shaken in a graduated cylinder, and foam height is recorded immediately and after a set time.[15]

- **Viscosity and Rheology**

Viscosity ensures optimal consistency for user experience and dispensing. Measured with a viscometer or rheometer, handwash formulations typically range from 500 to 5000 centipoise.

- **Skin Irritation and Sensitization**

Skin Irritation and Sensitization Patch tests or in vitro models like reconstructed human epidermis (RHE) assess potential irritation or allergies. The formulation is applied to the skin, and reactions are monitored for 24–72 hours.[16]

- **Microbial Load and Preservative Efficacy Testing (PET)**

Microbial load testing ensures the handwash is free from contamination, measuring Total Aerobic Microbial Count (TAMC) and Total Yeast and Mold Count (TYMC). Preservative efficacy testing involves inoculating the formulation with microbial strains (e.g., *E. coli, S. aureus, C. albicans*) and monitoring growth over time.[17]

- **Stability Testing**

Stability testing determines shelf life and resilience under varying conditions. Accelerated testing (40°C, 75% RH for 3–6 months) and real-time testing (25°C, 60% RH) evaluate parameters like appearance, pH, viscosity, and antifungal efficacy.[18]

- **Appearance, Color, and Odor Evaluation**

Visual and sensory evaluations ensure the product retains its intended appearance, color, and odor during stability studies. Changes indicate potential instability.

- **Spreadability (For Semi-Solid Handwash Gels)**

Spreadability assesses the ease of product application. A fixed amount of product is placed between glass slides, and the spread diameter under a specific weight is measured.

- **User Acceptance Studies**

Consumer panels evaluate the handwash for sensory attributes like foam quality, texture, cleansing power, skin compatibility, and post-wash feel to ensure user satisfaction.

- **Release Test**

The release test evaluates the antifungal agent's (API) release from the formulation using a Franz diffusion cell.

Procedure:

1. Cell Setup: A synthetic membrane is placed between donor and receptor compartments filled with receptor medium at 32°C.
2. Application: A fixed amount of the formulation is applied to the donor compartment.
3. Sampling: Samples are withdrawn at intervals (e.g., 5–60 minutes) and replaced with fresh medium.
4. Analysis: Concentrations are measured using HPLC or UV-Visible spectrophotometry [19].

CONCLUSION

The antifungal handwash as a novel drug formulation presents a promising approach to addressing superficial fungal infections and enhancing hygiene. Formulation combines the benefits of hand hygiene with targeted antifungal action, potentially reducing fungal transmission and contamination. Antifungal handwash formulations are especially valuable in clinical settings, public spaces, and homes, where frequent handwashing is essential for infection control.

By utilizing suitable antifungal agents like clotrimazole, ketoconazole, or miconazole, the formulation can offer broad-spectrum antifungal efficacy, while ensuring that active ingredients are released effectively and safely during use. Incorporating skin-compatible excipients helps in maintaining skin hydration and minimizing irritation, making the product suitable for frequent use.Release studies, stability tests, and antifungal efficacy evaluations confirm that a well-formulated antifungal handwash can consistently deliver therapeutic levels of active ingredients within the limited contact time typical of handwashing infections in the general population, making it a valuable addition to current antifungal and hygiene products. Thus, antifungal handwash products have the potential to fill a unique in personal hygiene and topical antifungal therapy, contributing to improved public health by reducing the prevalence and transmission of superficial fungal infections.

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