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Review Paper

A Study on Antifungal Hydrogel for Topical Drug Delivery

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ABSTRACT

One of the human body's largest and easiest-to-reach organs is the skin. About one-third of the blood that circulates through the body passes through the skin, which has a surface area of about 3000-inch² on an average adult body. Although there are several alternative routes of administration, topical Clotrimazole-containing preferred hydrogel was made and tested for its ability to effectively treat fungal infections. Based on the site, there are four different kinds of fungal infections. They are ringworm, jock itch, athlete's foot, and yeast infections. Following the hydrogel's preparation utilising various carbopol, gellangum, ascorbic acid, and polyethylene glycol compositions, it was assessed.

INTRODUCTION

Mycosis**,** is another name of fungal infection, is a fungal cause disease. Traditionally, the various forms are separated into superficial, subcutaneous, and systemic categories based on the body portion impacted. Yeast infections like pityriasis versicolour and common skin diseases like tinea of the body, groin, hands, feet, and beard are examples of superficial fungal infections. Subcutaneous forms, which typically affect tissues in and beneath the skin, include chromoblastomycosis and eumycetoma [3]. Cryptococcosis, histoplasmosis, pneumocystis pneumonia, aspergillosis, and mucormycosis are examples of more dangerous systemic fungal infections. There are many different signs and symptoms. A rash with a superficial infection is typically seen. A fungal infection under or inside the skin can cause skin changes and a bulge. Fungal infections of the skin are a common dermatological problem worldwide. Topical antifungal treatment is successful when the medicine penetrates the target tissue and is concentrated in the deeper layers of the skin [4]. Clotrimazole is an imidazole derivative with a broad spectrum of antifungal activity, used orally and topically. It treats candidiasis and yeast infections. Clotrimazole inhibits ergosterol production, leading to increased cellular permeability of fungal cells. Clotrimazole can endogenous respiration, interact with membrane

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phospholipids, and impede ion transport pathways in cell membranes. The creation of a clotrimazole hydrogel may solve the challenges associated with current formulations while simultaneously improving medication penetration to the deeper tissues of skin [5].

1.1. Topical delivery: Understanding the skin anatomy, physiology, and physiological characteristics is essential. The epidermis, dermis, and hypodermis (subcutaneous layer) are the three histological layers that make up skin under a microscope. The thickness of the epidermis is 0.1 to 1.5 mm. The stratum germinativum, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum are its five more divisions. Melanin is formed by the epidermis the thickest layer of the epidermis, the squamous cell layer, aids in the movement of specific chemicals into and out of the body. Ten to thirty thin layers of dead cells make up the stratum corneum [2]. Chronic wounds often have high levels of oxidative stress and bacteria that form biofilms. Current dressings designed to promote the healing of chronic wounds frequently require additional treatments, such as photothermal irradiation, or cause significant, undesired residues to build up. Through a crosslinked network with integrated antibacterial cationic polyimidazolium and antioxidative N-acetylcysteine, Pranantyo [19] created a hydrogel dressing for topical application with dual functionality, exhibiting intrinsic antibiofilm and antioxidative properties. In diabetic wounds in mice infected with carbapenem-resistant Pseudomonas aeruginosa biofilms or methicillin-resistant Staphylococcus aureus, this dressing promoted wound closure. The dressing also encouraged keratinocyte differentiation and re-epithelialization in a model that was similar to human skin, providing a flexible and contaminant-free option for the management of chronic wounds. In addition, some study is being conducted on natural composites in wound healing for topical medication therapy. Zmejkoski et al. used gamma rays to synthesise nanoscale chitosan dots (ChiD) and integrate them into a bacterial cellulose (BC) polymer matrix to form a novel photosensitive protective hydrogel using methicillin-resistant Staphylococcus aureus, demonstrating the hydrogel's potential against biofilm-associated infections, making it highly beneficial for wound healing. Zmejkoski et al. also created a new composite hydrogel made of bacterial cellulose (BC) and chitosan polymer (Chi-BC-Chi), as well as chitosan nanoparticles (nChiD-BC-nChiD). Their findings revealed outstanding dressing qualities, such as improved porosity, wound fluid absorption, and rapid cell migration, indicating the hydrogel's potential as an effective treatment for chronic wound healing [12].

1.2. Introduction of hydrogel: Cross-linked three-dimensional networks made of water-soluble polymers are called hydrogels. Traditionally, hydrogels have been used to transport hydrophilic small molecules. Large amounts of hydrophilic drugs are somewhat easier to load into swelling hydrogel in these networks than hydrophobic drugs. Since a hydrophobic drug and the hydrophilic hydrogel network 1 are incompatible, introducing a hydrophobic medication into a hydrogel-based formulation is difficult in a number of ways. A drug's water solubility can be improved by co-solvency, hydrotropism, complex formation, ionisation, and the addition of surfactants in order to get around the issue. [1] Physical hydrogels have a variety of medicinal Physical gels may deteriorate if natural domain conditions change, such as ionic purity, pH, and temperature. Physical hydrogels have a variety of medicinal applications, including pill delivery, wound dressing, tissue design, and more. Covalently cross-joined hydrogels, often known as

"smart" hydrogels, can change volume/shape with minor changes to specific parameters of nature's turf. Responsive hydrogels feature a variety of provisions, the bulk of which revolve around organic and therapeutic demands, as well as sensing requisitions. Single-system hydrogels have weak mechanical characteristics and a modest swelling reaction [22]. Various methods from material science, microscale design, and microfluidics have been used to synthesise biomimetic hydrogels. applications, including pill delivery, wound dressing, tissue design, and more. Covalently cross-joined hydrogels, often known as "smart" hydrogels, can change volume/shape with minor changes to specific parameters of nature's turf. Responsive hydrogels feature a variety of provisions, the bulk of which revolve around organic and therapeutic demands, as well as sensing requisitions. Single-system hydrogels have weak mechanical characteristics and a modest swelling reaction. Various methods from material science, microscale design, and microfluidics have been used to of synthesise biomimetic hydrogels. [8]

Properties of hydrogel: [23]

1. High water content:

Can absorb up to thousands of time their dry weight in water.

2. Soft and Elastic Nature:

Flexible and similar in mechanical properties to natural tissue.

3. Porosity:

Porous structure allows for the transport of nutrients, drugs, or cells.

4. Crosslinked Structure:

Can be physically or chemically crosslinked.

Crosslinking defines the strength, stability, and degradation rate

1.3. Ideal Characteristics of Hydrogel: - [21]

- High water absorption
- Biocompatibility
- Biodegradability
- Control swelling rate
- Porosity and permeability.

1.4. Classification of Hydrogel:

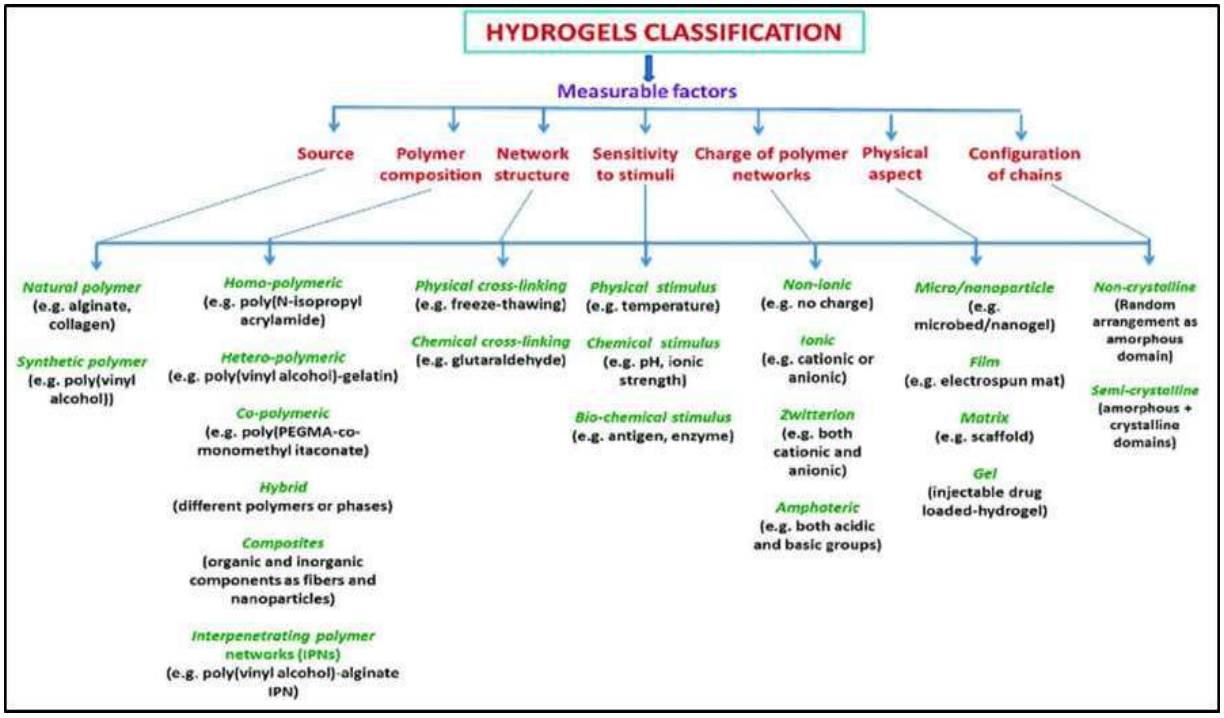

Fig no.1 Classification of Hydrogel

1.5. Hydrogel in Advance Drug Delivery System:

Parallel to these discoveries, hydrogels have become a hot topic due to their outstanding utility in devices developed for therapeutic agent targeting, bioadhesion, and controlled release. Hydrogels' unique qualities, such as their capacity to retain large volumes of water, biocompatibility, and controlled swelling behaviour, have all contributed to their use in drug delivery systems. These hydrogel formulations are designed to allow for progressive drug elution, resulting in elevated medicine concentrations in the target location and neighboring tissues over extended periods of time. This feature highlights their potential for systemic delivery of a wide range of medicinal medicines and bioactive substances. Furthermore, hydrogel-based delivery mechanisms have been developed in novel ways for oral, injectable, topical, and ophthalmic applications [12].

1.5.1Oral Hydrogel- Based Drug Delivery:

Oral drug delivery is useful in providing a wide range of therapeutic medicines aimed at treating both local and systemic disorders. Nonetheless, the oral route offers complications for delivering certain types of medications. For instance, peptide and protein therapies have problems with stability, solubility, and absorption in the gastrointestinal tract (GIT) and are especially susceptible to acidic denaturation and enzymatic destruction. Hydrogels are a viable alternative for site-specific delivery within the GIT, protecting therapeutic molecules in their complicated environment and allowing for regulated, site-specific drug release [13].

1.5.2. Injectable Hydrogel-Based Drug Delivery System:

Injectable hydrogels are a cutting-edge medication delivery method that enables administration using minimally invasive approaches. These hydrogels provide exquisite control over the kinetics and localisation of drug release, making them ideal for targeted therapy in a variety of medical problems. Injectable hydrogels require rheological qualities that are optimised for ease of administration and performance [18]. They must exhibit shear thinning behavior, reducing viscosity under shear stress during injection but fast recovering once injected, allowing for both ease of passage through needles and instant stability within the target site. Furthermore, an ideal balance of viscosity and elasticity is required—viscosity permits the hydrogel to flow smoothly during injection, whilst elasticity ensures that it preserves its structure once installed [13].

1.5.3. Ocular Hydrogel-Based Drug Delivery System:

Furthermore, hydrogels show promise as topical treatments for eye problems, with substantial research underway in this field. Ou et al. described a unique method for treating dry eye disease with aldehyde-functionalized F127 hydrogel eye drops containing antioxidant Cu2-xSe nanoparticles [14]. These nanoparticles work as superoxide dismutase and glutathione peroxidase mimics, scavenging reactive oxygen species and reducing oxidative damage. In a dry eye animal model, Cu2-xSe nanoparticles demonstrated therapeutic promise by regulating the NRF2 and p38 MAPK pathways, lowering apoptosis and inflammation, while AF127 hydrogel eye drops demonstrated effective ocular surface adhesion. This points to a highly effective therapy method for dry eye illness and reactive oxygen species-related disorders [12].

1.5.4. Challenges and perspectives:

In the field of drug delivery, hydrogels have evolved from typical chemical-based compositions to sophisticated supramolecular

architectures, representing a paradigm change. This change has been made possible by considerable advances in material chemistry and polymer science, as well as cutting-edge production techniques like three-dimensional (3D) printing and microfluidics. These sophisticated hydrogels are designed to have a variety of functional qualities, including the capacity to respond to specific stimuli, be injected directly into target areas, and provide controlled drug release kinetics that are suited to individual patient demands [14]. The ability to build complex microscale and nanoscale architectures not only increases the versatility of hydrogels, but also significantly increases their utility in overcoming difficult delivery obstacles. One of the biggest barriers to clinical integration of hydrogels is the regulatory and manufacturing challenges that come with their sophisticated nature. Storage, deterioration, and sterilisation challenges, as well as the delicate balance of material complexity and regulatory compliance, have hampered their translation from laboratory to clinical practice. Nonetheless, the integration of hydrogels with precision medicine and the rising field of bio fabrication, notably the development of bioinks for 3D bioprinting, heralds' new opportunities. Such improvements, aimed at creating personalised tissue constructs and improving drug delivery systems, highlight the importance of design simplification in enabling regulatory approval and commercial feasibility while maintaining functional integrity [13].

2. Overview of Human Skin: -

Epidermis: The epidermis is the outermost layer of the skin, providing a waterproof barrier and determining skin tone. The interior layers are the dermis and hypodermis. The epidermis consists of four primary strata or layers. The uppermost layer is referred to as the stratum corneum, which means "horny layer." The epidermis consists of five layers: stratum basale (deepest), stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum (most superficial) [2].

Dermis: Collagen is the protein that holds the dermis together. This layer promotes skin elasticity and strength. The dermis contains pain and touch receptors [19].

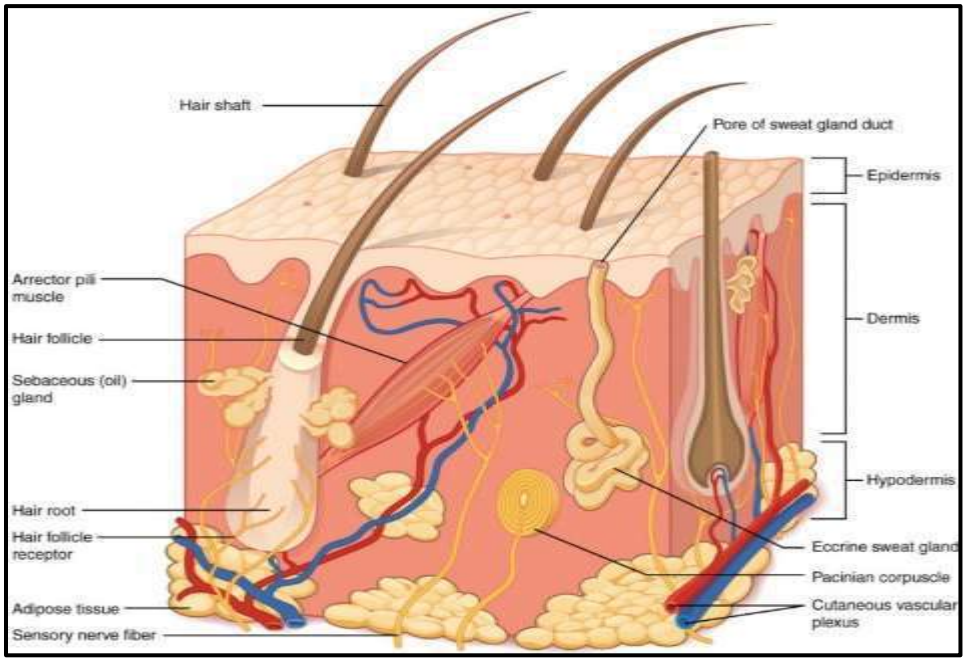

Fig no 2. anatomy of Human Skin

Hypodermis: The subcutaneous tissue (hypodermis) is not considered a true element of the structure connective tissues. The skin is made up of loose, white, fibrous connective tissue that houses blood and lymph arteries, sweat gland secretory pores, and nerves [2].

MECHANISM OF ABSORPTION: -

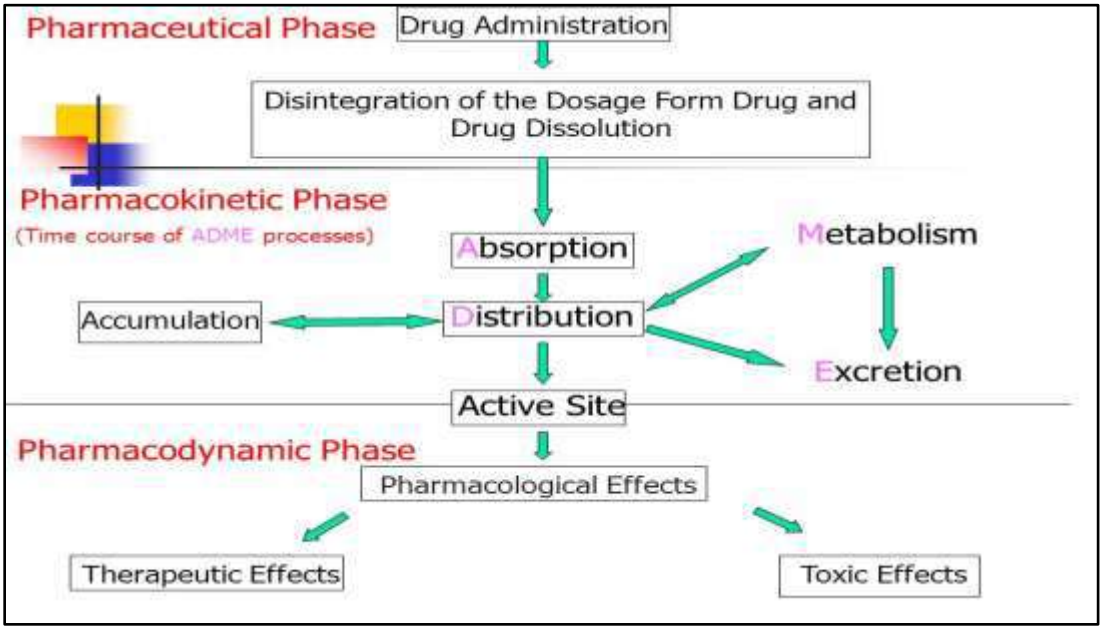

Fig no.3 ADME Process

3.1. Mechanism of drug permeation through skin:

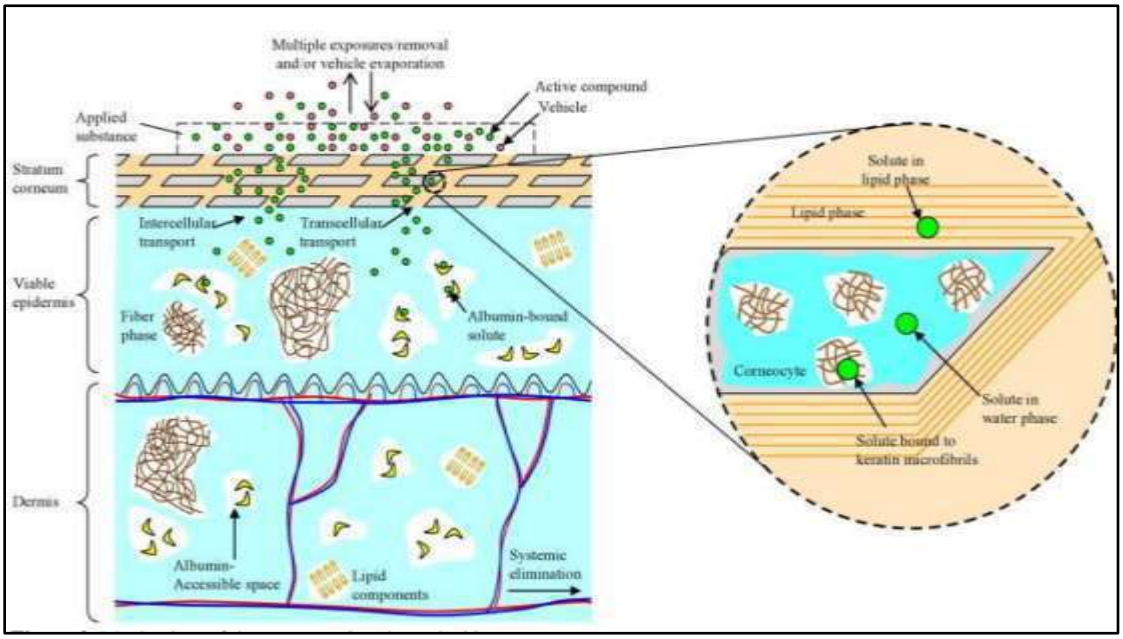

Fig no.4 Mechanism of drug permeation to skin.

The dermis layer, measuring 1.5-4 mm thick, sits beneath the epidermis. It is made up of collagen elastins, sweat and oil glands, hair follicles, nerve endings, blood, and lymph vessels. The dermis contains immune scavenger cells that absorb and destroy invading organisms. The sensation of touch is caused by nerve endings. The hypodermis, sometimes called subcutaneous tissue, is the deepest layer of skin that works as an insulator and shock absorber, protecting internal organs from harm. It also stores fat. Via these layers, the blood arteries, nerves, lymph vessels, and hair follicles also cross-link. [2].

3.2. Pharmacological profile: -

Mode of action:

Clotrimazole acts primarily by damaging the permeability barrier in the cell membrane of fungi. Clotrimazole causes inhibition of ergosterol biosynthesis, an essential constituent of fungal cell membranes. If ergosterol synthesis is either completely or partially inhibited, the cell is no longer able to construct an intact and functional cell membrane. Because ergosterol directly promotes the growth of fungal cells in a hormone-like fashion, rapid onset of the above events leads to dose-dependent inhibition of fungal growth [22] Though decreased ergosterol, due to the inhibition of lanosterol 14-demethylase (also known as CYP51) is accepted to be primarily responsible for the antimycotic properties of clotrimazole, this drug also shows other pharmacological effects. These include the inhibition of sarcoplasmic reticulum Ca2+-ATPase, depletion of intracellular calcium, and blocking of calcium-dependent potassium channels and voltage-dependent calcium channels. The action of clotrimazole on these targets' accounts for other effects of this drug that are separate from its antimycotic activity [10].

4.Marketed Hydrogel: [24]

Product	Application	Active Ingredient	Delivery Route	Manufacturer
SpaceOA Hydrogel	Prostate cancer radio therapy	None	Injectable	Augmenix,Inc
Vantas	Prostate cancer	Histrelin acetate	Subcutaneous implant	Endopharmaceutical
INFUSE Bone Graft	Spinal fusion	Recombinant human BMP-2	Injectable	Medtronic
Regranex gel	Diabetic foot ulcer	Becaplermin (PDGF)	Topical	Smith& Nephew
Acticoat hydrogel	Wound dressing	Silver nanoparticles	Topical	Smith& Nephew
Gynol II	Contraceptive	Nonoxynol-9	Vaginal	Johnson&Johnson

5.Methods of Preparation: - [8]

1. **Selection of Polymer:** Choose either a natural (e.g., alginate, chitosan, gelatin) or synthetic (e.g., polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyacrylamide) polymer.
2. **Dissolution:** Dissolve the polymer in water or an appropriate solvent under stirring and sometimes heating to form a uniform solution.
3. **Crosslinking Process**: Crosslinking turns the liquid polymer solution into a gel. This can be done through:

A. Physical Crosslinking:

1. Ionic gelation: This method involves the interaction between charged groups on polymer chains and counterions to form a gel.

2. Heating/cooling: Some polymers form gels when heated or cooled due to the association of polymer chains.
3. Radiation crosslinking: Exposing a polymer mixture to ionizing radiation can create a crosslinked network.

B. Chemical Crosslinking:

1. Free-radical polymerization: A common method where monomers are polymerized in the presence of a crosslinker and free radical initiator.
2. Enzymatic crosslinking: Enzymes can be used to modify polymer chains and facilitate crosslinking under mild conditions.
3. Hydrazone crosslinking: This method involves reacting aldehyde-modified polymers with carbohydrazide-modified polymers to form hydrazone bonds.
4. Glutaraldehyde crosslinking: Glutaraldehyde is a common crosslinking agent used to create covalent bonds between polymer chains.

4.Gelation: Allow the mixture to sit under appropriate conditions (time, temperature) until it transforms into a hydrogel.

5.Purification: Wash the hydrogel (e.g., with distilled water or ethanol) to remove unreacted monomers or crosslinkers.

6.Storage: Store the hydrogel in a hydrated state, usually in distilled water or buffer at a suitable temperature to maintain its properties.

5.1. Evalution of Hydrogel: [9]

1. **pH Measurement:** Ensure pH is within an acceptable range.

2. **Viscosity and Rheological Properties:**

- Brookfield Viscometer: Measures viscosity to ensure consistency in formulation.
- Spreadability Test: Determines ease of application and uniformity.

1. **Drug Content (Assay):** HPLC (High-Performance Liquid Chromatography): Determines the amount of clotrimazole in the formulation, ensuring it meets specifications.

2. **Biocompatibility**: Assesses how well the hydrogel interacts with living tissues. Tested via cytotoxicity, hemocompatibility, and cell viability assays.

3. **Degradation Rate / Stability**: Evaluates how long the hydrogel maintains its structure. Important for biodegradable applications like drug delivery.

4. **Drug Loading and Release Profile**: Measures how much drug a hydrogel can load and how it's released over time. Often studied using in vitro drug release kinetics.

5. **Thermal Properties**: Studied using DSC (Differential Scanning Calorimetry) or TGA (Thermogravimetric Analysis).

CONCLUSION: -

Clotrimazole hydrogel is an effective topical antifungal formulation that combines the potent antifungal activity of clotrimazole with the favorable properties of a hydrogel base. The hydrogel provides enhanced drug penetration, prolonged residence time on the skin, and improved patient compliance due to its non-greasy, cooling, and soothing nature. Overall, clotrimazole hydrogel offers a promising and efficient approach for the treatment of superficial fungal infections, ensuring localized delivery with minimal systemic absorption and side effects.

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