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Formulation and Evaluation of Antifungal Clotrimazole emulgel

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Abstract: *Clotrimazole is an imidazole derivative with a broad spectrum antimycotic activity, widely used for the treatment of Candida albicans. It acts by inhibiting biosynthesis of Ergosterol, an important component of fungal cell membranes. It is widely used for the treatment of local candidiasis, oral thrush, and vaginal yeast infections. Emulgels are emulsions, either of the oil-in-water or water-in-oil type, which are gelled by emulsion has been used widely in cosmetics and in pharmaceuticals preparations. Gel having a property to form cross linked network where it takes small drug particles and provides its release in a controlled manner. Through its mucoadhesive properties it prolongs the contact period of medication over the Emulgels have developed as one of the most intriguing topical delivery systems due to their dual release control mechanism, which includes both gel and emulsion pharmaceutical specialists are presently inquisitive about emulgel systems because of their vital potential to perform as a drug delivery vehicle by incorporating a various vary of therapeutic compounds. Characterization of clotrimazole emulgel was done by physical examination, pH determination, viscosity testing, in- vitro release study, drug content determination, swelling index.The aim of the present study was to develop an emulgel formulation of Clotrimazole using carbopol 940as a gelling agent*

Keywords: Clotrimazole, Emulgel, Antifungal, Emulsion, Carbapol

I. INTRODUCTION

Clotrimazole is an imidazole derivative with a broad spectrum antimycotic activity, widely used for the treatment of Candida albicans. Topical application includes fungal infections such as ring worm, athlete's foot and jock itch. Clotrimazole action leads to increased membrane permeability and apparent disruption (division) of enzyme systems bound to the membrane. Clotrimazole is an effective, safe and well tolerated drug with unusual chemistry that is broadly used in the treatment of skin, vulvovaginal and oropharyngeal fungal infections. The commercially available cream of Clotrimazole has the limitations of lower skin retention, poor residence ability and deposition at the target site. Clotrimazole has limitations such as poor water solubility, bioavailability and the short half-life (2 hours) as reported by Crowley et al 2014. Clotrimazole show poor bioavailability when administered orally because of low aqueous solubility and slow dissolution in water. Hence, to improve its bioavailability, an effort was made to develop transdermal Clotrimazole. Emulgels can be defined as the emulsions, either of the o/w or w/ o type, which are thicken by mixing the gelling agent. Emulsion has been used widely in cosmetics and in pharmaceuticals preparations. Through its mucoadhesive properties it prolongs the interact duration of medication over the skin. Since Emulgel having the characteristics of both emulsion and gel it acts as dual control release system.. Present days, they are being used for controlled delivery applications. Topical formulations apply a wide spectrum of the preperations for both cosmetic and dermatological preparation, to their healthy skin. Oil on water emulsions are most useful as water washable drug bases and for general cosmetic purposes , while water in oil emulsions are employed more widely for the treatment of dry skin and emollient applications.Emulgels have high patient acceptability as they have properties of both gel as well as emulgels. Topical formulations apply a wide spectrum of preperations both cosmetic and dermatological for healthy skin. When gels and emulsions both are used in combination , the dosage form are reffered to emulgel. Clotrimazole is an antifungal agent which inhibits the growth of pathogenic dermatophytes . Emulgels or gellified emulsion is stable one and better vehicle for hydrophobic or water soluble drugs such as clotrimazole.Its biggest and most favorable advantage has been the ability to incorporate hydrophobic drugs, thus making it emerge as a more popular choice these days. The emulgel is also greaseless, transparent; it can be easily spread and removed, has a long shelf- life, is

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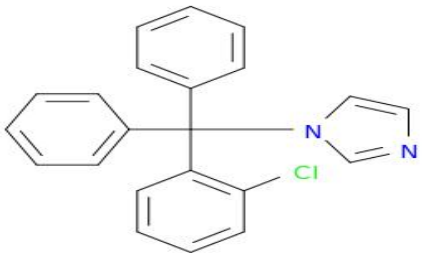
thixotropic and is also pleasant looking. The emulgel is turning out be a preferred choice for cosmetic and dermatological preparations and its use and application will accelerate in the coming future. The goal of this paper is to develop and optimize a Clotrimazole emulgel using polymers and evaluate its physical properties, drug release, and potential advantages for incorporating hydrophobic drugs.Emulgel is an emerging topical drug formulation which is becoming increasingly popular due to its advantages over the conventional topical preparations.The permeation of drugs through the stratum corneum can be enhanced by physical methods and chemical modification or by the use of chemical penetration enhancers. Chemical penetration enhancers modify the barrier properties of the stratum corneum and hence increase the drug permeability across the skin. Chemical enhancer should be non-toxic, nonallergenic and also compatible with the drugs and excipients.Also emulgels have highest patient acceptability having both properties gel and emulgels . Therefore they have been recently used as vehicles to deliver various drug to skin.

Drug profile

Clotrimazole : Clotrimazole is a medication used in management and in treatment of fungal infections. It is in the imidazole class of drug. It is an FDA – approved drug to treat oral candiasis, vaginal candiasis.Clotrimazole is effective in the treatment of skin infections such as athlete's foot, jock itch, ringworm, pityriasis versicolor, intertrigo, and erythrasma. In addition, clotrimazole has some activity against certain gram-positive bacteria, and at very high concentrations, has activity against Trichomonas spp. In adults and children older than 12 years, the FDA has approved the use of clotrimazole in combination with betamethasone propionate (corticosteroid) for the topical treatment of inflammatory tinea due to *Epidermophyton floccosum* and *Trichophyton*. However, caution should be exercised, as the use of such combinations can aggravate fungal infections.



Mechanism of action : Clotrimazole thereby inhibits the biosynthesis of ergosterol in a concentration-dependent manner by inhibiting the demethylation of 14 alpha lanosterol. When ergosterol synthesis becomes inhibited, the cell can no longer construct an intact and functional cell membrane. Ergosterol also directly promotes the growth of fungal cells in a hormone-like fashion; therefore, the rapid onset of the above events leads to a dose-dependent inhibition of fungal growth. clotrimazole exerts its anti-fungal action by decreasing ergosterol biosynthesis, clotrimazole exerts other pharmacological actions. 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.

Administration :

Oral Administration of Other Oral Formulations

Transmucosal administration

Patients should slowly dissolve troches in the mouth, do not chew.

Topical Administration Cream/Ointment/Lotion Formulations

Rub cream or solution gently into the cleansed affected skin.

Topical preparations should not be used in the eye; or used intravaginally.

Intravaginal Administration

Intravaginal application is only for those clotrimazole products labelled for intravaginal use. Some commercially available preparations contain both intravaginal tablets and vaginal cream in a combination package. The intravaginal

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cream may be applied externally to the affected area (vulva) to relieve itching and discomfort. Recent advances drug design and compounding have also increased the pace of the development of antifungal drug.

Fungal Infections

Increasing incidence of fungal infections of recent times requires immediate intervention. Fungal infections are seldom construed at initial stages that intensify the severity of infections and complicate the treatment procedures. Fungal pathogens employ various mechanisms to evade the host immune system and to progress the severity of infections. For the treatment of diverse superficial and systemic infections, antifungal drugs from the available repertoire are administered.Recent advances drug design and compounding have also increased the pace of the development of antifungal drug. Candidiasis is a infection caused by a yeast (a type of fungus) called *candida* . Some species of candida can cause infection in people; the most common is *candida albicans*. *Candida* normally lives on skin and inside the body, such as mouth, throat, gut, and vagina, without causing problems. *Candida* can cause infections if it grows out of control or if it is enter deep in body. For example, it can cause infection in bloodstream or in internal organs like kidney, heart, or brain. Here are some key points about *Candida albicans* infections:

- **Thrush**: This infection occurs when yeast overgrows inside the mouth and throat, resulting in white, raised bumps. Commonly seen in infants, children, older adultsand those with weakened immunity.
- **Vaginal yeast infection(Vaginal candidiasis):** UYeast multiplies within the vagina , leads to itching, discomfort, white discharge. Risk factor includes pregnancy, recent antibiotics use, hormonal changes, and weak immune system.
- **Oral thrush:** Also known as oral candidiasis occurs when Candida accumulates on lining of your mouth. Creamy white lesions appear on your tongue or inner cheeks. Stress, unmanaged diabetes, and a weak immune system can contribute to oral thrush.
- **Invasive Candidiasis:** A severe infection that affects the entire body, including the blood, bones, brain, and heart it is most common in hospitalised individuals, catheter users, surgery recipients, and those with weakened immunity.

Management and Treatment:

- **Oral:** Medicine taken by mouth (Tablet, Lozenges)
- **Topical:** Medication directly applied to affected area(Creams, Ointments)

Emulgel

When gels and emulsions are used in combined form the dosage form are referred as emulgel. Polymer can function as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. These emulgel are having major advantages on novel vesicular systems as well as on conventional systems in various aspects. Emulgels are the emerging drug delivery system nowadays that has become popular for the delivery of hydrophobic drugs. This formulation is considered a novel type of drug delivery system and a mixture of emulsion and gel. Emulgels are the emerging drug delivery system nowadays that has become popular for the delivery of hydrophobic drugs. This formulation is considered a novel type of drug delivery system and a mixture of emulsion and gel.

Emulsions are controlled-release systems that comprise two immiscible phases, one of which is dispersed (internal or discontinuous phase) into the other (external or discontinuous phase) with the help of an emulsifying agent. The drug particle captured in the internal phase travels through the exterior phase and then gently absorbs into the skin to deliver a regulated effect. Emulsions are of the oil-in-water or water-in-oil kind the USP defines a gel as a semisolid system containing and interpenetrated by liquid and composed of dispersions of small inorganic particles or large organic molecules. The gel traps small drug particles and maintains regulated drug release by containing a larger amount of aqueous or hydro alcoholic liquid in a cross connected network of colloidal solid particles.

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Advantages of Emulgels :

- Drugs that are hydrophobic are included.
- Improved loading capacity and stability.
- Controlled release is a term used to describe when something is released in a controlled manner
- There will be no intensive sonication.
- Avoiding the first-pass metabolic process.
- Keeping gastrointestinal incompatibility to a minimum.
- More focused on a single location.
- Patient compliance has improved.
- Convenient and simple to use.

Disadvantages of Emulgel :

- Contact dermatitis causes skin irritation.
- Allergic reactions are a possibility.
- Some medications have a low permeability through the skin.
- Drugs with large particles are difficult to absorb via the skin.
- The formation of a bubble during the emulgel formulation process.

Rationale: Many widely used topical agents like ointment, cream, lotion have many disadvantages. They have very sticky causing uneasiness to the patient when applied. Moreover they also have lesser spreading coefficient and need to apply with rubbing . And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. In spite of many advantages of gels a major limitation isin the delivery of hydrophobic drugs. Soto overcome this limitation an emulsion based approach is being used so that even a hydrophobictherapeutic moiety can be successfully incorporated and delivered through gels.

Drug delivery across the skin

The epidermis is the most superficial layer of the skin and is composed of stratified keratinised squamous epithelium which varies in thickness in different parts of the body. Itis thickest on with elastic fibres. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes. There are three primary mechanisms of topical drug absorption: transcellular, intercellular, and follicular. Most drugs pass through the torturous path around corneocytes and through the lipid bilayer to viable layers of the skin. The next most common (and potentially under recognized in the clinical setting) route of delivery is via the pilosebaceous route. The barrier resides in the outermost layer of the epidermis, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs toan affected site of the body. These include, among others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to soothe arthritis pain. New technologies now allow other drugs tobe absorbed through the skin (transdermal). These canbe used to treat not just the affected areas (for example, the skin) but the whole body.

Components of Emulgel

Oils are used as an oil phase to prepare an emulsion. Mineral oils and soft or hard paraffin are commonly used, either alone or in combination, in topically applied emulsions.

Examples: Castor and mineral oils, which have laxative effects, are the most commonly used oils for oral and topical preperations.

- **Vehicles:** In the emulgel preperations, oily and aqueous vehicles are used, and both hydrophobic and hydrophilic drugs are used.

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Examples: Alcohol, water, and other aqueous materials are used in aqueous phase emulsion.

- **Emulsifiers:** To improve shelf life stability, an emulsifier is used to increase the emulsification of the preparation.
  Examples: tween 80, span 80,Tween 20, stearic acid.
- **Gelling agent:** This are used for preparing gels for any dosage form. It enhances the consistency of any formulation.
  Examples: Carbopol 940, Carbopol 934, HPMC- 2190
- **pH adjusting agents:** These agents are used to maintain the pH of formulation.
  Example: triethylamine, NaOH.

Applications of Emulgels

A. Topical Applications

Skin Care: Emulgels are used as moisturizers, emollients and for treating conditions like roughness, dullness, irritation, etc.

Hair Care: Emulgels containing proteins, oils, keratin, etc. are used as conditioners, styling agents, treatment for dandruff, etc.

Cosmetics:Emulgels are used as foundations, lip balms, sunscreens, etc. Ingredientsinclude pigments, waxes, silicones,

B. Parenteral applicaitons

Emulgels provide sustained release of drugs through injection. They release drugs over prolonged periods, reducing dosing

frequency and maintaining adequate drug levels. Water soluble corticosteroids and antibiotics are commonly incorporated [18].

C. Oral Applications

Emulsion-based oral drug delivery systems include:

Emulgels: Emulgels contain both emulsions and gels for controlled release of drugs. Oil-in-water or water-in-oil emulsions are used based on solubility of drug.

Liquid filled gelatin capsules (LFGCs): Emulsions contained within gelatin capsules. LFGCs provide floating, sinking or remained buoyant to release drug at specific sites. Used for site-specific release .

Self-emulsifying drug delivery systems (SEDDS): Contain emulsifiers and solvents to produce fine O/W or W/O emulsions .

Microemulsions:Thermodynamically stable, isotropic and have a droplet size below 100 nm. Microemulsions pro-vide maximum surface area for absorption and enhance solubility. They are suitable for lipophilic, amphiphilic and hydrophilic drugs .

II. CONCLUSION

The solubility of drug in the oil phase is important for emulgel to maintain the drug insolubilized form. pH value indicates the suitability of emulgel for topical application.Emulgel is a novel approach that has been proven to be the most convenient, superior, and efficient delivery system. Because of its non-greasy nature and lack of oily bases, it gives gel-like properties and gives excellent drug release when compared to conventional topical delivery systems. Emulgel has a high drug loading capacity and is effective in drug delivery at the target site. Penetration of a drug through the skin is effective due to its small particle size. In the coming years, topical drug delivery system will be used extensively to impart better patient compliance. Since emulgels possesses an edge in the terms of spreadability, adhesion, viscosity and extrusion, they will become a popular drug delivery system.

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