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ADVANCE TECHNIQUES IN TREATING CUTANEOUS FUNGAL INFECTIONS.

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ABSTRACT

Fungal infections are most commonly occurring nowadays. Out of all fungal infections, cutaneous fungal infections are the most widespread. Currently available conventional dosage forms although they are able to treat these infections, they come with some drawbacks such as poor skin permeation of drugs and high dosing frequency which leads to reduction in effectiveness against these fungal infections. Present review highlights on different types of superficial fungal infections, their causative agent, drawbacks in conventional dosage forms. It also briefs different classes of antifungal drugs, their mechanism of action with some examples of each class. It emphasizes on different novel techniques of antifungal drugs, their advantages and disadvantages. Details of each novel technique with reference to fungal infection is focussed. This review concludes various different techniques to overcome the drawbacks and to increase the effectiveness of antifungal drugs using various novel strategies.

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INTRODUCTION

The occurrence of fungal infection is most common nowadays and among these fungal infections, cutaneous fungal infection is the most prominent type occurring in humans. [1]

Cutaneous fungal infections are the infections of the skin, hair or nails that cause pathological changes in the host. Cutaneous fungal infections are further divided into 3 categories such as superficial, deep and systemic infections. Superficial are those which are confined to dead keratinous tissue, the epidermis and hair follicles. These superficial fungal infections are caused by dermatophytes, non dermatophyte molds and yeasts. Deep fungal infections are those which involves all the skin layers and even extends into subcutaneous tissue. Systemic infections with cutaneous manifestations are not common but occurs in immune compromised hosts. [2]

Dermatophytes such as *Trichophyton spp., Microsporum spp*. and *Epidermophyton spp.* are responsible for cutaneous fungal infections especially superficial infections. These dermatophytes causes infection to the stratum corneum of the epidermis and also the keratinized tissues such as hair and nail. [3]

Some of the examples of superficial fungal infections are tinea pedis, tinea corporis, tinea cruris, tinea versicolor, tinea capitis, tinea faciei, tinea manuum, cutaneous candidiasis and onychomycosis. Tinea pedis is also called as the athlete's foot or ringworm of foot and is caused by *Trichophyton rubrum.* Tinea corporis is the dermatophytosis of the skin of trunk and extremities which is also caused by trichophytum rubrum. Tinea cruris is a fungal infection at the site of thighs and buttock which also invades hair follicles. This infection is also termed as Jock itch. The most common causative agent that is found in tinea cruris is E floccosum. Tinea versicolor is a dermatophytic condition at the region of the body that have sebaceous glands such as upper trunk, neck and arms. This condition is caused by *Pityrosporum ovale.* Tinea capitis is a dermatophytic infection of the head and scalp which are majority caused by *Trichophyton tonsurans.* Tinea faciei, another fungal infection which is caused by *T rubrum* and *T mentagrophytes* at non bearded areas of the face. This infection is represented by itch and red skin without a proper border. Tinea manuum is an unusual fungal infection of the interdigital and palmar surfaces. Cutaneous candidiasis is a skin infection caused by C albicans and other species. Cutaneous candidiasis is more susceptible for the skin with increased moisture. [4]

Treatment of cutaneous fungal infection consists of oral and topical antifungal drugs or combination of both depending on severity, site of infection and causative organism. Some of these antifungal drugs, their mechanism of action and adverse effects are given in the Table 1. The conventional dosage forms used for the treatment of cutaneous fungal infections are cream, lotion, gel or sprays which has side effects such as redness of the skin, erythema, stinging and burning sensation. Some of the major drawbacks are poor skin permeation of hydrophilic antifungal drugs and high dosing frequency which lead to reduction in effectiveness against cutaneous fungal infections. These topical formulations for the treatment of cutaneous fungal infections may be fungi static or fungicidal depending on the therapeutic nature of antifungal drug used. [5-6] Fungicidal drugs are often preferred over fungi static drugs. [7] Topical antifungal therapy needs high amount of drug at the site of action, which is mainly stratum corneum. Newer and advanced techniques have attracted wide attention for topical antifungal therapy by enhanced skin permeation as well as controlled and sustained release of encapsulated drug ingredients. [8] This review article describes the available advance techniques for treating cutaneous fungal infection and also systemic fungal infection to some extent.

Table No.1: List of common antifungal agents, class and their mechanism of action.

Class	Sub class	Mechanism of action	Drugs
Azoles	Imidazoles	Inhibition of cytochrome p450-dependent lanosterol 14α-demythalase, an enzyme involved in ergosterol biosynthetic pathway.	Clotrimazole Ketoconazole Miconazole Econazole Tioconazole
	Triazoles		Fluconazole Itraconazole Posaconazole Voriconazole Oxiconazole Sulconazole
	Thiazoles		Abafungin
Echinocandins		These inhibit the synthesis of the structural polymer β-1, 3-glycan. Beta-glucan destruction prevents resistance against osmotic forces, which leads to cell lysis.	Caspofungin Micafungin Anidulafungin Pneumocandins Cilofungin
Polyenes		Polyenes bind to the membrane sterols resulting in the formation of pores that disrupt the stability and structure integrity of cell membrane.	Amphotericin B Nystatin Netamycin
Allylamines		Allylamine blocks the ergosterol biosynthetic pathway leading to accumulation of toxic squalene. The	Terbinafine Naftifine

	increase of squalene in the cell membrane is toxic to the cell, causing pH imbalances and breakdown of membrane-bound proteins.	

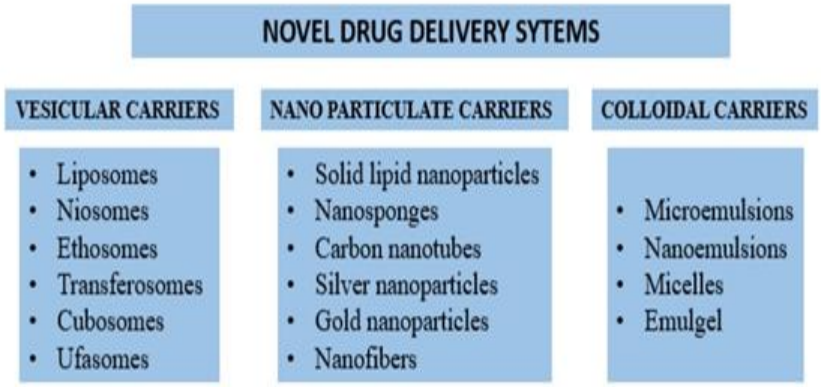

Fig.1: The present image shows the list of novel delivery systems in the treatment of cutaneous fungal infections.

ADVANCE TECHNIQUES IN DELIVERING ANTIFUNGAL AGENTS

VESICULAR DRUG DELIVERY SYSTEMS

Liposomes:

Liposomes are vesicular concentric bilayered structures, which are biocompatible, biodegradable and nonimmumnogenic. Liposomes control the delivery of drugs by targeting the drug to the site of action or by site avoidance drug delivery or by prolonged circulation of drugs. [9]

Mechanism of action of liposomes

Liposomes are basically formed by phospholipids, which are amphiphilic molecules (hydrophilic head and hydrophobic tail). When these phospholipids are dispersed in aqueous medium they organize in such a way that polar head group (hydrophilic head) faces towards aqueous region while fatty acid group (hydrophobic tail) face each other and form spherical structures called liposomes. [10]

Liposomes consists aqueous region inside the hydrophobic membrane, and hydrophobic chemicals can be dissolved into the lipid membrane; in this way liposomes are able to carry both hydrophilic and hydrophobic molecules.

Steps involved in the liposomal drug delivery

- **Adsorption:** Adsorption of liposomes to cell membranes causes its contact on the cell membrane.
- **Endocytosis:** Engulfment and internalization into the liposomes.
- **Fusion:** fusion of lipid bilayers of liposomes with the lipoidal cell membrane by lateral diffusion and intermingling of lipids results in direct delivery of liposomal contents in the cytoplasm.
- **Lipid exchange:** Due to the similarity of liposomal lipid membrane with cell membrane phospholipids, lipid transfer proteins in the cell membrane easily recognize liposomes and cause lipid exchange. [11]

Advantages and disadvantages [10]

Advantages

- Liposomes increase efficacy and therapeutic index of drugs.
- Liposomes reduce the toxicity of encapsulated agent.
- Liposomes are flexible, non-toxic, bio-compatible, and completely biodegradable.
- Flexible to couple with site specific ligands to achieve active targeting.

Disadvantages

- Shorter half-life.
- Lower solubility.
- Leakage and fusion of encapsulated drug.
- Sometimes phospholipids undergo oxidation and hydrolysis like reaction.

Liposomes have generated a great interest because of their versatility, biocompatibility, biodegradability and non-immunogenicity. Alur *et al* (2017) prepared liposomes of itraconazole using lipid thin film hydration technique. They prepared four formulations of ITZ liposomes, two with soyalecithin and cholesterol and other two formulations with soyalicithin and stearic acid. These formulations showed a vesicular size 16.5µm to 18.15µm. Drug content and entrapment efficiency were up to 38%. One of the formulation (F2) showed a drug release of 85% at the end of 6th hour which then mixed with carbopol 934 (3% w/w) to form ITZ liposomal gel for prolonged release and increased skin permeation through stratum corneum in treating topical fungal infection. [12]

Ethosomes:

Ethosomes are the non-invasive type of carriers which help the drugs to reach the deep layers of the skin and/or systemic circulation. These are soft and malleable vesicles which will enhance the delivery of active agents. [13] In ethosomes, ethanol interacts with lipid molecules in the polar head group region which results in reducing the rigidity of stratum corneum lipids, increases their fluidity. [14]

Mechanism of action [13]

The possible mechanism of ethosomes is by two steps, first is 'ethanol effect', whereby ethanol intercalates into intercellular lipids increasing lipid fluidity and decreasing density of lipids which results in increased permeability. This step is followed by 'ethosome effect' it includes inter lipid penetration and releasing the drug.

Advantages and disadvantages [13]

Advantages	**Disadvantages**
• Improved permeation of drug.	• Very low yield
• Increased efficacy and therapeutic index	• Limited for potent drug
• Reduction in toxicity of encapsulated drug	• Chances of skin irritation due to permeation enhancer
• Smaller size and improved pharmacokinetic effect	

Ethosomes are characterized by simplicity in their preparation, safety and efficacy and for their ability of enhancing skin permeation of active drugs. Mittapally *et al* (2016) formulated ethosomal gel of flucanozole and chlorohexidine in combination using 2-3% of phospholipid, 10-30% ethanol, 5% of polyethylene glycol (PEG) and 0.005gm of cholesterol and carbopol 934 (gelling agent). The prepared ethosomal gels were subjected to various physical evaluations in which the diffusion studies have shown that the percentage drug release of optimized ethosomal gel formulation after 3 hours were found to be 98.7% Fluconazole B.P, 95.3% Chlorhexidine B.P. PH was 6.7, viscosity was 40500 cps, zeta potential 23.1 mV and specific size and shape were confirmed by TEM and SEM. From this study they concluded that ethosomes are one of the best delivery systems to deliver the drug via topical with increased skin permeation. [14]

Transferosomes:

Transferosomes are ultra-deformable vesicular carrier composed of phospholipid, surfactant and water for enhancing the delivery by overcoming the barrier function by passing through stratum corneum. The surfactant in the transferosomes helps in solubilizing the lipid present in the stratum corneum and thus increases permeation of the transferosomes. [15]

Mechanism of action

These transferosomes overcome the difficulty of skin penetration by squeezing themselves along the intracellular sealing lipids of stratum corneum. The drug delivery through transferosomes relies on the carrier's ability to widen and overcome the hydrophilic pores in the stratum corneum. Proposed mechanisms for delivering drugs into the skin are

- They act as drug vectors by remaining intact after entering the skin.
- They act as penetration enhancer by disrupting the highly organized intercellular lipids of stratum corneum. [16]

Advantages and disadvantages [17]

Advantages

- They can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter)
- Can act as carrier for both low as well as high molecular weight drug molecules.
- They are biocompatible and biodegradable.
- High entrapment efficiency
- It can accommodate molecules with wide variety of solubility.

Disadvantages

- They are chemically unstable due to oxidative degradation.
- Expensive to formulate.

Transferosomes have been reported to overcome the barrier function of the skin. Hence Mona Quashawy *et al* (2018) designed a transferosomal Gel of Miconazole Nitrate using the thin lipid film hydration technique to increase its skin permeability which helps in treating Candida Skin Infections. The transferosomes prepared were evaluated for entrapment efficiency, particle size and quantity of in-vitro drug release. The optimized transferosomal formulation was incorporated to carbopol 934 gel base and then evaluated for EE% which is in the range of 67.98% to 91.47%, particle size in the range of 63.5nm to 84.5nm and the in-vitro drug release has suggested that prepared MIC transfersomal gel showed higher antifungal activity than Daktarin ® cream 2% which makes miconazole nitrate transfersomes having the high ability to penetrate the skin, overcoming the stratum corneum barrier. [15]

Niosomes:

Niosomes are non-ionic surfactant vesicles, these are microscopic lamellar structures obtained on an admixture of non-ionic surfactant and cholesterol with subsequent hydration in aqueous media. Niosomes have the advantages of chemical stability, high purity, content uniformity, low cost, convenient storage and increased drug bioavailability. [18]

Mechanism of action [19]

Several mechanisms have been suggested to describe the niosomal drug delivery topically as well as transdermally.

i. Niosomes diffuse from stratum corneum layer as a whole.
ii. High thermodynamic activity gradient of the drug at the vesicle-stratum corneum surface is developed due to niosomal interaction with stratum corneum with aggregation, fusion and adhesion to cell surface. This thermodynamic activity gradient is the driving force for penetration of lipophilic drugs across the stratum corneum.
iii. Non- ionic surfactant present in the noisomes act as a permeation enhancer for topical delivery.

Advantages and disadvantages [20]

Advantages

- The vesicles can act as depot to release the drug slowly and offer a controlled release.
- The vesicle suspension is water based system which is better patient compliant over oil based systems.
- These are osmotically active and stable.

Disadvantages

- Fusion and aggregation of niosomes
- Possibility of leakage
- Hydrolysis of encapsulated drug

Niosomes play important role in delivering drug as they are capable of reducing toxicity and modifying pharmacokinetic and bioavailability. SB Shrisand *et al* (2019) formulated ketoconazole niosomal gel by incorporating niosomes prepared by a thin film hydration method using span 60 and cholesterol (1:0.2) with 1% carbopol 934 gel. The prepared niosomes were evaluated for size and shape which were in the range 4.86 -7.38 µm, entrapment efficiency of 55.14-78.63 % and in vitro drug release was up to 72.37 in 24 hours. Niosomal gel was evaluated for in vitro drug diffusion and compared with ketoconazole plain gel and marketed ointment which showed 36.18%, 73.21% and 82.06% of drug respectively at the end of 12 hours, thus proving prolonged action of ketoconazole niosomal gel compared to ketoconazole plain gel and marketed ketoconazole ointment. [18]

Cubosomes:

Cubosomes are nanostructured particles with a bicontinuous cubic liquid crystalline structure which forms colloidal dispersion with water using surfactant. They are self-assembled liquid crystalline particles which possess solid like rheology. Their size ranges from 10-500nm. [21]

Advantages and disadvantages [22]

Advantages

- They are thermodynamically stable for longer time.
- Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.
- Method of preparation is simple and economic.
- It is non-toxic as well as bio-compatible.

Disadvantages

- Presence of large amount of water in the cubosomes is the reason for low entrapment of hydrophilic drugs.
- Large scale production is difficult because of high viscosity.

Cubosomes are the potential technique of nanocarrier to improve the solubility of poorly water soluble drugs. Bachhav *et al* (2017) formulated cubosomal emulgel of ketoconazole for topical application. Cubosomes were prepared by fabrication and emulsification method using Glyceryl monooleate (GMO) 4.4%, poloxemer-407 0.6%, and 1gm ketoconazole in 100% of water and the resulting suspension is mixed with carbopol 2% gel. The resulting cubogel was evaluated for PH, viscosity, particle size, PDI, entrapment efficiency and antifungal activity studies showed that all the parameters were in the acceptable range with PH 6.4-7.5, viscosity 7209cps, particle size 111.7nm with PDI of 0.193, entrapment efficiency of optimized formulation (F3) was 89.03, and antifungal activity showed zone of inhibition of around 18mm which indicates 100% efficacy of ketoconazole cubogel for treating topical fungal infections. [23]

Ufasomes:

Ufasomes are also called as unsaturated fatty acid vesicles. Ufasomes are suspensions of closed lipid bilayers that are composed of fatty acids, and their ionized species (soap) which are restricted to narrow pH range from 7 to 9. In ufasomes, fatty acid molecules are oriented in such a way that their hydrocarbon tails are directed toward the membrane interior and the carboxyl groups are in contact with water. Stable ufasome formulation critically depends on proper selection of fatty acid, amount of cholesterol, buffer, pH range, amount of lipoxygenase, and the presence of divalent cations. [24]

Advantages and disadvantages [25]

Advantages

- Easy penetration of drug in case of topical formulation.
- Cost effective compared to liposome and noisome due to easy availability of fatty acid.
- High drug entrapment.

Disadvantages

- Stability problem for fat based drug substances.
- Atherosclerosis
- Some of the oxidation by-product tends to be rather toxic in biological system.

Investigators have also explored the potential of fatty acid vesicles (ufasomes) for the topical delivery of clotrimazole. They are oleic acid vesicles and are prepared using a thin film hydration method. Further, characterization of these prepared vesicles exhibited many important properties. Transmission electron microscopic (TEM) images confirmed the formation of vesicular dispersion (ufasomes) of clotrimazole. Oleic acid vesicles possessed high drug entrapment (49.5 ±1.0%) and optimum size (455± 22 nm) along with good colloidal characteristics (polydispersity index= 0.210 ± 0.035 & zeta potential = - 22.45 ± 0.25 mv) at 4:6 drug-to-oleic acid ratio. *In-vitro* drug release study showed sustained release of drug from the vesicular dispersion. Skin permeation and skin retention studies suggested accumulation of drug in the epidermal part of the skin. *In-vivo* study confirmed prolonged release of drug from oleic acid vesicle up to five days indicating its usefulness for long-term therapy. These results from the present study proposed ufasomes to be a good approach to treat topical fungal infections, suggesting further explorations. [26]

NANOPARTICULATE SYSTEMS.

Solid lipid nano particles:

These are spherical particles in the nanometre range, constituted of physiological and biodegradable lipids, such as stearic acid (SA), of low toxicity and generally obtained by high pressure homogenization or microemulsion methods. The main advantage of SLNs is its lipid matrix, being constituted by physiological lipids, decreases the risk of toxicity. [27]

Advantages and disadvantages [28]

Advantages

- They have better control over release kinetics of encapsulated compounds.
- High and enhanced drug content.
- Excellent biocompatibility.
- Improved stability.

Disadvantages

- Particle growth.
- Unpredictable gelation tendency.

Solid lipid nanoparticles (SLNs) are very potential formulations for topical delivery of antifungal drugs. Hence S. El-housiny *et al.* (2017) formulated Fluconazole (FLZ)-loaded SLNs topical gel to improve its efficiency for treatment of Pityriasis Versicolor (PV). FLZ SLNs were prepared by modified high shear homogenization and ultra-sonication method using different concentration of solid lipid (Compritol 888 ATO, Precirol ATO5) and surfactant (Cremophor RH40, Poloxamer 407). The optimized FLZ-SLN formula was incorporated into gel using Carbopol 934. A randomized controlled clinical trial (RCT) of potential batches was carried out on 30 well diagnosed PV patients comparing to market product Candistan ® 1% cream. The evaluation parameters such as drug entrapment efficiency ranged 55.49% to 83.04%. The zeta potential values lie between -21 and -33 mV presenting good stability. FLZ showed prolonged in vitro release from SLNs dispersion and its Carbopol gel following Higuchi order equation. This study suggest that the developed FLZ loaded SLNs topical gels have superior significant fast therapeutic index in treatment of PV over commercially available Candistan ® cream. [29]

Nanosponges

The nanosponges are a three-dimensional network of polyester that are capable of degrading naturally. These polyesters are mixed with a cross linker in a solution to form Nanosponges. Here, the polyester is generally biodegradable, so it breaks down in the body moderately. Once the network of nanosponges breaks down it releases the drug molecules which is loaded, in a derogatory fashion. [30]

Advantages and disadvantages [31]

Advantages

- Nanosponges are stable over the pH range of 1 to 11
- These are stable at the temperature up to 130^0 C
- Polyester used here is biodegradable.
- This drug delivery system is non-irritating, non-mutagenic and non-toxic.

Disadvantages

- They have the capacity of encapsulating only small molecules but not large molecules.
- Dose dumping may occur sometimes.

Anjali S. Kumar *et al.,* formulated Clotrimazole nanosponges for topical delivery. Nanosponges were prepared using ethyl cellulose as polymer and PVA as surfactant by an emulsion solvent diffusion method. The prepared nanosponges were formulated to hydrogels using carbopol 934 as a gelling agent. The mean particle size of all nanosponge formulations was found in the range of 561-701 nm. Surface morphology of optimized nanosponges was evaluated by scanning electron microscopy and concluded that nanosponges were spherical in shape and uniform in size and its surface was porous in nature. The nanosponge based gel were estimated for pH, viscosity, spreadability, in vitro drug release and the results of optimized formulation F4 were found to be 5.9 ± 0.02 in pH, and % drug release at 12^{th} hour was found to be 91.73 ± 0.45. Based on the observations the optimized formulation was safe and effective for topical use as Clotrimazole nanosponge loaded hydrogel and shows a controlled release effect with reduced side effects. [32]

CARBON NANOTUBES

These are tube shaped material made up of carbon. Its diameter is too small which is measured in nanoscale. The inner core of the carbon nanotubes can be filled with drugs or drug can also be adsorbed on to the surface of carbon nanotubes. [33]

The development of nanobiotechnologies provides novel potential drug delivery systems that make use of nanomaterials such as functionalized carbon nanotubes (f-CNTs), which are emerging as an innovative and efficient tool for the transport and cellular translocation of therapeutic molecules. Benincasa *et al*. (2011) studied antifungal activity of Amphotericin B conjugated to carbon nanotubes. In this study, they prepared two conjugates between f-CNTs and AMB. The antifungal activity of these conjugates was compared to that of Amphotericin B (AMB) alone or Amphotericin B with sodium deoxycholate (AMBD). Measured Minimum Inhibition Concentration (MIC) values for f-CNT-AMB conjugates were better than those displayed by AMB and AMBD. [34]

SILVER NANOPARTICLES

These are the class of materials with size range 1-100nm.These are specifically used in agriculture as well as in medicines as antibacterial, antifungal and antioxidants. Silver nanoparticles have unique properties in terms of toxicity, surface plasmon resonance and electrical resistance.

Silver nanoparticles produce reactive oxygen species and free radicals which cause apoptosis leading to cell death preventing their replication. Since silver nanoparticles are smaller than the microorganisms, they diffuse into cell and rupture the cell wall. [35]

Since ancient times it was known that silver and its compounds were effective antimicrobial agents but their effect against fungal pathogens was unknown. Hence, Kim *et al*. synthesized silver nanoparticles (nano-Ag) to investigate its antifungal activity on fungal pathogens on the skin. Antifungal susceptibility study was conducted on six fungal species as follows C. albicanns, C. tropicalis, C. glabrata, C. parapsilosis, C. krusei and T. mentagrophytes. In this study amphotericin B and fluconazole were used as a positive control toward fungi, in which nano-Ag exhibited similar activity with amphotericin B but more potent activity than fluconazole. Thus the present study indicated nano-Ag have considerable antifungal activity, deserving further investigation for clinical applications. [36]

COLLOIDAL CARRIERS

MICROEMULSIONS

Micro emulsions are clear, stable, isotropic liquid mixtures of oil, water and surfactant in combination with a cosurfactant. Compared to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The two basic types of microemulsions are o/w type and w/o type. [37]

Advantages and disadvantages [38]

Advantages

- It enhances the solubility of poorly water soluble drugs.
- High absorption and diffusion rates compared to other solvent systems without surfactants.
- It acts as a penetration enhancer and a well as taste masking agent.

Disadvantages

- Large concentration of surfactant and cosurfactant is required for stabilizing droplets of microemulsion.
- Toxicity due to large concentration of surfactant.

Microemulsions have been proved to increase the cutaneous absorption of both lipophilic and hydrophilic medicaments compared to other delivery systems. Patel *et al*. has worked on developing microemulsion based drug delivery system of anti-fungal agent Itraconazole via topical route. The microemulsion was optimized using 3^2 full factorial designs and was prepared by the spontaneous emulsification technique. The mean droplet size of the optimized microemulsion (ME7) was found to be 298.3 nm with PDI of 0.090, zeta potential of - 4.20 mV, viscosity of 96.5cps and pH of 7.40. The in-vitro diffusion study showed that optimized formulation was having highest drug release at the end of the 6^{th} hour with 98.74% and in-vitro antifungal activity showed that optimized formulation was having highest zone of inhibition with 3.5 cm compared to marketed product with zone of inhibition 2.8cm which proves that microemulsion successfully increased the permeation of the Itraconazole. [39]

Jadhav *et al* formulated and evaluated antifungal non-aqueous microemulsion for topical drug delivery of griseofulvin. This non-aqueous microemulsion system is obtained with glycerine and olive oil stabilized with glycerol monosterate with cosurfactant. Pseudo ternary phase diagram was constructed to determine the microemulsion region. Further characterization of microemulsion resulted in pH of 5.0-5.5 which was similar to normal skin pH. Viscosity 9857.467 cPs which is suitable for topical application. The globule size was in the range 5.59-33.63nm. *In-vitro* drug release at 7^{th} hour was only 5.55% which concludes that non aqueous microemulsion was showing sustained release. This has proved that microemulsion can improve stability of griseofulvin in addition it also showed enhancement in skin retention of the griseofulvin. From the above studies they concluded that nonaqueous microemulsion can be used as vehicle for the water sensitive materials. [40]

NANOEMULSIONS:

Nanoemulsions are submicron sized colloidal particulate systems considered as thermodynamically and kinetically stable isotropic dispersions, which consist of two immiscible liquids like water and oil, stabilized by an interfacial film consisting of a suitable surfactant and co-surfactant to form a single phase. They have the droplet size which ranges from 50 to 1000nm. [41-42]

Advantages and disadvantages [43]

Advantages

- Increased rate of absorption.
- Helps in solubilizing lipophilic drug.
- Increased bioavailability.
- Improved efficacy and minimal side effects.

Disadvantages

- Toxicity due to surfactants
- Stability is dependent on environmental parameters such as pH and temperature.

Ravi Shankar *et al* designed and developed nanoemulsion of ketoconazole for solubility enhancement to treat fungal infections via topical delivery. Nanoemulsion was formulated by aqueous titration method using myritol 318 as oil, kolliphor HS 15 as surfactant and PEG 200 as co-surfactant. Pseudo-ternary phase diagram was constructed on triplot software to identify nanoemulsion area using different concentrations of oil, Smix (surfactant and co- surfactant) and water. The optimized formulation was having a particle size of 627.5nm and zeta potential of -15.4mV, pH was found to be 7.3 ± 0.057, and in-vitro diffusion study showed 86.33% drug release within 5hrs. This study revealed that nanoemulsion can be formulated to increase the solubility of BCS class II drug for topical drug delivery. [44]

Jyotsana suyal *et al* designed and developed nanoemulsion of Itraconazole which lead to higher dissolution rate and improved bioavailability. The nanoemulsion was prepared by solvent displacement method and characterized for droplet size, polydispersity index, drug content, entrapment efficiency, and % cumulative release and the results were found to be 318.43nm, 0.436, 55.46, 32.55 % and 95.92 % respectively. This study showed that lipid based nanoemulsion can be formulated to enhance the oral bioavailability by enhancing drug solubility. [45]

EMULGEL

Gels have many advantages but a major limitation is delivery of hydrophobic drugs. So to overcome this limitation, an emulsion based system is being used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. When gels and emulsion are used in combined form the dosage form are referred as emulgel. [46]

Advantages and disadvantages [47]

Advantages

- Avoidance of first pass metabolism.
- Ability to easily terminate medication when needed.
- Controlled release.
- Incorporation of hydrophobic drugs.

Disadvantages

- Skin irritation on contact dermatitis.
- Drug of large particle size not easy to absorb through the skin.
- Possibility of allergic reactions.

Salunkhe Pranali *et al* developed an emulgel using gelling agent carbopol 934. Span 20 and tween 20 used as emulsifiers. Propylene glycol used as a penetration enhancer. Methyl paraben and propyl paraben used as a preservative and Ketoconazole as hydrophobic drug. All the formulation designed and evaluated for the post formulation studies like colour, pH, viscosity, spreadability, Extrudability, drug content, In-vitro drug diffusion and Antifungal studies. The optimized formulation showed drug content of 81%, spreadability and extrudability was found to be 27 g.cm/sec and 13gm/cm^2 respectively. The pH was in the range of 6 to 6.4. Viscosity 2346 Cps. Drug release was found to be 68.91%. Antifungal activity for Aspergillus Niger shown 0.4-0.6 cm zone of inhibition. From the In – vitro drug diffusion study they concluded that the Emulgel prepared from Carbapol 934, controls the drug release for longer period of time which will be helpful. [48]

CONCLUSION

Cutaneous fungal infections are the infections of the skin, hair and nails which cause pathological changes in the host. These infections when left untreated or poorly treated leads to certain degree of fungal penetration into the skin tissue which may even lead to some secondary systemic disorders. A variety of conventional topical dosage forms which helps in treating or eradicating these infections have certain drawbacks. These drawbacks can be overcome by amending the drug related and dosage form related properties. Topical treatment is the highly preferred approach for the treatment of cutaneous fungal infections because of their superior properties like drug localisation at the site of infection and avoidance of systemic side effects which makes compliance with patient as well. The major drawbacks in conventional topical dosage forms include poor skin permeation and high dosing frequency which are leading to reduction in effective against cutaneous fungal infections. However to overcome these drawbacks and to increase the effectiveness of antifungal drugs certain novel strategies have been discussed in this review which includes nanoparticulate carriers, vesicular systems and colloidal carriers. In this review, these novel delivery systems which are emerged as an effective and prolonged therapeutic action of antifungal drugs have been highlighted and discussed in detail.

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Conflict of Interest

The authors declare No conflict of Interest.

List of abbreviations

ITZ : Itraconazole
µm : micro meter
w/w : weight by weight
PEG : polyethyleneglycol
TEM : Transmission electron microscopy
EE : Entrapment efficiency
MIC : Minimum inhibitory concentration
Nm : nanometer
PDI : Polydispersity index
Mv : mili volts
FLZ : Fluconazole
PV : Pityriasis Versicolor
AMBD : Amphotericin B with sodium deoxycholate
cPs : centipoise

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