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BIFONAZOLE LOADED NOVEL DRUG DELIVERY SYSTEM- A REVIEW

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ABSTRACT
Bifonazole is an imidazole antifungal agent used to treat various fungal infections. This review aims to provide an overview of bifonazole loaded novel drug delivery system includes cubosomal, microemulsion and microsponges, solid lipid nanoparticles, transethosomal, multiple emulsion, organogel, nanosponges, emulgel, film forming gel, multiple emulsion based hydrogel, tranferosomal. Clinical efficacy of topical antifungal therapy depends on the drug ability to penetrate into the stratum corneum (SC) and the duration of treatment. Thus, topical novel drug delivery system of bifonazole with increased bioavailability will be favourable for the treatment of fungal infections and symptomatic relief. Bifonazole-loaded novel drug delivery systems aim to enhance the efficacy, safety, and patient compliance of bifonazole treatment.

KEYWORDS: Bifanozole, Antifungal, cubosomal, efficacy.

INTRODUCTION[2]
Superficial mycosis are caused by fungi that are limited to the outermost layer of the skin, incidence are increasing nowadays especially in immunosuppressive patient. When fungal infection extend deeper into the skin epidermis known as cutaneous mycosis or dermatomycosis they also involve to hair and nails unlike superficial mycosis the cutaneous mycosis causes cellular immune response.

Cutaneous mycosis causing fungi- dermatophytes belongs to family Mycosporum, Tricophyton and Epidermophyton that cause tinea carporis, tinea pedis.

If the infection further extend into the dermis and subcutaneous tissue it is known as subcutaneous mycosis ex: sporotrichoss.

The tropical agents used to treat the skin fungal infection are usually formulated as the lotion or gel since the side effects of the fungal agents applied tropically are less compare to the oraladministration.

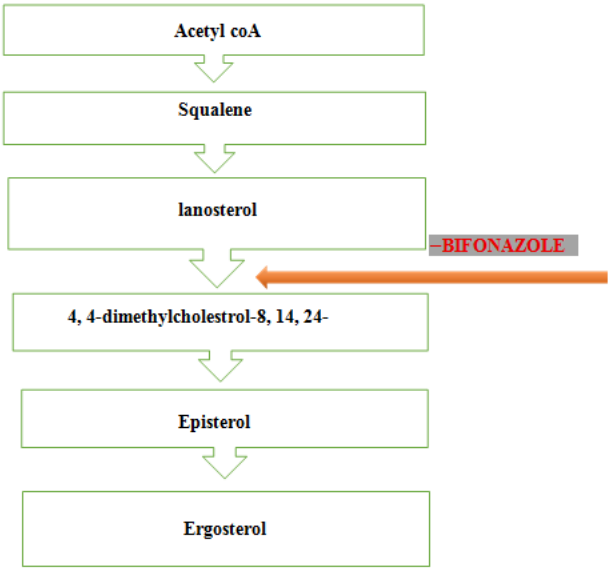
Bifonazole (BFZ), 1-[phenyl(4-phenylphenyl) methyl]-1H-imidazole, is a substituted imidazole antifungal agent having a broad spectrum of activity against dermatophytes, moulds, yeasts, dimorphic fungi and some Gram-positive bacteria. BFZ is indicated in the treatment of superficial fungal infections of the skin such as dermatophytes, cutaneous candidiasis and pityriasiss versicolor. It is practically insoluble in water with a very short half‐life of 1-2 h and is minimally absorbed (0.6% of applied dose) following dermal application.

CLASSIFICATION[3]
1. Therapeutic category: Antifungal 2. harmacological class: Imidazole Indications indication[3]

1. Topical treatment of
- Athlete's foot (tinea pedis)
- Jock itch (tinea cruris)
- Ringworm (tinea corporis)
- Skin candidiasis

2. Treatment of fungal nail infections (onychomycosis)
3. Vaginal yeast infections (candidiasis)

MECHANISM OF ACTION[4]
Bifonazole inhibits fungal ergosterol synthesis, disrupting cell membrane integrity and leading to fungal cell death.



PHARMACOKINETICS[5]

Bifonazole has low systemic absorption, with most of the applied dose remaining at the siteof application.

BIFONAZOLE IN NOVEL DRUG DELIVERY SYSTEM[6]

Bifonazole loaded novel drug delivery system has increased like Nanoparticles which is lipid- based, polymeric, or metallic nanoparticles can encapsulate bifonazole, enhancing its topical delivery and targeted efficacy, Liposomes which improve bifonazole's skin penetration, reduce systemic absorption, and enhance its antifungal activity, Hydrogels this provide controlled release of bifonazole, improving its topical delivery and reducing side effects, and microemulsions which will enhance bifonazole's skin penetration, improve its antifungal activity, and reduce systemic absorption.

This novel drug delivery system of bifonazole is advantages in improved efficacy, which leads to enhances skin permeation, targeted delivery and controlled release can improve bifonazole antifungal efficacy. They reduce the side effects by reducing systemic absorption and improved patient compliance. They are more convenient easy to use formulations can improve patient adherence to treatment regimens.

BIFONAZOLE APPLICATION

1. Topical Delivery: Bifonazole is used to treat superficial fungal infections. Novel deliverysystems, such as nanoparticles, liposomes, and hydrogels, can enhance its topical delivery, improving efficacy and reducing side effects.
2. Targeted Delivery: Bifonazole can be encapsulated in targeted nanoparticles, which can selectively bind to fungal cells, reducing off-target effects and improving treatment outcomes.
3. Controlled Release: Novel delivery systems can provide controlled release of bifonazole, maintaining therapeutic concentrations over an extended period, and reducing the frequencyof applications.
4. Enhanced Penetration: Bifonazole can be formulated with penetration enhancers, such as liposomes or nanoparticles, to improve its skin penetration and reach deeper fungal infections.

MICROSPONGE AND MICROEMULSION[1]

This research is based on invitro antifungal activity of two different bifonazole formulation i.e, microsponges which are tiny, spherical, polymeric particles that consist of interconnecting voids and microemulsion which are fluid system obtained by titration to point of ordinary milky emulsion by addition of medium chain alcohol.

Composition of bifonazole loaded microsponge based gel.

Ingredients	Quantity(%w/w)
BFZ(entrapped microsponges, equivalentto)	1
Propylene glycol	40
Carbopol 940	1
Methyl paraben	0.18
Propyl paraben	0.02
Tri ethanol amine	q.s
water	q.s 100

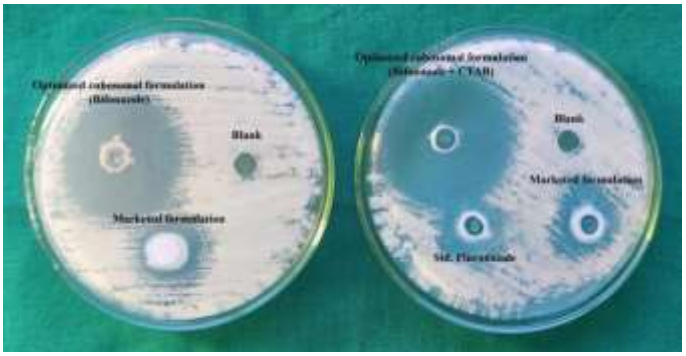
Composition of bifonazole microemulsion based gel.

Ingredients	Quantity
Oil%	3
Smix%	24
Water%	71
Drug%	1
Xanthan gum%	1

In vitro antifungal susceptibility test was performed for the above two formulations by cup plate method and it was compared with the marketed product, microsponge based gel and microemulsion based gel showed 4.10+0.07 and 4.3+0.5 where marketed formulation had zone of inhibition 3.5+0.45 which is less than the prepared formulation.

CUBOSOMA[7]

The study focused bifonazole loaded cubosomal gel which is the topical antifungal agent the aim is to increase the permeability and reduce the side effects. The bifonazole loaded cubosomal was prepared by top-down method and it was optimised by using 3^3 box-behnken experimental design consist of independent parameter glyceryl monooleate, polaxomer 407 and cetyl trimethyl ammonium bromide with dependent variable particle size, zetapotential and entrapment efficiency. The optimised formulation showed a particle size of 170nm zetapotential of 26.64 Mv and entrapment efficiency 80.45%. The optimised gel has shown higher antifungal activity when compared to marketed formulation.



This shows that zone of inhibition in optimised cubosomal formulation is higher as compared to marketed formulations.

HYDROGEL[8]

In this research total 10 batches of bifonazole (1%w/w) hydrogel formulations were prepared by using two different polymers i.e., HPMC K100M and chitosan. SLS, PEG 400, and oleic acid were used as permeation enhancers. Methyl paraben and propyl paraben are used as a preservatives. Prepared hydrogel evaluated for ph., viscosity, rheology, spreadability, drug content, in-vitro diffusion studies, ex-vivo skin permeation studies, release kinetics studies andshort term stability studies. All batches of gel formulation shows the uniform homogeneity and spreadability. The physical appearance of the gel formulations was white translucent in nature. ph of the gel formulation was suitable for topical application. Highest percentage of drug release and permeability was achieved from formulation F8.

Thus, permeation enhancer based bifonazole hydrogel formulations was effectively produced to boost the release of the drug and permeability.

MULTIPLE EMULSION[9]

An efficient bifonazole(BFZ) multiple emulsion with increase skin retention & decreased skin permeability to achieve good antifungal action over the conventional cream formulation was formulated & its evaluation revealed better pseudoplastic shear thinning behaviour for good retention. The amphoteric & non-ionic surfactant combination decreased its penetration which is advantages in reducing the frequency of application, with harmless effects to skin were analysed.

ORGANOZEL[10]

Bifonazole organozel was formulated as topical drug delivery system using sorbitan monostearate. Totally seven formulation was developed & evaluated the rheological property, appearance, texture, viscosity, pH, & gelling capacity including drug content. From this formulation BF4 containing 10% sorbitan monostearate showed prolong release 83.92% at end of 8hrs, which was stable.

NANOSPONGES[11]

Bifonazole loaded nanosponges in hydrogel for antifungal treatment were developed using emulsion solvent diffusion tectnique. These formulation was evaluated and shown increasedefficiently& safety due to encapsulation of both the hydrophilic & hydrophobic drug in nanosponges.

Particle size = 183.7-506.2nm

Zeta potential= 17.77-21.9Mv

Surface= spherical & porous.

Drug entrapment efficiency= 45.44-99.71%

EMULGEL[12]

The emulgel are emulsion combined with gelling agent which shows dual action, where the bifonazole incorporated emulgel 6 formulation was prepared using varing different amount of carbomer 941, lipuid paraffin, span 20, tween 20, propylene glycol showed accepted diffusion, rheological properties & physical appearance.

TRANSETHOSOMAL GEL[13]

Bifonazole-loaded transethosomal gel showed better permeation through the and effective in antifungal activity.

* This study was intended to develop and optimize the transethosomal gel of Bifonazole forthe treatment of fungal infection.
* For the optimization purpose, Box-Behnken Design was used.
* Concentration of excipient substance were selected as independent variables on vesicle size, Polydispersity index and entrapment efficiency.
* Transmission electron microscope was used to study the surface of the drug particles.
* Gel was prepared by cold method. The optimized transethosomes were incorporated into % Carbopol 940 gel.
* Prepared gel was evaluated for pH (by using electric pH meter), Spreadability (by using wooden block), Viscosity test (by using brookfield viscometer), Invitro drug release, invitropermeation test (by using foat skin), Antifungal activity (by using cup plate method).
* PH of the prepared gel should be compatible with skin pH (4.5 to 5.5).
* Spreadability range should be 5 to 7.
* Invitro drug release study and Invitro drug permeation study shows that Transmethosomal gel was more effective in rate compares to convinient gel.

SOLID LIPID NANOPARTICLES[2]

Solid lipid nanoparticles (SLNs) are colloidal carrier systems developed in the beginning of 1990s as alternative to existing pool of carrier systems such as particles, liposomes and polymeric nanoparticles for the delivery of poorly water soluble drugs. SLNs combine their advantages such as controlled release, biodegradability, and protection of active compounds1-3. SLNs have been used in topical delivery as they can allow penetration of drug into the skin, offer sustained release of drug to avoid systemic absorption. The system also reduces irritation to the skin as they are made up of biocompatible excipients most of them have been in an approved status or are excipients used in commercially available cosmetic or pharmaceutical preparations. Bifonazole (BFZ), 1-[phenyl (4-phenylphenyl) methyl]-1H- imidazole, is a substituted imidazole antifungal agent having a broad spectrum of activity against dermatophytes, moulds, yeasts, dimorphic fungi and some Gram-positive bacteria. BFZ is indicated in the treatment of superficial fungal infections of the skin such as dermatophytes, cutaneous candidiasis and pityriasis versicolor.

1. **Drug content:** nanoparticle equivalent to 10 mg of Bifonazole was taken in 10 ml volumetric flask containing 5 ml ethanol and stirred for 30 min. Volume was made up to 10 ml with ethanol. From the above solution, 1 ml was further diluted with 10 ml ethanol to get 100µg/ml.
2. **Particle size:** Particle size and size distribution measurement of Nanoparticle was carriedout by dynamic light scattering using Malvern Hydro 2000 SM particle size analyzer (Malvern instruments, UK). Nanoparticle was added to the sample dispersion unit with stirrer, and stirred so as to minimize the particulate aggregation by inter particle interaction.
3. **Solubility of drug in optimized nanoparticle:** 2 g nanoparticle were taken, excess amountof drug was added into it. This composition was mixed for 72 hrs. On mechanical shaker. Centrifuge it, separate the supernatant layer make dilutions with ethanol.
4. **Stability study of nanoparticle:** Stability testing evaluates a products ability to maintain its original aesthetic, physical and chemical characteristics under controlled conditions designed to accelerate aging. The stability studies were carried out for the selected formulations which were placed in lacquered collapsible aluminum tubes. These tubes were subjected to room temperature for 2 months and then the transparency/ clarity, color change, viscosity and appearance was determined.

FILM FORMING GEL[14]

This research is based on formulation and evaluation of film forming agent of bifonazole forlocal drug delivery. Tenia pedis is superficial skin fungal infection mainly occurs in athlete's foot. Bifonazole is a broad spectrum imidazole antifungal used in tenia pedis and possess high resistance towards fungus. It is an effective and well tolerated treatment for superficial fungal infections. In the treatment of skin fungal infections, the antifungal agent requires to be present at the site of infection for longer period of time. Film forming gel makes transparent film on the skin and provides the delivery of Bifonazole for prolonged period of time. So, this reduces duration of therapy and improves the patient compliance. Eudragit RL (PO) as a film forming polymer, HPMC K100M as a gel forming agent and Triethyl citrate as a plasticizer were selected. It was concluded that drug was compatible with all excipients from FTIR study. % Drug diffusion and Tensile strength were taken as dependent variable. The prepared film forming gel was evaluated for all parameters including mechanical properties and % drug diffusion. The optimised formulation shows.

Tensile strength- 0.875 N/m^2

% Drug diffusion- 96.09 at 12 hour

Stability study of optimized formulation showed that formulation was stable at acceleratedcondition.

TRANSFEROSOMAL[15]

Bifonazole is a class 4 drug which is low solubility and low permeability. The presence study was performed to improve the permeability of bifonazole by loading it into one of the best vesicular system known as transferosomes which has ultra-deformable flexibility. 12 formulation was prepared by reverse phase evaporation method using soya lecithin, span 60, span 80, and tween 80.The ratio 2:1 and 4:1 of soya lecithin and span 60 shows highest drug release of 75.905 and 94.8% respectively. It has acceptable range of zeta potential.

MICROEMULSION BASED HYDROGEL[16]

Microemulsion based hydrogel incorporated with bifonazole was prepared successfully HPMC K100M (2%) as gelling agent to import viscosity to the preparation which increase the resident time, increase solubility and increase skin permeability. The drug release from system was observed to follow zero order kinetics .They are considered as a market comparable. It has been concluded that microemulsion based hydrogel (F5) has potential forsustained action of drug release and promising vehicle for topical delivery.

CONCLUSION

Bifonazole is an effective and safe antifungal agent for the treatment of superficial fungal infections. Its broad-spectrum activity, low systemic absorption, and favorable safety profilemake it a valuable treatment option.

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