Review Article

Nanomicelles Formulation: *In Vitro* Anti-Fungal Study

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ABSTRACT

Fungal infections of the skin are one of commonly faced diseases in worldwide. Topical therapy is more advisable choice for the treatment of these fungal infections. The physiological characteristics of drug molecules and types of the formulations are one of the effective factors in topical drug delivery. Nanoformulations is an emerging platform for the penetration of drugs through the targeted layers of the skin at their effective concentrations. Nanomicelles are one of the novel formulation strategies for the convenient delivery of antifungal agents into the receptive sites. Nanomicelles can be prepared by simple dissolution method, dialysis method, oil in water type method, solvent evaporation and lyophilisation method. This review mainly focuses on the various strategies of nanomicelles for the delivery of antifungal agents. Topical drug delivery through nanomicelles can be carried out by incorporating drug into the polymer and in the form of micellar gel etc. This concluded that these strategies are developed ways of nanomicelles for the antifungal drug delivery.

Keywords: Nanomicelle, Antifungals, Micellar gel.

INTRODUCTION

Every year many people was suffering from fungal infections. 25% of world population was reported with risk of developing fungal infections[1]. Fungal infections disturbs various parts of our body such as eye, nails, skin or main organs. The warm and moist condition of skin provide suitable environment for fungal growth. In addition diseases such as cancer, diabetes and HIV/AIDS increases the rate of superficial fungal infections in effective drug administration encompasses the optimal delivery of therapeutics at the site of action within the given time frame. However, owing to frequent with antifungal drugs, topical delivery is one of the appropriate route for effective delivery[2]. Topical antifungal therapy needs high drug amount at the site of action, that is in the stratum corneum, hence reduces unwanted side effects, avoids hepatic first pass metabolism, gastric pH variations etc..[3] In treating skin diseases, the central purpose of applying drug to the skin is to induce local effect at the site of application.

Hydrophilic drugs are mostly diffuse through the corneocytes along with the keratinous fibers in the stratum cornem, by the transcellular route while lipophilic drugs tends to diffuse through the lamellar lipid structure in between the cells. In the stratum corneum hydrophilic drugs show low permeability whereas for a greater extent they do not partition to the lipohilic domains of the intercellular pathway. On the other hand, highly, lipophilic drugs can readily partition in to stratum corneum, but they cannot diffuse easily in to the hydrophilic viable epidermis. This can slow down the diffusion process and can lead to an enhancement of the drug at the interface stratum corneum and stratum granulosum where drug with hydrophilic and lipophilic moieties are less problematic as they can partition hydrophilic as well as into lipophilic domains. [4]

Nanotechnology is the field of art and science to operate the matter at the nanoscale to create a new special materials and products with enormous potential to change community. Novel drug delivery system (NDDS) assign to the approaches, technologies, and systems for carrying a pharmaceutical compound in the body as required to safely accomplish its therapeutic effects. One of the most promising drug delivery systems for enhancing skin permeation of drugs is colloidal drug carriers such as microemulsion, vesicular carriers (including liposomes, ethosomes, niosomes), nanomicelles, lipidic and polymeric particulate carrier systems etc. At the infection site, such formulation has the potential to provide local drug concentrations without significant systemic distribution[5].

Nanomicelles are nanosized (usually with particle size within a range of 1 to 10nm) colloidal dispersions which are self-gathering, with a hydrophobic core and hydrophilic shell. Because of its low toxicity, it is convenient for fungal infections. Nanomicelles will also increase the solubility and thereby increases the penetration of drugs. In aqueous solution amphiphilic block copolymer can self-assemble into nanoscale micelles and can be used to encapsulate hydrophobic drugs due to its core structure and drug loading capacity[6]. Amphiphilic copolymer micelles will promote the skin permeation and deposition of drug due to good surface activity.

Advantages of Nanomicelle

1. Carriers for solubilizing hydrophobic drugs
2. Ability to prevent or minimize drug degradation
3. Lower adverse side effects
4. Improve drug permeation
5. Minimal or no irritation,
6. Enhanced ocular bioavailability

Mechanism of Antifungal Drugs

Fungal infection usually caused by decrease in the human defense and also due to heavy exposure with fungus. When fungi enter the skin surface, by desquamation they invade the stratum corneum to avoid being shed from the skin surface. So, the treatment of fungal infection is beginning with topical agents that can penetrate stratum corneum cells. Antifungal agents are mainly work by exploiting difference between mammalian and fungal cells to kill the fungal organism without causing dangerous effects on the host. Antifungal agents are mostly applied to the topical surface for the treatment of the infection of mucous membrane, nails or skin by Candida, dermatophyte fungi including epidermophyton, trycophyton etc.. Antifungal agents used in prophylactic regimen or to prevent relapse[7].

Preparation Methods of Nanomicelles

Nanomicelles can be prepared by various methods which are divided into major groups including simple dissolution method, dialysis method, oil in water emulsion, solvent evaporation method and lyophilization or freeze drying method.

i. Direct dissolution method

This method is for micelle preparation from copolymers having high water solubility. It includes dissolving drug and blocks the copolymers directly in the aqueous media. This method is employed for moderately hydrophobic polymers such as poloxamers and formulates polyion complex micelles.

ii. Dialysis method

This method is employed for the micelle preparation from amphiphilic copolymers with low water solubility. The drug loading procedure is also useful for copolymers which require common organic solvents to solubilise. In the case of water miscible organic solvents, the copolymers mixture can be dialyzed against aqueous medium to produce micelles due of the organic solvents.[8]

iii. Solvent evaporation method

In this method both the copolymers and active agent are dissolved in a common solvent or the mixture of the miscible solvents. The drug copolymers film is formed upon stirring and drying the mixture. Micelle is spontaneously formed when the film is reconstituted with warm water or buffer. The samples may be sonicated or passed through a high pressure extruder to prevent multimodal size distribution.

iv. Lyophilisation method

This method is to formulating micelles by the dissolution of both the copolymers and the drug in a mixture of aqueous and organic solvent. Dimethylacetamide and tert-butanol have generally employed as a copolymer because of their high vapour pressure which offers by the rapid sublimation followed by lyophilisation. The micelles also demonstrate adequate shelf-life along with high water dispersibility.[9]

Antifungal Drugs Formulated as Nanomicelle

Topical therapy is a most relevant choice for the treatment of the cutaneous infections. In the clinical treatment of local and systemic fungal infections azoles are the most commonly used antifungals. Commonly used antifungal drugs that can be formulated to nanomicelle is as follows:

- Clotrimazole
- Miconazole nitrate
- Econazole
- Fluconazole
- Sertaconazole
- Amphotericin B
- Itraconazole
- Nystatin
- Isavuconazole
- Voriconazole
- Posaconazole
- Ketoconazole
- Griseofulvin
- Terbinafine

NANOMICELLES IN DRUG DELIVERY APPLICATION

i. Formulations of antifungal agents

There is a need for safe and effective modalities for delivering therapeutic agents to treat fungal infections. Due to the low solubility and sometimes high toxicity of these agents provide a greater challenge for the delivery. These agents successively incorporated into polymer that is by formulating these agents into nanomicelle will cause an enhancement in the solubility and also the permeability. They are less toxic and bioavailability are seemed to be high.[10,11]

ii. Chemotherapy of cancer

A series of pioneering studies by kataok's group used polymeric micelles for passive targeting of various anticancer agents and chemotherapy of tumours.[12]

iii. Drug delivery to brain

There is a restriction to target the brain due to presence of blood brain barrier which represent a formidable impediment for the treatment of brain tumour, stroke etc..

so in order to achieve therapeutic response either carryout the modification of polymeric micelles with antibodies or ligand molecules which are capable for trancytosis or use pluronic block co polymer to inhibit the drug efflux system and increase the permeability through blood brain barrier.[13]

iv. Delivery of imaging agents

Efficient delivery of imaging agents to the sites of diseases in the body can improve early diagnosis of cancer and other diseases. The studies in this area using polymer micelles as carriers for imaging agents were initiated by the group of Torchilin.[14] Polymer micelles loaded with various agents which are used for gamma, magnetic resonance, and computed tomography imaging represent promising method for non-invasive diagnostics of various diseases.

v. Delivery of polyneucleotides

These systems used for intravitreal delivery of an antisense oligonucleotide and suppression of gene expression in retina.[15]

vi. Ocular drug delivery

Nanomicelles are one of the convenient formulation for the drug delivery to back of the eye disorders such as age related macular degeneration, diabetic retinopathy, diabetic macular edema and posterior uveitis. This provide higher uptake in ocular tissues, glands and were well tolerated in patients[16].

Strategies for Development of Antifungal Agents

The nanomicellar drug delivery platform appears to be potential pharmaceutical carrier for topical administration of hydrophobic drugs.

Feilong Zhou et.al concluded that α-linoleic acid modified pluronic 127-cs copolymeric micelles are used for the skin targeted delivery of amphotericin B. It was obvious that the drug loaded micelles were much effective for topical delivery of AMB. The prepared micelles showed higher skin deposition, negligible skin irritation and better in vitro / in vivo antifungal activity with improved AMB solubility as compared to commercial AMB gel or injection. He proved that prepared nanomicelles was much better fungal skin infections.[17]

Ghareb M Soliman et.al was developed poly(ethylene glycol)- block-poly(ε caprolactone) nanomicelles for the solubilisation and enhancement of antifungal activity of sertaconazole. Drug was incorporated by co-solvent evaporation method and micelle size, drug loading capacity, drug release properties were analyzed. Antimicotic studies showed that nanomicelle incorporated sertaconazole was shown higher activity than drug alone against *fusarium miscanthi* and *microsporium Canis.*[18]

Vigyan singh et.al were formulated miconazole loaded micellar gel for improved topical delivery. MCN was entrapped into the micelles at CMC by dialysis method and its entrapment efficiency, micelles size, cumulative drug permeation was determined. This study concluded that the prepared micellar loaded gel have high permeability and used for the treatment of deep seated infection.[19]

E Pierri, et al. Concluded that PLA-PEG micelles of griseofulvin exhibited sustained release properties and adequate stability in PBS and in simulated gastric and intestinal fluids. The copolymer exhibited sufficiently low CMC to provide the stable micelles in vivo. Drug loading capacity of micelles is sufficiently improved.[20]

Mohammed irshad reza et.al formulate nano dispersive gel loaded with ketoconazole using swollen micelles technique and carried out its in vitro characterization. This lead to enhancement in solubility and dissolution behaviour of poorly soluble antifungal drug ketoconazole. The formulation of SMT for preparing nanodispersion was found to be satisfactory as it produce a good product with high yield or high drug content.[21]

Tanvi Chaudhary et.al evaluated the feasibility to formulate clotrimazole loaded kolliphor 188 based polymeric nanomicellar gels for topical applications. From the studies of nanomicelles, the best optimized formulation was further screened for in vitro antifungal study against fluconazole resistant and susceptible Candida albicans clinical isolates. The results showed synergism against the isolates. This study also suggest that CLZ loaded kolliphor 188 based polymeric nanomicellar gels can be considered as an alternative delivery system for CLZ in topical application.[22]

Tianyang zhou et.al developed micelle carriers which is based on macrogol 15 hydroxystearate used for ocular delivery of terbinafine hydrochloride and carried out its in vitro characterization and in vivo permeation. The diffusion of drugs topically through the cornea can be improved by delivering in the form of non ionic surfactant micelles. The conveniently prepared, small, physically stable and biocompatible TH-HNMs with good ocular bioavailability secure great security as an efficient carrier for topical ocular delivery of terbinafine hydrochloride.[23]

Shih-Hung Hsich et.al encapsulated antifungals in micelles which protects during gall bladder infection. They concluded that treatment of gall bladder and bile duct infections is hampered by the ability of bile salts to encapsulate antifungals in micelles. Treatment of gall bladder or bile duct infections should favour the use of small hydrophilic drugs that are not solubilized in micelles.[24]

Francisco M.Marty et.al investigated that isavuconazole has been used for the treatment of invasive fungal diseases caused by more than one fungal species. Multiple studies on efficacy and safety of isavuconazole for the treatment of invasive fungal diseases were carried out and concluded that isavuconazole is an effective drug for the treatment of invasive fungal diseases to an extend[25].

Blanca L.V et.al formulated cyclodextrin amphiphilic copolymer supramolecular assemblies for topical ocular

delivery of natamycin. They encapsulate natamycin to solplus and pluronic p103 micelles as well as αCD. Mixed micelles and their poly(pseudo) rotaxanes leads for tuning the features that copolymer system exhibits separately. Therefore, he concluded that formulation of mixed micelles may be useful tool for the convenient drug release and enhance ocular permeability[26].

CONCLUSION

Conventional topical formulation are not able to provide prolonged drug release and also associated with many side effects. Nanomicelles enhanced the skin permeation and provide sufficient therapeutic effect. Various strategies for the delivery of nanomicelles are well studied which provide antifungal drugs at the infection site.

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