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FORMULATION AND EVALUATION OF KETOCONAZOLE POLYMERIC FILMS FOR TOPICAL APPLICATION

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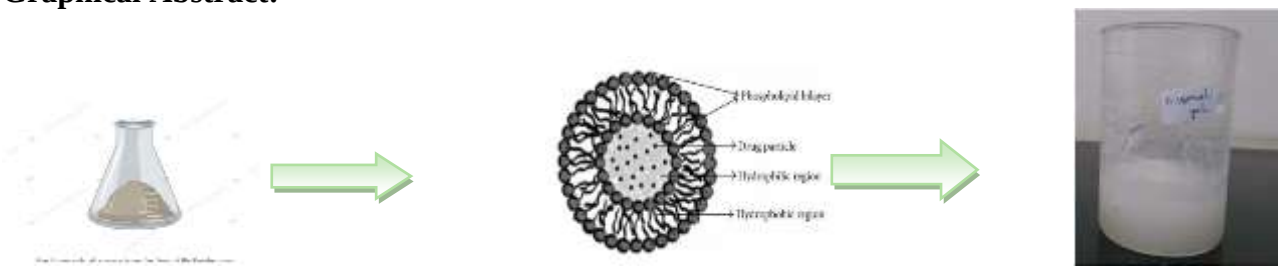
Ketoconazole, Niosomes, Topical, Antifungal.

ABSTRACT

Today, treatment of infectious disease through Novel drug delivery system has been a revolutionary thing. Niosome are one of the types of novel drug delivery system having potential ability to treat infectious disease topically. Niosomes play an important role in treatment as they can reduce toxicity and modify pharmacokinetics bio-availability. Antifungal drugs are designed to deliver the topically to avoid gastrointestinal irritation and to avoid the first pass effect and also to provide maximum concentration of drug at the site of action. Also, it is well known that have better potential than compared to ointment in case of drug administration. Ketoconazole is an effective and broad spectrum anti-fungal drug to treat wide variety of infection.

Graphical Abstract:



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1. Introduction

Several antifungal agents are available in different topical preparation ex: -cream, ointments and powders for local dermatological therapy. Ketoconazole is abroad antifungal agent active against systemic and superficial mycoses. As it is readily but incompletely absorbed after oral administration, its topical preparation is good for its activity (1) . Some common side effects associated with ketoconazole therapy are mild burning at the site of application, irritation, redness etc. Topical drug delivery system is considered as a novel drug delivery system due to its targeted drug delivery system and controlled release of drug (2). Niosomes are example of such novel drug delivery system in which drug is encapsulated in a vesicle to enhance the bioavailability of the drug (3). Niosomes are made up of non-ionic surfactant of alkyl or dialkyl polyglyceral ether class and cholesterol with subsequent hydration in aqueous medium (4). Niosomes increases the stability of the topical drug delivery of drugs. The drug in the vesicle can decrease the chance of side effects of drug and increases the bio-availability of the drug.

2. Niosomes

Niosomes are non-ionic surfactant vesicles, microscopic lamellar structure forms an admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aq. media (5). In niosomes, the vesicles forming amphiphile is a nonionic surfactant such as span60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetylphosphate (6).

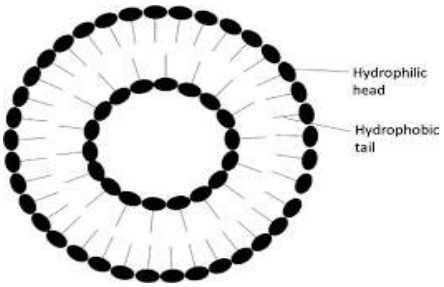

Fig.1 - of niosome

2.1) Salient Features of Niosomes

a) Niosomes are osmotically active and stable they also increase the stability of entrapped drug.
b) Handling and storage of surfactants require no special conditions.
c) Niosomes exhibit flexibility in their structure characteristics.
d) Niosomal surfactant are bio-degradable, biocompatible and non-immunogent (7, 8).

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2.2) Type of Niosomes

2.2.1) Multi-Lamellar Vesicles (MLV): These vesicles comprises several number of by layer around the aq-lipid compartment separately. These are the most commonly used niosome prepration (9, 10).

2.2.2) Large-unilamellar vesicles (LUV): Large amount of bio active materials incapsulated in large-unilamellar vesicles. These types of niosomes have greater aqueous/lipid compartment ratio (9, 10).

2.2.3) Small unilamellar vesicles (SUV): Theses vesicles are commonly formulated from multilamellar vesicles by sonication process (9, 10).

3. Basic Components Used in Prepration of Niosomes

3.1) Non-Ionic Surfactants:

The nonionic surfactants arrange themselves in by layer structure in which the polar (hydrophilic heads) faces towards the aqueous bulk, while the hydrophobic part arrange in such manner that the interaction with the media residues (11, 12).

3.2) Cholesterol:

Steroids are essential components of cell membrane and their existence in membrane effects the by layer fluidity as well as permeability. Cholesterol being a steroid derivative is principally used for the preparation of nisomes. It does not show any role in the preparation of by-layer but it influences the formation of nisomes as well as manipulation of later attributes cannot be disregarded. It also influences membrane permeability, rigidity, encapsulation, efficiency, etc. (13, 14).

3.3) Charged Molecules:

Various charged molecules are incorporated to niosomes to increase stability of niosomes with the aid of electrostatic repulsion which restricts coalescence. The negatively charged molecules used in such preparation are diacetyle phosphate (DCP) and phosphotidic acid (13).

4. Methods of Preparation of Niosomes

Niosomes were prepared by a thin film hydration method using a lipid mixture consisting of surfactants (span40,span60 and twen60) and CHO, at different specified ratio. Surfactant, CHO and drug were dissolved in

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10ml of chloroform. The lipid mixture was then transferred to a 100ml round bottom flask, and the solvent was evaporated under reduced pressure at a temperature of 55 to 65°C, using a rotary flask evaporator until a thin lipid forms. The formed film was hydrated with 20ml of phosphate buffer saline ph7.4. The hydration was continued for one hour, while the flask was kept rotating at 55to65°C in the rotary evaporator. The hydrated niosomes were sonicated for 20 mins using a bath sonicator to obtaion niosomal dispersion containing both free and entrapped drugs of varying sizes (15, 16).

5. Prepration Of Niosomal gel of Ketoconazol

The formulation of niosomes prepared by using span 80 and tween 80 containing ketoconazol equivalent to 2% w/w was incorporated into the gel base composed of carbopol 940(150mg), glycerol(250mg), triethanolamine (q.s) and distilled water upto 15gm and the gel was further evaluated (17,18,19).

Carbopol 940 is added into distilled water

This mixture is then heated at 50°C till it becomes viscous

The triethanolamine is added when the solution becomes enough viscous

The gel base is formed

The preparation is added separately into their resp. bases and stirred to form niosomal gel

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6. Mechanisms of Action of Niosomes as Permeation Enhancers

There is no single mechanism that can sufficiently explain the ability of niosomes to increase drug transfer through the skin, and several mechanisms (Figure 2) have been proposed, including: alteration of the barrier function of the stratum corneum, as a result of reversible perturbation of lipid organization;(20) reduction of transepidermal water loss, which increases hydration of the stratum corneum and loosens its closely-packed cellular structure;(21) and adsorption and/or fusion of niosomes on the surface of the skin, as revealed by freeze fracture electron microscopy and small angle X-ray scattering, leading to a high thermodynamic activity gradient of drug at the interface, which is the driving force for permeation of a drug.(22)

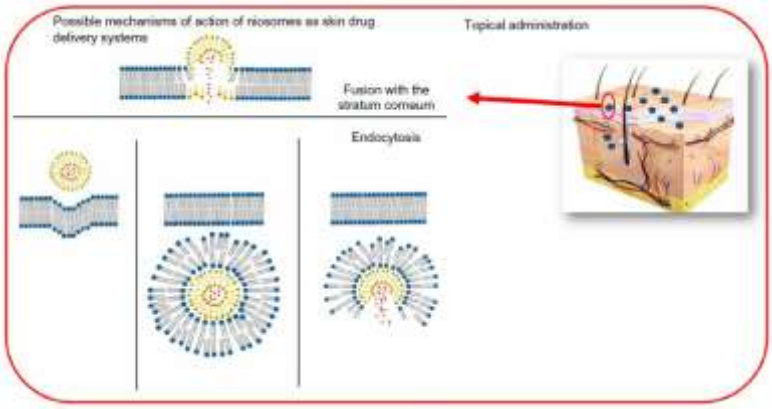

Fig.2 – Mechanism of action of niosomes as skin drug delivery system.

Adsorption of niosomes onto the cell surface occurs with little or no internalization of either aqueous or lipid components; it may take place either as a result of attracting physical forces or as a result of binding by specific receptors to ligands on the vesicle membrane and transfer of drug directly from vesicles to the skin. On the other hand, niosomes may fuse with the cell membrane, resulting in complete mixing of the niosomal contents with the cytoplasm. Finally, niosomes may be engulfed by the cell (endocytosis), with lysozymes present in the cytoplasm degrading or digesting the membranous structure of the niosome, thereby releasing the entrapped material into the medium. (23-24)

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7. Parameters to be evaluated for niosomal gel

7.1) Physical Appearance:

The prepared gel was examined for clarity, color, homogeneity and the presence of foreign particles.

7.2) Ph:

The ph of the gel was measured using digital ph meter and was made sure that the ph is accurate so does not cause skin irritation.

7.3) Viscosity:

The viscosity of the resulting gel was measured using Brookfield viscometer.

7.4) Content Uniformity:

For determining the content uniformity of the prepared gel a process was carried out by dissolving accurately weighed quantity of gel equivalent to 10mg of the drug in 100ml of volumetric flask and volume was made up to 100ml with methanol. The content was filtered through whatman filter paper no-41. 5ml of above solution was taken into a 25ml volumetric flask and volume was made up to mark with methanol. The content of ketoconazole was determined at 243nm against blank by using the simadzu uv\visible spectrophotometer.

7.5) Intro Drug Diffusion Study:

The apparatus consist of a glass cylinder open at both ends. A dialysis membrane soaked in distilled water (24hour before use) is fixed to the one end of the cylinder with the aid of a adhesive. 100ml of PBS (ph 7.4) containing 10%v/v methanol (to main sink condition), act as receptor compartment . The whole assembly is fixed in such a way that the lower end of the cell containing gel is just above the surface of the diffusion medium (1-2mm deep) and the medium was agitated using a magnetic stirrer at the temp. 37±0.5°C. 5ml sample are withdrawn from the receptor compartment time to time and replaced with same volume of fresh buffer. The sample were analyzed by UV visible spectrophotometer at 225nm. (25, 26)

Conclusion

Tropical drug administration is a localized drug delivery system. However, the major barrier of the skin is the stratum corneum, low molecular weight, lipophilicity and effectiveness at a dose are the ideal characteristics for tropical drug delivery system. Thus, therapeutic effectiveness of the drug ketoconazole was improved by formulating in the form of niosomal gel. Also in this niosomal for it shows prolonged action and better anti fungal activity due to enhanced penetration.

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