Formulation and Evaluation of a Niosome-Based Gel for the Treatment of Fungal Infections

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Abstract - Fungi as pathogens are a growing concern in global health, even more with their rising resistance to standard antifungal treatment. Niosomes, non-ionic surfactant-based vesicles, are emerging drug delivery systems with great promise, particularly in improving bioavailability, targeted delivery, and sustained release of drug substances. This article reviews the formulation and evaluation of niosome-based gels for treatment against fungal infections towards alternatives intervention of the existing antifungal therapies. Important areas discussed were preparation methods of niosomes such as thin-film hydration, reverse-phase evaporation, etc., surfactant composition, size, and encapsulation efficiency, and their roles in antifungal effectiveness. It also discusses the formulation and evaluation of niosomes and how they may be used for therapeutic purposes, combining the advantages of both niosomes and gels whilst increasing skin penetration and prolonging drug release. Evaluation methods include in vitro and in vivo methodology, while gel characteristics include viscosity, spreadability, and skin irritation. Future directions in the development of gels based on niosomes for the treatment of fungal infections are therefore discussed in detail; thus, providing an overview on the challenges in the future from clinical applications toward better patient outcomes with respect to niosome-based gels will be received in such a perspective.

Keywords - Fungal infections, Antifungal resistance, Drug delivery systems, Gel formulation, Gel evaluation, Patient outcomes, Niosome-based gel therapy

ABOUT DISEASE

Superficial mycotic infections are those that involve primarily the uppermost layers of the skin, the nails, hair, and mucous membranes. Their incidence has been on the rise in recent years, mainly owing to the ever-enlarging population of immunocompromised people who are increasingly having access to more public facilities such as health clubs and swimming pools which are aimless for infections. All this makes them some of the most common skin diseases and among major burdens in the world, affecting millions. The diagnosis is key to successful treatment. Tinea infections are superficial mycotic infections caused by dermatophytes belonging to three genera: Trichophyton, Microsporum, and Epidermophyton. These infections are customarily referred to as tinea followed by a locality denoting the body site affected (examples: tinea barbae for the beard area, tinea corporis for the body surface, tinea manuum for the hands, tinea pedis for the feet, tinea unguium for the toenails). These terms do not indicate the specific causative species. When fungi penetrate into tissues, they may manifest localized infections of skin, invade deeper tissues developing infections of bones and organs, or even involve the entire body in general infection.

TINEA CORPORIS:

Tinea corporis, or ringworm, describes a fungal infection occurring on any part of the body except the scalp, bearded areas, feet, or hands. It shows up clinically as an annular plaque with a slightly elevated, scaling, and advancing mural border. The lesion may have one or more concentric rings and has red papules or plaques at the center. As it advances, the center commonly clears, leaving areas of postinflammatory hypopigmentation or hyperpigmentation. Risk factors for tinea corporis include living in crowded, humid environments, excessive sweating leading to a moist environment for fungal growth (most often in armpits, groin, and skin folds of the abdomen), and participating in close-contact sports like soccer, rugby, or wrestling. Tight, poorly ventilated clothing exacerbates the problem, as does immunocompromised states such as HIV infection and immunosuppressive therapy.

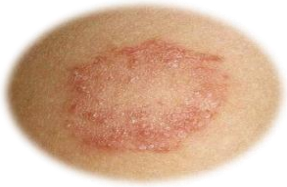

Fig.- Tinea corporis

TINEA CRURIS:

Tinea cruris, popularly recognized as jock itch, is a fungal infection in which the infection is superficial and contagious. It usually occurs in the groin area. Tinea cruris is mostly found in men but not restricted to them, as women also develop similar infections. Other skin diseases highly associated with this type of fungal infection include athlete's foot, infections of the nail, and tinea cruris. Tinea cruris is characterized by red scaly plaques found in the medial thighs and inguinal folds. The plaques are bilateral, although they may be usually spare the penis and scrotum, distinguishing them from candidiasis. Very often, an individual with tinea cruris also has tinea pedis, which is the famous athlete's foot, and the infection is believed to travel from foot to groin indirectly by hand contact.

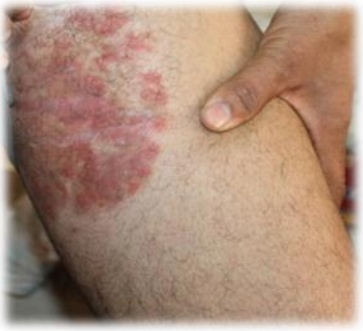

Fig.-Tinea cruris

TINEA PEDIS (feet):

Athlete's foot, or tinea pedis, is one of the most common fungal infections of the skin on feet. Symptoms usually include itching, redness, scaling, and cracking of the skin. Flea infestations can also spread within the home; however, in some cases, they are capable of being transferred from animal species to human. Diagnosis is usually based on clinical signs or symptoms but can also be confirmed through a culture or by observing hyphae under a microscope. A special light can also aid in diagnosis by causing the characteristic coral-red fluorescence of erythrasma; this is especially useful when it comes to differentiating tinea from other skin maladies.

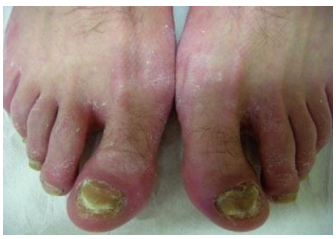

Fig – tinea pedis (feet)

INTRODUCTION

Drug targeting is the ability of a therapeutic agent to be delivered specifically to the required site of action while lessening the interactions of those areas from other tissues. A system of controlled drug delivery is designed to achieve a sustainable and desirable profile of drug release over time. Among the various techniques available to achieve controlled release, niosomes are a notable option. Niosomes are microscopic lamellar structures from 10 to 1000 nm in size, composed of surfactants that are non-immunogenic, biodegradable, and biocompatible. These properties provide niosomes better advantages over liposomes than that of chemical stability surfactants because phospholipids can be hydrolyzed due to the ester bonds found in them. In addition, niosomes are less expensive. All vesicular systems including lipid and non-ionic surfactant vesicles are useful for cosmetics as well as therapeutics because they offer the following: -

1) Better patient compliance than oily dosage forms.

2) Acts as a depot for drugs with a controlled drug release feature.

3) Capacity to hold drug molecules having a wide solubility range.

STRUCTURE OF NIOSOMES:

Niosomes are engineered microscopic structures with lamellar technologies which biodegradable, biocompatible, and nonimmunogenic. These consist of nonionic surfactants having alkyl or dialkyl polyglycerol ethers combined with cholesterol and formed by hydration. In these structures, the surfactants are so arranged that their hydrophilic ends face outward and their hydrophobic ends inward, thus creating a bilayer, as a result of the self-orienting character of the surfactant molecules.

STRUCTURAL COMPONENTS OF NIOSOMES:

Surfactants are the essential part of niosome formulation; the different variants and combination sufficed all the drugs encapsulated for different purposes. These are biodegradable, biocompatible, and non-immunogenic amphiphilic molecules. The characteristics of niosomes like their formulation, concentration of additives, size, lamellarity, and surface charge rely on the surfactants being used.

ETHER-LINKED SURFACTANTS: These surfactants are polyoxyethylene alkyl ethers; they can

be defined as surfactants which have connected hydrophilic and hydrophobic groups via ether bonds. Their general formula is (CnEOm), wherein n is 12 to 18 and m is 3 to 7. There are some formulations that also use surfactants that have polyhydroxyl head groups and have ethylene oxide units.

ESTER-LINKED SURFACTANTS: They have an ester bond joining the hydrophilic and hydrophobic portions of the molecule. Their study involves their use as sole surfactants or in combination with other surfactants in the process of formulation and drug delivery such as sodium stibogluconate.

SORBITAN ESTERS: These surfactants are of a very popular ester type and are mostly used in the food industrial application. Commercially, it is selling mixtures of partial esters of sorbitol and its mono- and dianhydrides with oleic acid. For example, drugs like doxorubicin have been successfully formulated with sorbitan esters in making niosomes.

ALKYL AMIDES: In alkyl amides, alkyl galactosides and glucosides are combined with amino acid spacers. The alkyl groups are therefore of fully or partly saturated C12 to C22 hydrocarbons, and some of the novel amide compounds include fluorocarbon chains.

FATTY ACIDS AND AMINO ACID COMPOUNDS: These compounds are able to be amphiphilic because they have attached hydrophobic alkyl side chains or long-chain fatty acids to them. They will therefore form "ufasomes," which are derived from fatty acid bilayers with vesicular structures.

CHOLESTEROL: The waxy steroid cholesterol is typically incorporated into nonionic surfactants to be used in increased rigidity. It has the capability of being amphiphilic, due to which it is incorporated into the bilayer by placing alternating positions of its steroidal skeleton along surfactant molecules. This also prevents the possible leakage as it impedes transition.

CHARGE INDUCERS: Charge inducers have gained attention from researchers in engaging with surface charge offerings to vesicles, thus creating electrostatic repulsion to avoid their fusion and also increasing their zeta potential. Some common negative charge inducers include dicetyl phosphate, dihexadecyl phosphate, and lipoamine acid, while positive charge inducers comprise stearylamine and cetyl pyridinium chloride.

ADVANTAGES

1. Niosomes encapsulate all kinds of drugs, including hydrophilic, lipophilic, and amphiphilic molecules.

2. The vesicles differ in their properties such as composition, size, lamellarity, surface charge, encapsulation volume, and concentration.

3. All these can be varied according to the particular need. Sustained or controlled-release of the drug is accomplished by it.

4. Surfactants need no special conditions for handling or storing in niosomes. Its depot form provides future releases of drugs in a controlled manner.

5. Niosomes will enhance oral bioavailability for poorly soluble drugs.

6. Properties of surfactants include biodegradability, biocompatibility, non-toxicity, and non-immunogenicity.

7. They protect active molecules of the drug against degradation in the biological environment, niosomes shield molecules of drugs against enzymatic metabolism.

8. They improve stability for the drug molecules to be contained.

9. Niosomes improve the permeation of different drugs through the skin. Decrease time of circulation of drug molecules and increase therapeutic efficacy.

DISADVANTAGES

1. They have a propensity to agglomeration of vesicles.

2. Leaking the drug that is entrap sealed.

3. Problems with physical instability.

4. It can take a long time in the preparation phase.

5. Hydrolyze encapsulated of drugs for shortened storage life of the dispersion.

APPLICATIONS OF NIOSOMES

Applications of niosomal technology are various and differ in diseases for which they can be used.

Hailed as Drug Transporters, Niosomes: Niosomes were used as carriers for diagnostic agents such as iobitridol for X-ray imaging.

Targeting of Bioactive Agents: -

They get mostly taken up by the Reticulo-Endothelial System (RES) cells: There are circulating serum components that are called opsonins and tag the vesicles for clearance. This has been successfully used in the treatment of metastasizing animal tumors to the liver and spleen as well as in parasitic liver infestations.

Beyond the RES: Specific body sites can be targeted by use of antibodies attached on the niosomal carrier systems. The immunoglobulins are well known to bind to lipid surfaces, thus creating a simple procedure for targeting drug carriers. Some cells also recognize and bind specific carbohydrate structures, allowing for precise delivery to target cells.

Anti-Tumor Treatment:

Niosomes would also be able to modify the pharmacokinetics of antineoplastic drugs to reduce metabolism, prolong circulation time, and reduce side effects. Tumor proliferation is slowed as well and induces a higher plasma-maintained drug level, thus slowing drug elimination.

Treatment of Leishmaniasis:

Leishmaniasis is a disease by the Leishmania organism that entirely occupies the liver and spleen cells through niosome studies. These administered medications through niosome treatments can be given at higher doses without an expected side effect, therefore increasing the efficacy of treatment.

Peptide Drug Delivery:

Niosomes are being studied for their potential in protecting peptides from degradation in the gastrointestinal tract. An in vitro oral study where a derivative of vasopressin entrapped in niosomes was used demonstrated that the stability and bioavailability of the associated peptide were increased.

Studies on Immune Response:

The main use of niosomes in the present research is in comparative immune response studies due to their selective interaction with the immune system, low toxicity, and even relatively high stability. Non-ionic surfactant vesicles prove to be quite effective adjuvants after their parenteral administration with various antigens and peptides.

Applications Cosmetic:

Niosomes were the first thing wen introduced by L'Oréal in the 1970s and 1980s for cosmetic applications. Lancôme was the first company to sell this commercial product in 1987 under the name "Niosome." Niosomes provide better cosmetic and skin care applications by improving the stability of encapsulated ingredients, enhancing the bioavailability and skin absorption of poorly absorbed ingredients.

Other Applications:

Sustained Release: The sustained release of drugs such as niosomes is a means of ensuring the maintenance of prolonged circulation of these agents in the body by encapsulating them; they involve medications with low therapeutic-index and low water solubility.

Localized Drug Action: Restricted drug penetration through epithelial and connective tissues can cause local-type effects, wherein only specific parts would receive the drug since the higher concentration remains concentrated at the site of administration.

NIOSOMAL GEL:

The drugs can be incorporated into niosomal vesicles, and these vesicles can further be combined with an appropriate gelling base to form a niosomal gel.

Benefits of New Gel Formulations:

1. Targeted drug delivery at sites.
2. Avoidance of first-pass metabolism.
3. Prevention in gastrointestinal irritation caused by some of the drugs.
4. Prolonged therapeutic effect with sustained and controlled drug release.
5. Reduced frequency of dosing,
6. Self-administration and localized delivery to minimize drug side effects.
7. Rapid withdrawal from drug action at need.

Mechanism of Absorption of Niosomal Gel:

As intact vesicles, niosomes penetrate the stratum corneum layer of skin. They are encountering the stratum corneum through aggregation, fusion, and adhesion to the cell surface. Such interaction creates a considerable thermodynamic activity gradient of drug at the vesicle-stratum corneum interface making them penetrate through the stratum corneum with lipophilic drugs. Niosomes also cause some changes on the surface of the stratum corneum, loosening and increasing permeability of intercellular lipid barrier, thus increasing drug absorption.

FORMULATION OF NIOSOME GEL:

In distilled water, the prepared niosome consists of preservatives added. Three percent xanthan gum will give it gel-like consistency. Niosomal gel has been designed from the niosomal dispersion and a suitable gel base, such as Carbopol U21, Carbopol 934, Carbopol 974 NF, or xanthan gum, in order to identify the best gelling agent and ensure the vigor of the final dosage form.

Niosomes in Carbopol U21 Gel:

Preparing niosomal gel involved using niosomal dispersion in Carbopol U21 gel base. Various batches were made: 0.1, 0.5, 1, and 1.5% w/w Carbopol. A required polymer was sprinkled little by little into a vortex formed by stirring double distilled water and stirred for 25-30 minutes. Gelling was induced by neutralization in Triethanolamine. Hydrated gel was mixed with continuous stirring with niosomal dispersion.

Niosomes in Carbopol 934 Gel:

Using the drug, span, and cholesterol as raw materials, the niosomes were prepared. These niosomes were further incorporated in 1% w/w Carbopol 934 gel base, comprised of 10% w/w propylene glycol and 30% w/w glycerol.

Preparation of Niosomal Gel with Xanthan Gum:

Here is the optimized formulation of a niosome converted into gel by dispersing 2% of it in xanthan gum. A niosomal pellet amounting to 1% w/w of the drug was weighed and transferred into a 50 mL beaker holding 5 mL of distilled water. The mixture was shaken well until a uniform mixture was obtained. Xanthan gum was weighed accurately and added gradually under stirring to niosomal dispersion. The whole weight was then made 10 g by adding distilled water drop-wise the whole mixture was allowed to hydrate at room temperature.

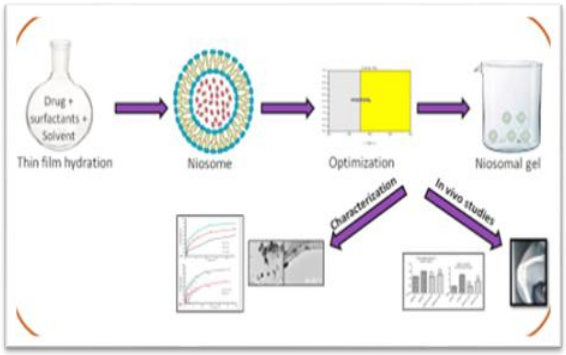

Fig.- Niosomal gel formulation.

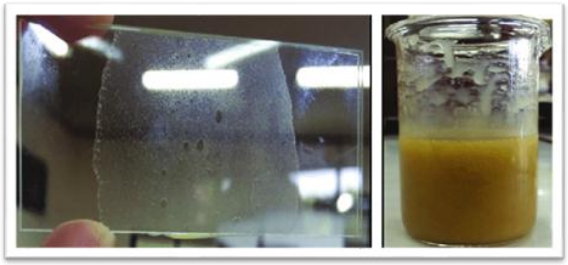

Fig. - Niosomal gel

IT'S BEEN THE EVALUATION PARAMETERS FOR THE NIOSOMAL GEL :

1.pH: The pH of the gel is estimated to be compatible with the skin and stability.

2. Viscosity Study: The viscosity of the gel is to be measured for analysis of its consistency and ease of application.

3. Spreadability: The spreadability of the gel can be evaluated in terms of how even it is spread over the skin surface.

4. Stability Study: Study of physical and chemical stability of the gel over time under different conditions.

5. In Vitro Diffusion Study-to study the drug release profile from the gel to predict the behavior.

6. Skin Irritation Effects: To test the gel for any skin irritation tendency or negative reaction.

1. PH - A careful weighing of 2.5 g of the gel was performed, and then it was dispersed in 25 mL of distilled water and was measured using a digital pH meter. For this study, the pH measurement of niosomal gels was done by dissolving about 1 g of gel in 100 mL of distilled water and letting it stand for approximately 2 hours. pH was measured thrice and the average was calculated with the digital pH meter for all the formulations.
2. Viscosity study - A Brookfield Viscometer was used to determine the viscosity of niosomal gel formulations. The gel was rotated at different speeds of 0.3, 0.6, and 1.5 rotations per minute with the corresponding dial readings taken at every speed. The viscosity of gel was then calculated from the dial readings multiplied with the relevant factor given in the Brookfield Viscometer catalog.
3. Spreadability - The niosomal gel preparations were subjected to spreadability assessment by taking 0.5 g of gel into an already marked circle of 1 cm diameter on a glass plate. The top of the

glass plate was sandwiched with another glass plate and a load of 500 g was applied on the upperside of the glass plate. It was then measured that the increase in diameter of the gel spread.

4. Stability Study - Frozen thawed cycling stability studies were carried out for all the prepared formulations of gels. All gels were put through cold hot cycles: one month under refrigeration at 4 Â°C, after which gels were kept at 25Â°C for a month and then at 40 Â°C for another month. Lastly, the samples were placed in the environment for a certain period of time, and observing separation of liquid exudates was done.
5. In Vitro Diffusion Study - Evaluation of in vitro release profiles of niosomal dispersion and niosomal gel was facilitated through the dialysis bag experiment. The dialysis bag was then washed, soaked in distilled water, and filled with niosomal dispersion and sealed. It was then placed in a beaker containing 200 mL of PBS at pH 7.4. The arrangement was placed on a magnetic stirrer (50 rpm) and kept at a temperature of 37 deg Celcius +or- 0.5 degrees celcius. Samples were taken at specific time intervals, diluted, and analyzed for drug release using UV/vis spectrophotometer.
6. Skin Irritation Effects - Studies of primary skin irritation from niosomal gel have been conducted according to Draize testing. Erythema and edema scores were recorded for both intact and abraded skin of the rabbits at 24 and 72 hours.

Fig.- Skin irritation.

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