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"NOVEL APPROACHES FOR THE TREATMENT OF ATOPIC DERMATITIS"

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by intense pruritus, erythema, and compromised skin barrier function. The objective of this study was to formulate and evaluate a niosomal gel containing crisaborole, a phosphodiesterase-4 (PDE-4) inhibitor, for enhanced treatment efficacy in AD. Niosomes, which are vesicular carriers composed of non-ionic surfactants, were chosen for their ability to encapsulate drugs, improve skin penetration, and enhance drug stability. Crisaborole-loaded niosomes were prepared using a thin-film hydration method and optimized by varying surfactant-to-cholesterol ratios. The optimized niosomes were characterized for particle size, zeta potential, encapsulation efficiency, and in vitro drug release. A carbopol-based gel containing the crisaborole-loaded niosomes was subsequently formulated. The niosomal gel was evaluated for physicochemical properties, rheological behavior, in vitro drug release, and ex vivo skin permeation studies using rat skin. The results demonstrated that the optimized niosomes had a particle size in the nanometer range with high encapsulation efficiency and sustained drug release over 24 hours. The niosomal gel exhibited desirable viscosity and stability, with significantly enhanced skin permeation compared to a conventional crisaborole gel. In vivo studies on a murine model of AD revealed a marked reduction in erythema, scaling, and inflammation, confirming the therapeutic potential of the niosomal gel. In conclusion, the crisaborole niosomal gel offers a promising approach for the effective management of atopic dermatitis, with improved drug penetration, sustained release, and enhanced therapeutic

outcomes. Further clinical studies are warranted to validate its efficacy and safety in human subjects.

KEYWORDS: Atopic dermatitis, Crisaborole, Niosomes, Niosomal gel, Phosphodiesterase-4 inhibitor, Thin-film hydration, Encapsulation efficiency, Skin permeation, Sustained drug release, Ex vivo studies, In vivo studies, Murine model, Carbopol gel.

INTRODUCTION

INTRODUCTION TO ATOPIC DERMATITIS

Atopic dermatitis, one of the most common skin disorders in infants and children, usually manifests itself during the first six months of life. Atopic dermatitis is becoming more common, similar to other atopic conditions like asthma, and its prevalence is comparable to that of the US, Europe, and Japan. Atopic dermatitis has three stages: infantile, childhood, and adult. Each stage has unique physical characteristics.

One of the most prevalent skin conditions affecting babies and kids is atopic dermatitis, which affects 45% of children during their first six months of life, 60% during their first year of life, and at least 85% of affected individuals before the age of five.[1] Even though eczema is a term that is commonly used, A more precise way to describe this particular dermatotype Atopic dermatitis irritation is a better term to describe this subtype of dermatitis.

Atopic dermatitis affects 17.2% of children in the US[2], which is comparable to the 15.6% prevalence in children in Europe[3] and the 24% prevalence in Japanese children aged 5 to 6.[4]

is not contagious, so it cannot spread from person to person. Atopic dermatitis causes the skin to become extremely itchy.[5]

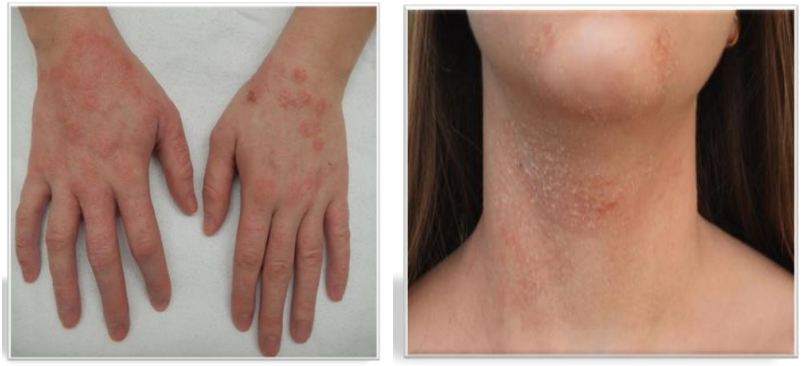


Figure: Atopic Dermatitis.

Symptoms of Atopic Dermatitis:

- The most common symptom of atopic dermatitis is itching, which can be severe**.**
- Red, dry patches of skin.
- Rashes that may ooze, weep clear fluid, or bleed when scratched.
- Thickening and hardening of the skin.

Causes of Atopic Dermatitis:

- The protective layer of the skin can cause it to lose moisture. This can cause the skin to become dry, leading to damage and inflammation in the skin.
- Inflammation directly triggers sensations of itch which in turn cause the patient to scratch. This leads to further damage of the skin as well as increased risk for infection with bacteria.
- Main causes include: Changes (mutations) in genes. Problems with the immune system. Exposure to certain things in the environment.

Complications of Atopic Dermatitis:

- Atopic dermatitis as a child can lead to the development of asthma and hay fever later in life.
- Bacterial skin infections that can worsen from scratching.
- Viral skin infections like warts or cold sores.
- Sleep loss that can lead to behavior issues in children.
- Eye problems such as: Conjunctivitis, Blepharitis.[6]

Management of Atopic Dermatitis

The patient's age and the severity of their illness determine the therapeutic approach (Figure 1). A multifaceted strategy is needed for management, with the goals of reducing inflammation (anti-inflammatory), itching (anti-pruritic), bacterial superinfection (anti-bacterial), and restoring the skin barrier (moisturiser). Practice clinical guidelines outline the available treatments for AD in adults and children, and Figure 1 provides a summary of these options. The method takes a step-by-step approach to evaluating the severity of the disease based on clinical features, the location and extent of skin lesions, the intensity of pruritus, and sleep disturbance.[7][8]

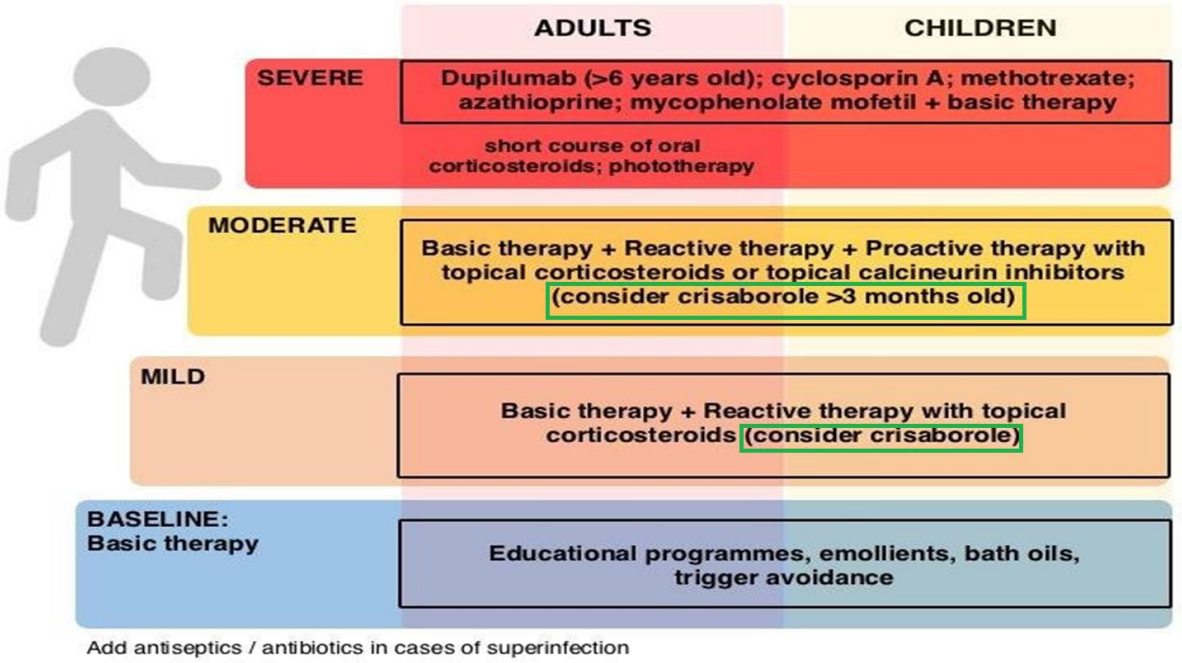


Figure: Management of Atopic Dermatitis.

Pathophysiology

Patients with atopic dermatitis have a compromised skin barrier that makes them vulnerable to environmental allergens and irritants, xerosis, and inflammation, which result in pruritus and other classic atopic dermatitis symptoms. Reduced amounts of ceramides, sphingolipids that are important for the skin's barrier function and are found in the stratum corneum, may contribute to the barrier deficiency. and prevent trans epidermal water loss. Due to a compromised skin barrier, allergens and irritants can enter the skin and induce inflammation in acute lesions by inducing an excessive Th2 response, which increases IL- 4 and IL-5 cytokines. Th1 response (with IFN-gamma and IL-12) in chronic lesions. In addition, keratinocytes stimulated by skin scratching release pro-inflammatory cytokines such TNF-alpha, IL-1, and IL-6. Decreased anti-microbial peptides (human beta-defensins, cathelicidins).[9][10]

Although there is a noticeable loss of water through the epidermis in Atopic dermatitis, the cause of the dysregulation of the epithelial barrier remains unclear. Filaggrin, which is essential for maintaining epithelial integrity, may not be functioning properly.[11][12]

INTRODUCTION TO DRUG PROFILE:

Crisaborole is a non-steroidal, topical medication designed to address the therapeutic needs of patients with mild-to-moderate atopic dermatitis (AD). As a phosphodiesterase-4 (PDE-4)

inhibitor, crisaborole represents a targeted approach to managing the inflammatory processes underlying this chronic skin condition. First approved by the U.S. Food and Drug Administration (FDA) in 2016, it is suitable for use in both pediatric and adult populations, including children as young as three months old.

Atopic dermatitis, a multifaceted disease with significant impacts on skin barrier function and immune response, requires safe and effective treatment options, particularly for long-term use. Crisaborole's mechanism of action involves the inhibition of PDE-4, leading to reduced levels of pro-inflammatory cytokines and a corresponding decrease in inflammation and pruritus. Its unique formulation and favorable safety profile distinguish it from other topical therapies, such as corticosteroids and calcineurin inhibitors, which may pose risks of skin thinning or systemic side effects with prolonged use.

This introduction provides a foundation for exploring the pharmacodynamics, pharmacokinetics, clinical efficacy, and real-world application of crisaborole, highlighting its contribution to the management of atopic dermatitis and its role in advancing dermatological care.

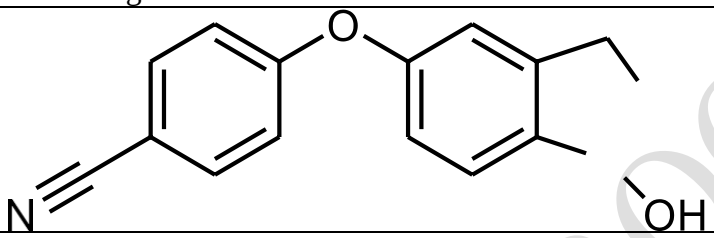
Mode of Action of Crisaborole:

Crisaborole is a selective phosphodiesterase-4 (PDE-4) inhibitor, a mechanism that directly targets the inflammatory pathways implicated in atopic dermatitis (AD). PDE-4 is an enzyme predominantly expressed in immune cells, where it degrades cyclic adenosine monophosphate (cAMP), a crucial secondary messenger in cellular signaling. The breakdown of cAMP by PDE-4 leads to the activation of pro-inflammatory pathways, resulting in increased production of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-31 (IL-31). These cytokines play a significant role in the pathogenesis of AD by contributing to inflammation, itch, and skin barrier dysfunction.

By inhibiting PDE-4, crisaborole increases intracellular levels of cAMP, which in turn suppresses the release of pro-inflammatory cytokines. This reduction in inflammatory mediators helps alleviate the symptoms of AD, including erythema, pruritus, and skin lesions. Crisaborole’s targeted action on PDE-4 allows it to modulate the immune response without the broad immunosuppressive effects associated with other therapies like corticosteroids or calcineurin inhibitors.

Crisaborole's localized effect when applied topically ensures minimal systemic absorption, contributing to its favorable safety profile. This mode of action positions crisaborole as an effective and well-tolerated treatment for mild-to-moderate atopic dermatitis, offering a steroid-sparing option for long-term disease management.

Table: Crisaborole profile:

Name	**CRISABOROLE**
Category	Anti-Fungal
Chemical Structure	
IUPAC Name	4-[(1-Hydroxy-1,3-dihydro-2,1-benzoxaborol-5-yl) oxy]benzonitrile
Molecular Formula	$C_{14}H_{10}BNO_3$
Molecular Weight	251.05 g/mol
BCS Class	Class II
State	Solid
MeltingPoint	128.8°C to 134.6°C
Appearance	White or off-white power
Solubility	Crisaborole drug substance is freely soluble in common organic solvents such as isopropyl alcohol and propylene glycol, and insoluble in water.

INTRODUCTION TO DOSAGE FORMULATION

Structure of Niosomes:

The spherical niosomes are made up of microscopic lamellar structures, which can be unilamellar or multilamellar (Figure 1). Non-ionic surfactants, with or without cholesterol, and a charge inducer combine to form the bilayer.[13][14] Niosomes are formed by varying the combinations and molar ratios of different types of surfactants. Alkyl and alkyl glyceryl ethers, for example.[15]

By keeping the bilayer rigid, cholesterol addition reduces the amount of leaky niosomes. Charge inducers, on the other hand, give the vesicles a charge and enlarge them, improving the effectiveness of drug entrapment.[16][17] Niosomes contain non-ionic surfactants that orient themselves to form a closed bilayer structure that encloses solutes in an aqueous solution. The hydrophilic end of the surfactants faces outward, while the hydrophobic end faces inward. [13]

Consequently, the hydrophilic outer and inner surfaces of niosomes' closed bilayer structure are surrounded by a lipophilic region.[18] It takes energy, such as heat or physical agitation, to form the closed bilayer structure. It was discovered that a number of forces within the vesicles were crucial in preserving the vesicular structure.[13][14][19]

Based on the size of their vesicles, niosomes can be divided into three groups: large unilamellar vesicles (>0.10 mm), multilamellar vesicles (>0.05 mm), and small unilamellar vesicles (0.025–0.05 mm).[19]

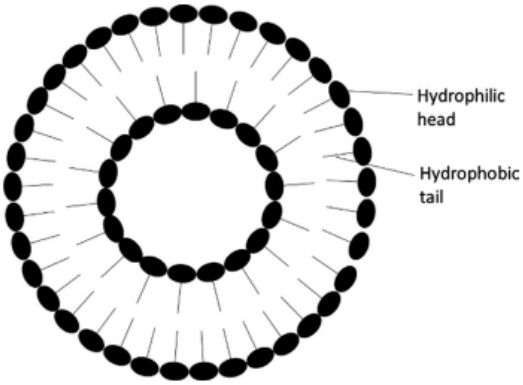


Figure: Structure of Noisome

COMPOSITION OF NIOSOMES:

The two main ingredients used to prepare niosomes are cholesterol and non-ionic surfactants. Proper shape and stiffness are provided by cholesterol. A significant part of the formation of niosomes is played by the surfactants. For the preparation of niosomes, non-ionic surfactants such as spans (span 20,40,60) and tweens (tween 20,40,60) are typically utilised.[20][21]

The following are a few other surfactants that have been linked to niosomes:

- Sorbitan esters,
- Poly-sorbates,
- Ether-linked surfactants,
- Di-alkyl chain surfactants,
- Ester-linked surfactants

Method of preparation:

To prepare niosomes, first a lipid mixture and surfactant are hydrated at high temperatures. Next, niosome size reduction is optional to produce a colloidal suspension.[22] Niosome preparation can be done using a number of well-researched conventional techniques.

Examples include sonication, micro fluidisation techniques, ether injection, and hand shaking.[15],[19],[23] Then, by centrifugation, gel filtration, or dialysis, the unentrapped drug is separated from the entrapped drug.[24]

Hand shaking method (Thin film hydration technique):

In a round-bottom flask, the mixture of surfactant and other vesicles-forming ingredients, such as cholesterol, is dissolved in a volatile organic solvent such as diethyl ether, chloroform, or methanol. By removing the organic solvent at room temperature (20°C) with a rotary evaporator, a thin layer of solid mixture is left on the flask wall. Multilamellar niosomes can be formed by rehydrating the dried surfactant film with an aqueous phase at 60°C and gently stirring.[25]

Advantages:

1. Niosomes have low toxicity, are non-immunogenic, biodegradable, biocompatible, and patient compliance.
2. They have a lengthy storage duration and are osmotically active.
3. They work together as a pool to release medication in a consistent, well-organised, and long-lasting manner.
4. They offer accommodations for drug molecules with different types of medication solubility, such as lipophilic, hydrophilic, and amphiphilic medication moieties.
5. Niosomes may increase the medication's stability when it is encapsulated.
6. Niosomes can increase the way that drugs penetrate the skin.
7. Niosomes have the ability to cross the blood-brain barrier and enter the brain to deliver drugs.
8. By altering the drug's surface and limiting its effects to the intended cells, they enhance its therapeutic performance while lowering the drug's clearance.
9. Niosomes can increase a drug's oral bioavailability.
10. Because of the functional groups on their hydrophilic heads, surface modification is quite easy.
11. The vesicle formulation's properties, such as size, lamellarity, concentration, surface charge, and drug sting, are controllable.
12. There is no need for particular conditions when handling, storing, or preparing noisome.
13. Niosomes must be manufactured and produced on a large scale using straightforward techniques.

Application of Niosomes

Niosome-based drug delivery methods via transdermal, parenteral, and ocular routes have been extensively researched. The slow penetration rate of traditional transdermal methods can be overcome by niosomal delivery via transdermal routes. Drugs like diclofenac, flurbiprofen, and nemesulide become more bioavailable and effective when incorporated into niosomal formulations. [19][26][27]

CONCLUSION

This study highlights the promising potential of crisaborole-loaded niosomal gel as an innovative approach to the treatment of atopic dermatitis (AD). By employing niosomal technology, the formulation demonstrated enhanced drug encapsulation, improved skin penetration, sustained release, and a favorable stability profile. These attributes translated into superior therapeutic outcomes in vitro, ex vivo, and in vivo, including significant reductions in erythema, scaling, and inflammation in a murine model.

Compared to conventional formulations, the niosomal gel displayed enhanced efficacy, likely due to its ability to overcome barriers posed by the compromised skin structure in AD. Furthermore, the localized action and favorable safety profile of crisaborole as a PDE-4 inhibitor make it a valuable alternative to conventional treatments like corticosteroids, reducing the risk of adverse effects associated with long-term use.

In conclusion, the crisaborole-loaded niosomal gel offers a novel and effective strategy for managing atopic dermatitis, with potential clinical benefits for patients. Further clinical trials in human subjects are warranted to validate its safety, efficacy, and applicability in routine dermatological care.

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