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Formulation and Characterization of Crisaborole Loaded Cubosomal Gel for Topical Application

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Abstract:
The aim of the present research is to develop a topical Cubosomal gel formulation of Crisaborole, an anti-inflammatory non-steroidal phosphodiesterase 4 inhibitor currently being investigated for its potential in treating atopic dermatitis. Pre-formulation studies included determination of melting point, DSC (differential scanning calorimetry), FT-IR spectroscopic analysis, wavelength determination, calibration curve establishment, and drug-excipient compatibility studies. Top-down techniques were employed to prepare cubosomes. Thirteen different formulations (C1-C13) were developed to optimize parameters such as particle size, size distribution, zeta potential, and entrapment efficiency. The physical characteristics including appearance, pH, viscosity, spreadability, and Transmission Electron Microscope (TEM) analysis were evaluated. In-vitro drug release studies were conducted for the crisaborole-loaded cubosomal gel formulation (CRB-C1), which utilized Glyceryl monooleate as the lipid, Poloxamer 407 as the stabilizer, and Carbopol 934 as the gel base. CRB-C1 showed optimized parameters with a particle size of 135.70 ± 0.58 nm, polydispersity index (PDI) of 0.249 ± 0.01, zeta potential (ZP) of -21.50 ± 4.25 mV, and entrapment efficiency of 91.95 ± 0.50%. The developed cubosomal gel formulation (C1) exhibited clarity without any aggregates, indicating excellent homogeneity. In-vitro drug release studies demonstrated favorable release kinetics for formulation C1.

Keywords: Cubosomal gel, Crisaborole, Topical drug delivery, Atopic dermatitis, Glyceryl monooleate, Top-down approach.

I. Introduction

Atopic Dermatitis:

Atopic dermatitis is one of the most prevalent skin disorders observed in infants and children, commonly appearing within the first 6 months of life. Its prevalence is similar across the United States, Europe, and Japan, and is increasing, akin to other atopic conditions such as asthma. Atopic dermatitis progresses through three distinct phases: infantile, childhood, and adult, each characterized by specific physical symptoms.

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The disorder typically begins in infancy, affecting 45% of children within the first 6 months, 60% within the first year, and at least 85% before the age of 5 [1]. While often referred to as eczema, atopic dermatitis is a more precise term describing this subset of dermatitis.

In the United States, approximately 17.2% of children are affected by atopic dermatitis [2], a prevalence comparable to the 15.6% seen in European children [3] and the 24% prevalence observed among 5- to 6-year-olds in Japan [4].

Phases of Atopic Dermatitis:

The infantile phase of atopic dermatitis manifests from birth to 2 years of age (Fig. 1). Erythematous papules and vesicles typically develop on the cheeks, forehead, or scalp, accompanied by intense itching. These lesions may initially localize to the face or spread to the trunk and extensor surfaces of the limbs in irregular, often symmetrical patches.

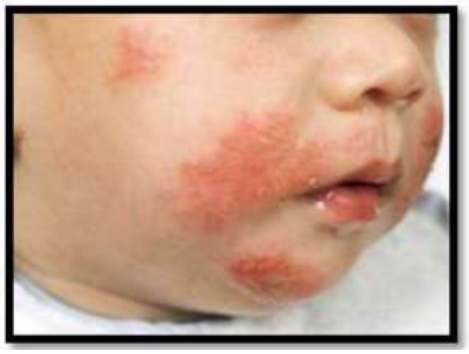

Figure 1: Atopic dermatitis phase 1

The childhood phase of atopic dermatitis often follows the infantile stage without interruption, typically occurring from 2 years of age until puberty. During this phase, children are less likely to experience the exudative lesions seen in infancy and instead present with more lichenified papules and plaques, indicating chronic disease. These manifestations commonly involve the extensor areas of the body[5].

Classic sites of involvement in children include the hands, feet, wrists, ankles, and the antecubital and popliteal regions (Fig. 2). While flexural areas are commonly affected, some children exhibit an "inverse" pattern with predominant involvement of intertriginous areas.

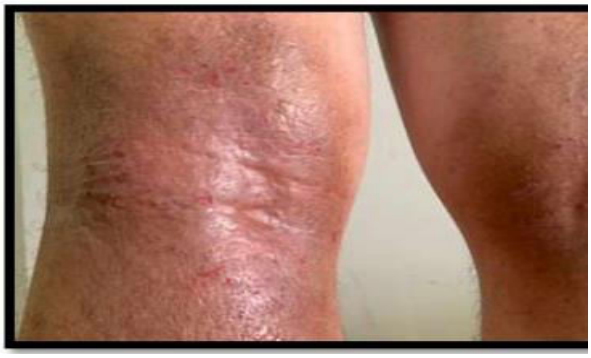

Figure2: Atopic dermatitis phase 2

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The adult phase of atopic dermatitis typically begins at puberty and often persists into adulthood. Commonly affected areas include the flexural folds (such as the bends of elbows and knees), the face and neck, upper arms and back, as well as the backs of the hands, feet, fingers, and toes.

Symptoms in this phase manifest as dry, scaly erythematous papules and plaques, often leading to the formation of large lichenified plaques due to chronicity of the condition. Weeping, crusting, and exudation may occur, typically secondary to superimposed staphylococcal infections[6].

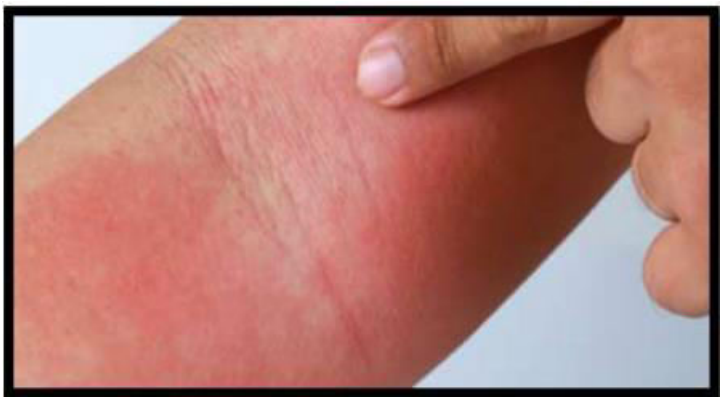

Figure3: Atopic dermatitis phase 3

STRUCTURE OF CUBOSOMES:

Cubosomes exhibit a large interfacial area and honeycomb-like features that separate their two internal aqueous channels. These nanostructure particles are a type of nanoparticle with cubic crystallographic symmetry, formed through the self-assembly of amphiphilic or surfactant-like molecules.

These cubosomes are characterized by their high internal surface area and cubic crystalline structure

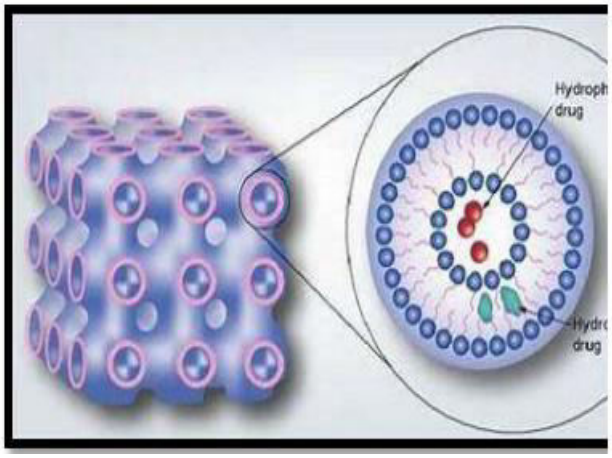

Figure 4: Structure of cubosome

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PREPARATION OF CUBOSOMES:

Cubosomes can be prepared by two distinct methods:

1. Top-down technique

2. Bottom-up techniqu

1. Top-Down Technique:

The top-down technique, first reported by Ljusberg-Wahren in 1996, is widely used for producing cubosome nanoparticles. Initially, a bulk cubic phase is created, resembling a clear, rigid gel formed by water-swollen crosslinked polymer chains. These cubic phases represent a single thermodynamic phase with a periodic liquid crystalline structure.

The process involves breaking the cubic phases in a direction parallel to the shear direction, requiring energy equivalent to the number of tubular network branches that break. High-energy methods such as high-pressure homogenization are employed to transform the bulk cubic phase into cubosome nanoparticles.

The yield stress of cubic phases increases with the concentration of oils and surfactants forming bilayers. According to research by Warr and Chen, dispersed liquid crystalline particles develop at transitional shear rates, while the dominant free bulk phase reforms at higher shear rates. Cubic phases exhibit behavior similar to lamellar phases during dispersion under increasing shear.

Recent studies indicate that dispersion methods like sonication and high-pressure homogenization produce complex dispersions containing vesicles and cubosomes, with time-dependent ratios of each particle type.

The surface structure of cubosomes on a micron scale mirrors that of their initial bulk cubic phase. However, following homogenization, the dominant P-surface emerges due to the incorporation of polymers.

2.BOTTOM-UP TECHNIQUE

Cubosomes from precursors are permitted to develop or crystallize.The formation of cubosomes by dispersing inverse micellar phase droplets in water at 80°C, and allow them to cool slowly, gradually droplets get crystallizes into cubosomes. This is more vigorous in large scale production of cubosomes. The cubosomes at room temperature is by diluting monoolein ethanol solution with aqueous poloxamer 407solutions. The cubosomes are automatically formed by emulsification.

Another method has been developed for producing cubosomes from powdered precursors using the spray drying technique. In this process, spray-dried powders containing monoolein coated with starch or dextran are hydrated to form cubosomes.

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The colloidal stabilization of cubosomes occurs spontaneously due to the presence of polymers. This method allows cubosomes to develop or crystallize from their precursors, employing a bottom-up approach where nanostructure building blocks are first formed and then assembled into the final material.

This approach is a more recent development in cubosome formation, facilitating the crystallization of cubosomes from molecular-scale precursors. A key aspect of this method is the use of a hydrotrope, which can dissolve water-insoluble lipids into liquid precursors. This dilution-based approach enables the production of cubosomes with lower energy input compared to the top-down technique.

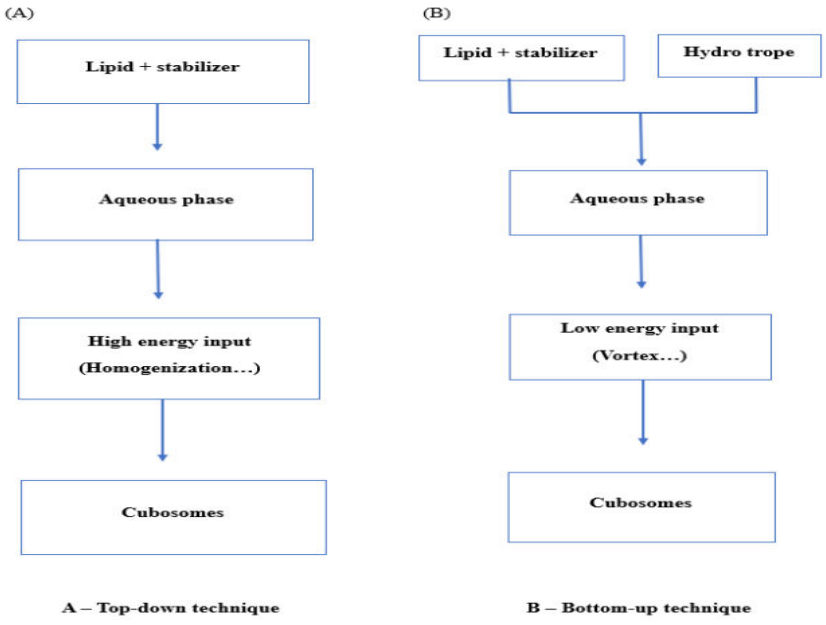

Figure 5. Preparation of Cubosomes.

V. APPLICATIONS OF CUBOSOMES:

- Cubosomes exhibit high internal surface area and cubic crystalline formations, allowing for high pharmacological payloads.
- They offer a relatively straightforward method of preparation.
- Cubosomes are biodegradable due to their lipid composition.
- They have the capability to encapsulate hydrophilic, hydrophobic, and amphiphilic substances.
- Cubosomes enable targeted and controlled release of bioactive ingredients.
- They act as penetration enhancers, facilitating drug penetration through the stratum corneum and into deeper layers of the skin.
- The cubic phases of cubosomes can be fractured and dispersed to form particulate dispersions that remain colloidally and thermodynamically stable over extended periods.

2. METHOD:

Preparation of Crisaborole Loaded Cubosomes:

Cubosomes composed of Glyceryl monooleate (GMO) and poloxamer 407 were prepared using the top-down method. Poloxamer 407 (F127) and GMO were melted at 60°C using a water bath. Crisaborole was then added to the molten mixture with continuous stirring until completely dissolved. Deionized water (3 ml) was gradually added with vortex mixing until a homogeneous state was achieved. The cubic phase was obtained after equilibration for 24 hours at ambient temperature. To disrupt the cubic phase, 10 ml of deionized water was added with stirring on a magnetic stirrer. The coarse dispersion was further fragmented by intermittent probe sonication for 15 minutes. High-pressure homogenization was then conducted for a specified number of cycles to obtain cubosomes. The cubosomes were stored in a refrigerator (4–8°C) until further use. The composition of the prepared cubosomal formulation is detailed in Table 1.

Preliminary Trial Batches of Crisaborole Cubosomes:

The influence of Poloxamer 407 concentration, GMO concentration, sonication time, and homogenization speed on the formation of cubosomes will be evaluated.

Formulation code	GMO %(w/v)	Poloxamer407 % (w/v)	Drug % (w/v)	Sonication time (min)	Homogenization speed (cycles)
C1	2	0.5	2	15	2
C2	4	0.5	2	15	2
C3	6	0.5	2	15	2
C4	2	1	2	15	2
C5	4	1	2	15	2
C6	6	1	2	15	2
C7	2	1.5	2	15	2
C8	4	1.5	2	15	2
C9	6	1.5	2	15	2
C10	2	0.5	2	10	2
C11	2	0.5	2	20	2
C12	2	0.5	2	15	1
C13	2	0.5	2	15	3

Table:1: Preliminary Trial Batches of Crisaborole Cubosomes.

VIII. RESULT AND DISCUSSION:

1. Organoleptic Properties of Crisaborole:

Colour	White
Odour	Odourless
Appearance	White Solid

Table:2: Organoleptic Characterization

2. Melting Point of Crisaborole:

Drug	Reported value	Observed Value (n=3; mean ±SD)
Crisaborole	128.8 to 134.6°C	130°C (±2.75)

Table:3: Melting Point Determination

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3. FT-IR STUDY of Crisaborole:

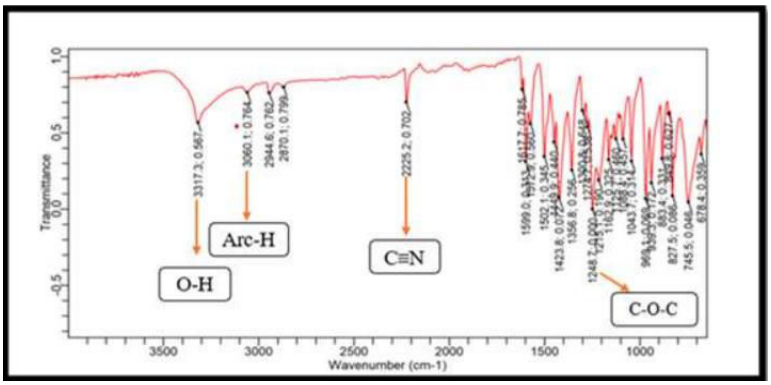

Figure:6: Identification of Crisaborole by FT-IR:

Conclusion:

The topical cubosomal gel is significant due to its unique 3D structure and ease of formulation. Cubosomes can be prepared using a combination of biocompatible lipid (GMO), Poloxamer 407 stabilizer, and water as a vehicle. GMO, a biocompatible lipid, accommodates both hydrophilic and hydrophobic drugs. Poloxamer 407 serves as a stabilizer to prevent aggregation. Crisaborole, a BCS class II drug, is formulated into cubosomes to achieve sustained release. The cubosomal formulation, prepared with GMO (2%) and Poloxamer 407 (1%), demonstrates high entrapment efficiency and consistent drug release (91.95 ± 0.50). The C1 formulation of cubosomes is incorporated into gel using Carbopol 934 for sustained release. This research highlights the utility of cubosomes as a prolonged-release drug carrier in topical gel formulations.

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