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Development and Evaluation of a Topical Antifungal Gel of Crisaborole for Atopic Dermatitis

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ABSTRACT
Atopic dermatitis (AD) is a chronic inflammatory skin condition often complicated by secondary fungal infections. Crisaborole, a non-steroidal phosphodiesterase-4 (PDE4) inhibitor, has demonstrated anti-inflammatory properties in the treatment of mild to moderate AD. This study focuses on the development of a crisaborole -based antifungal gel designed to treat fungal complications commonly associated with AD. The gel formulation was evaluated for its physicochemical properties, antifungal efficacy, and skin compatibility. Results indicate that the crisaborole gel exhibits significant antifungal activity against *Candida albicans* and *Malassezia furfur*, microorganisms frequently associated with AD. Additionally, the gel showed good stability and excellent skin compatibility, making it a promising option for integrated treatment of AD with concurrent fungal infections.
Keywords:
Crisaborole, Topical Antifungal Gel, Atopic Dermatitis, Pharmacology, Gel Formulation, Fungal Infections, Anti-inflammatory.

INTRODUCTION:

Atopic dermatitis, frequently referred to as eczema or atopic eczema, represents one of the most prevalent inflammatory conditions, impacting as many as 20% of children and 10% of adults in affluent nations. [1,2] The worldwide incidence of atopic dermatitis is on the rise, although the estimates in affluent nations appear to be stabilizing. This condition is marked by severe pruritus and the presence of recurrent eczematous lesions, exhibiting a diverse range of clinical manifestations.[3]

Atopic dermatitis may manifest at any stage of life; however, it predominantly presents during early childhood, generally between the ages of 3 to 6 months. Research indicates that this condition is also prevalent among adults, encompassing both chronic cases and those that arise for the first time.[4,5]

The etiology of atopic dermatitis is intricate and involves multiple factors. A significant genetic influence is evident, with various mechanisms contributing to genetic susceptibility. Notably, loss-of-function mutations in the filaggrin (FLG) gene are the most frequently and reliably identified genetic variants, underscoring the importance of the skin barrier, given that filaggrin serves as a principal structural protein within the epidermis.[6]

The significance of genetics in atopic dermatitis is well established; however, the rising global incidence of this condition underscores the influence of environmental factors. Those affected by atopic dermatitis face a heightened likelihood of developing asthma, allergic rhinitis, and food allergies, and they may also be at an elevated risk for various health and psychosocial issues.[3]

Clinical Signs

Key characteristics of the condition include eczematous lesions, severe itching, and a chronic or recurrent disease trajectory. The distribution of eczematous lesions is often age-dependent (see figure 1A). In infants, acute lesions are typically observed, marked by ill-defined erythema accompanied by edema, vesicles, excoriations, and serous exudate. These lesions can be widely distributed but predominantly affect the face, cheeks, and trunk, sparing the

diaper area. As children reach the age of two and older, eczema tends to become more localized and chronic compared to infancy, presenting with paler erythema, xerosis, and poorly defined lesions that commonly involve flexural areas, often leading to thickening (lithification) in chronic regions (see figure 1). In adolescents and adults, while diffuse eczema is common, localized lesions may also occur, particularly on the hands, eyelids, and flexural areas (see figure 1). Adults may experience chronic hand eczema or dermatitis affecting the head and neck, which can extend to the upper trunk, shoulders, and scalp (see figure 1). Morphological variants of eczema include the follicular type, characterized by closely packed follicular papules, often seen in individuals of Asian and African descent (refer to appendix p 1), and the prurigo type, which features excoriated papules and indurated nodules in patients with a long-standing history of the disease. [3,7]

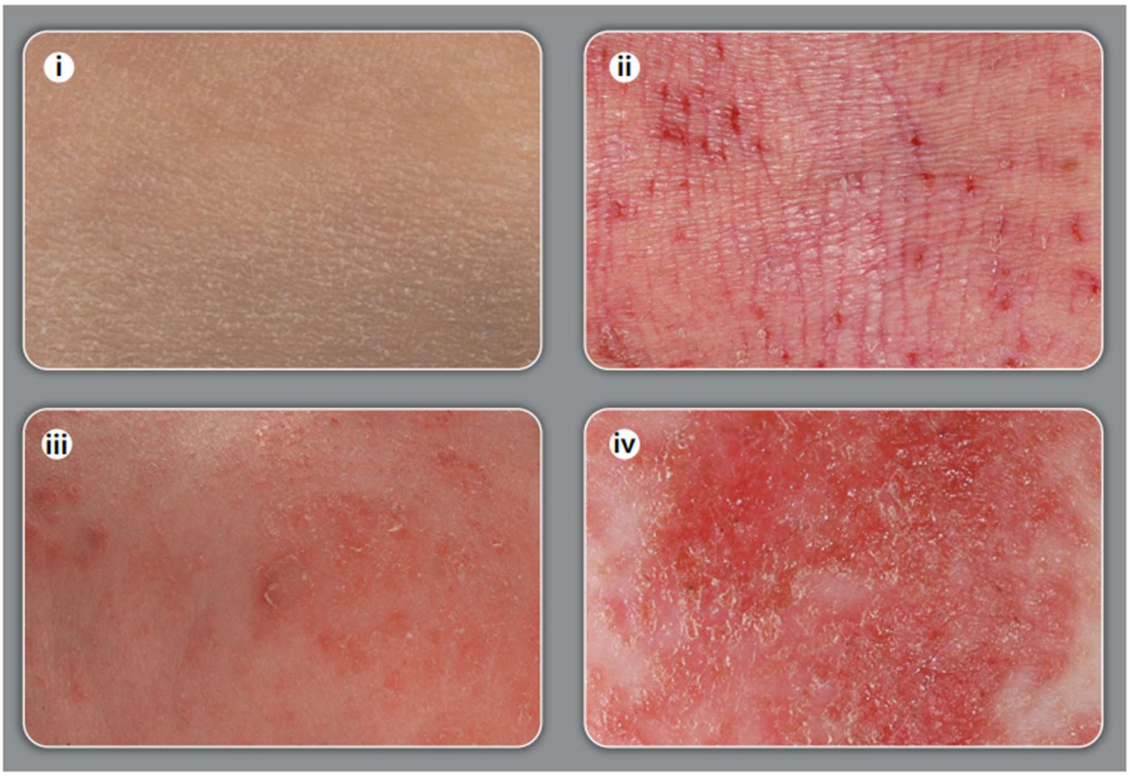


Fig.01:-Appearance of atopic dermatitis

Epidemiology

Atopic dermatitis is prevalent in high-income nations, affecting nearly 20% of children and 10% of adults, according to annual self-reported prevalence data.[3,8,9] In 2010, it was estimated that approximately 230 million individuals globally were living with eczema, which has been identified as the non-fatal skin condition with the most significant disease burden.[10] Although data regarding the severity of the disease are limited, a multinational survey indicated that between 10% and 20% of adult patients with atopic dermatitis experienced severe manifestations.[11] Furthermore, a population-based study conducted in the UK revealed that around 4% of adults presenting to primary care exhibited severe forms of the disease.[12]

Pathophysiology and mechanisms of disease:

The pathophysiology of atopic dermatitis is characterized by a multifaceted interaction among an impaired epidermal barrier, irregularities in the skin microbiome, and a predominant type-2 immune dysregulation (see figure 2A).[13,14] These mechanical factors can both promote and interact with one another. For instance, a deficiency in filaggrin leads to a compromised skin barrier, which in turn fosters inflammation and T-cell infiltration. Additionally, colonization or infection by Staphylococcus aureus not only damages the skin barrier but also triggers inflammatory responses. Concurrently, localized Th2 immune responses further compromise barrier integrity, exacerbate pruritus, and encourage dysbiosis, favouring the proliferation of Staphylococcus species, particularly Staphylococcus aureus.

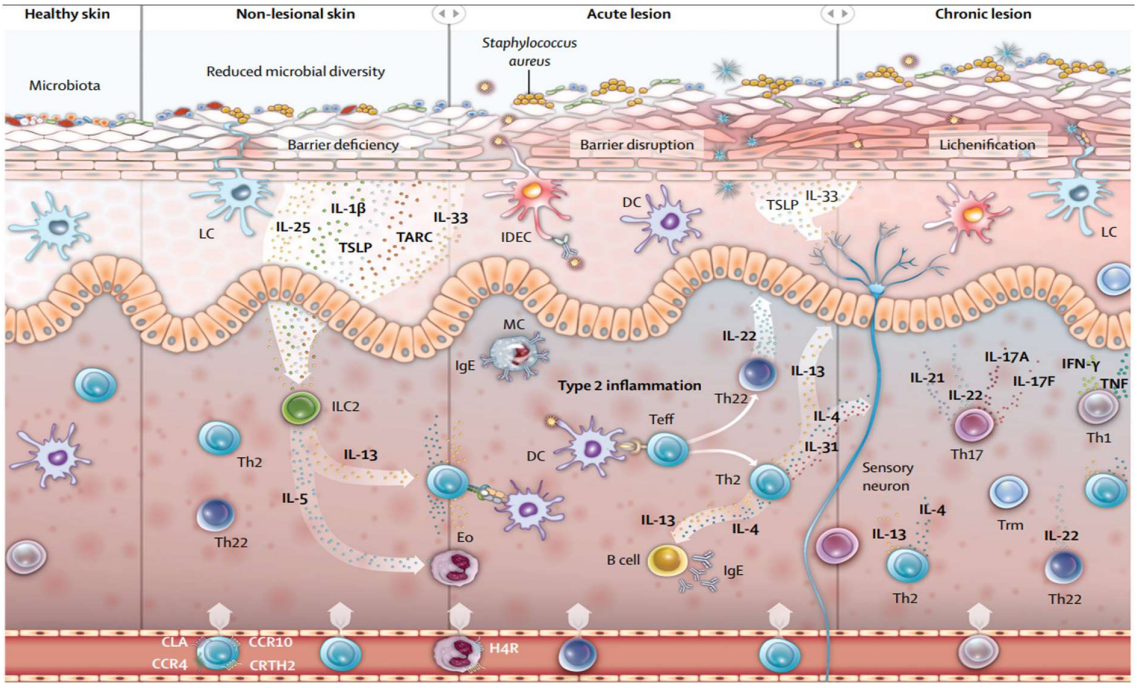


Fig:- 02 pathophysiology of atopic dermatitis

Bacterial, fungal, and viral complications in atopic dermatitis:-

Atopic dermatitis often presents challenges due to the occurrence of bacterial, fungal, or viral infections, which may arise individually or in conjunction. The interplay between Staphylococcus aureus and atopic dermatitis is intricate, as is the differentiation between mere colonization and the manifestation of a clinically significant infection [15,16] S. aureus is the predominant bacterial pathogen associated with atopic dermatitis, despite the relative rarity of true infections. The characteristic clinical manifestation often observed is the presence of impetigo-like lesions, which are painful, exudative, and exhibit golden crusts. Additionally, individuals with atopic dermatitis frequently experience viral infections, including molluscum contagiosum, herpes simplex virus infections that can vary from mild to severe forms such as eczema herpeticum, herpes zoster, and cutaneous warts.[17]

Role of Crisaborole in AD Management:

There are various strategies for the therapeutic management of atopic dermatitis, aimed at reducing symptoms and preventing triggers due to its complex pathogenesis. Topical treatments, including anti-inflammatory medications like corticosteroids and calcineurin inhibitors, serve as the cornerstone of therapy. However, similar to any therapeutic agent, their application is not without limitations, highlighting the necessity for alternative treatment options.[18,19,20]

In 2016, the United States Food and Drug Administration granted approval for crisaborole, a topical agent that inhibits the intracellular enzyme phosphodiesterase 4, to treat individuals aged 2 years and older who suffer from mild to moderate atopic dermatitis. In phase 3 randomized clinical trials, 32% of participants receiving crisaborole achieved the primary outcome, defined as a clear or nearly clear status (Investigator Static Global Assessment [ISGA] score of 0 or 1), along with a minimum 2-point improvement in ISGA scores (which range from 0 to 4), without experiencing any serious adverse effects. [21,22]

Crisaborole is a small molecule containing boron, with a molecular weight of 251.1 Da, that acts as an inhibitor of phosphodiesterase 4 (PDE4).[23] The small molecular weight of crisaborole facilitates efficient penetration into the skin and access to target cells. The inclusion of the boron atom is believed to enhance the compound's ability to bind to its targets and its selectivity, as substituting this atom leads to a reduction in the activity of the PDE4 enzyme and its associated cytokine inhibitory effects.[24,25] The precise mechanism by which crisaborole achieves its therapeutic effect in atopic dermatitis remains uncertain; however, the inhibition of phosphodiesterase

4 (PDE4) by crisaborole leads to elevated intracellular levels of cyclic adenosine monophosphate (cAMP), which in turn inhibits the production of pro-inflammatory cytokines and T-cell cytokines.[23,25]

MATERIALS AND METHODS

Crisaborole was obtained from Dharmtec Pharma located in Navi Mumbai. Carbopol 934P and polyethylene glycol were acquired from S.D. Fine Chem. Ltd, also based in Mumbai. Propylene was sourced from Yarrow Chemicals Ltd, Mumbai. All other reagents utilized in this study were of analytical grade.

Pre-Formulation Studies

Characterization of Crisaborole:

Molecular Formula:	• C14H10BNO3
Molecular Weight:	• 251.05 g/mol
Physical State:	• Solid (White to off-white powder)
Melting Point:	• 138-140°C (this may vary slightly depending on the source).
Solubility:	• Slightly soluble in water. Soluble in organic solvents like ethanol and dimethyl sulfoxide (DMSO).
LogP (Partition Coefficient):	• LogP ≈ 2.1 indicating moderate lipophilicity, which is useful for skin penetration in topical formulations.

(Table NO.1:- Properties of crisaborole)

Crisaborole's characteristics render it suitable for topical use, as it effectively traverses the skin barrier while maintaining stability and exhibiting minimal absorption into the systemic circulation.

Drug Excipient Compatibility Studies

The analysis of interactions between drug polymers and polymer-polymer combinations was performed using a Shimadzu 8400-S FTIR spectrometer, produced in Japan. A sample concentration of 2% (w/w) was prepared in relation to a potassium bromide disc, which was mixed with anhydrous KBr. This blend was subsequently ground into a fine powder using an agate mortar and then pressed into a KBr disc with a hydraulic press, applying a pressure of 1000 psi. Each KBr disc was subjected to 16 scans at a speed of 2 mm/sec, with a resolution of 4 cm-1, utilizing cosine apodization for data collection. The characteristic peaks were accurately documented.

PROCEDURE

Polymers (Carbopol, PEG 400, and Propylene Glycol) were combined in four ratios with distilled water to create four formulations with varying polymer concentrations. After thorough mixing, the solutions were stored in the dark for 24 hours to allow for swelling. Crisaborole was dissolved in a suitable solvent and gradually added to the polymer dispersion using a high-speed stirrer at 500 rpm to avoid air incorporation. The remaining components were then added to achieve a consistent gel. Formulations F1 to F4 were evaluated for clarity, pH, viscosity, spreadability, extrudability, skin irritation, drug content, and in-vitro diffusion.

Table 2: Formula for the preparation of Crisaborole Transdermal gels using Carbopol , PEG 400 and Propylene Glycol.

Ingredient	F1	F2	F3	F4
Drug	1	1	1	1
carbopol	0.5	1	1.5	2
PEG 400	5	5	5	5
PROPYLENE GLYCOL	10	10	10	10
Glycerine	5	5	5	5
Alcohol	10	10	10	10
D.W.	Q.S	Q.S	Q.s	Q.s

Evaluation of Physiochemical Properties of Various Formulations

The assessment of clarity, homogeneity, extrudability, spreadability, surface pH, viscosity, and drug content across different formulations is summarized as follows:

Clarity

Formulations were evaluated for clarity through visual inspection against black and white backgrounds, using a grading scale: turbid (+), clear (++), and very clear (+++). Results are in [Table 03]. Homogeneity was assessed visually after gel solidification, focusing on overall appearance and aggregates, with findings also in [Table 03].

Consistency

A cone attached to a rod was dropped from 10 cm into a gel-filled cup, and the penetration depth was measured after 10 seconds. Results are recorded in [Table 03].

Homogeneity

All gels were visually inspected for homogeneity post-solidification, noting any separation, phase transitions, or color and texture variations.

Extrudability

An extrudability test was conducted using a Pfizer hardness tester. Fifteen grams of gel were placed in a collapsible aluminum tube, subjected to 1 kg/cm² pressure for 30 seconds, and the extruded amount was measured at three points along the tube, repeated in triplicate. Results are in [Table 05].

Spreadability:

Spreadability was evaluated using a wooden block and glass slide apparatus. An excess sample was placed between two glass slides and compressed to a uniform thickness. Results are in [Table 6].

Code Ph:

2.5 grams of gel were dissolved in 25 mL of distilled water, and the pH was measured with a digital pH meter. Findings are in [Table 7].

Viscosity:

Viscosity was measured with a Brookfield viscometer at ambient temperature (25-27°C). Results are in [Table 8].

Drug Content:

100 mg of both the developed and marketed gels were dissolved in 100 mL of phosphate buffer (pH 6.8) and

shaken for 2 hours for complete solubility. The solution was filtered and analyzed spectrophotometrically at 285.0 nm, using phosphate buffer as the blank. Results are in [Table 9]

Gel double-diffusion test

Agar plates are prepared with standard procedure and 1 ml of marked gel is introduced in the them at four precised point with equal distance and data is collected.[table 10]

1. RESULTS & DISCUSSION

- [Table :- 3] Clarity

Formulation	Code Clarity
F1	+
F2	++
F3	++
F4	+++

Excellent +++, Good ++, Satisfactory +, No grittiness –

[Table:-4]Homogeneity

Formulation	Homogeneity
F1	Satisfactory
F2	Good
F3	Good
F4	Excellent

- (Homogeneity is evaluated qualitatively, with descriptors ranging from "Satisfactory" to "Excellent.")

[Table :- 5] Extrudability

Formulation	Extrudability
F1	+
F2	++
F3	++
F4	+++

Excellent +++, Good ++, Satisfactory +, No grittiness –

[Table :- 7] Spreadability

Formulation	1	2	3	Average	S.D
F1	13.90	14.95	15.40	14.75	0.62
F2	17.80	18.90	19.85	18.85	0.84.
F3	22.20	22.65	22.80	22.55	0.25
F4	27.45	27.05	27.67	27.39	0.26

Spreadability is quantified through numerical values that indicate the formulation's ability to spread effectively.

[Table :- 8] Code pH

Formulation	1	2	3	Average	S.D
F1	5.45	5.75	5.93	5.71	±0.05
F2	5.63	5.81	5.94	5.79	±0.15

F3	6.07	6.13	6.16	6.12	±0.02
F4	6.15	6.27	6.39	6.27	±0.03

2.

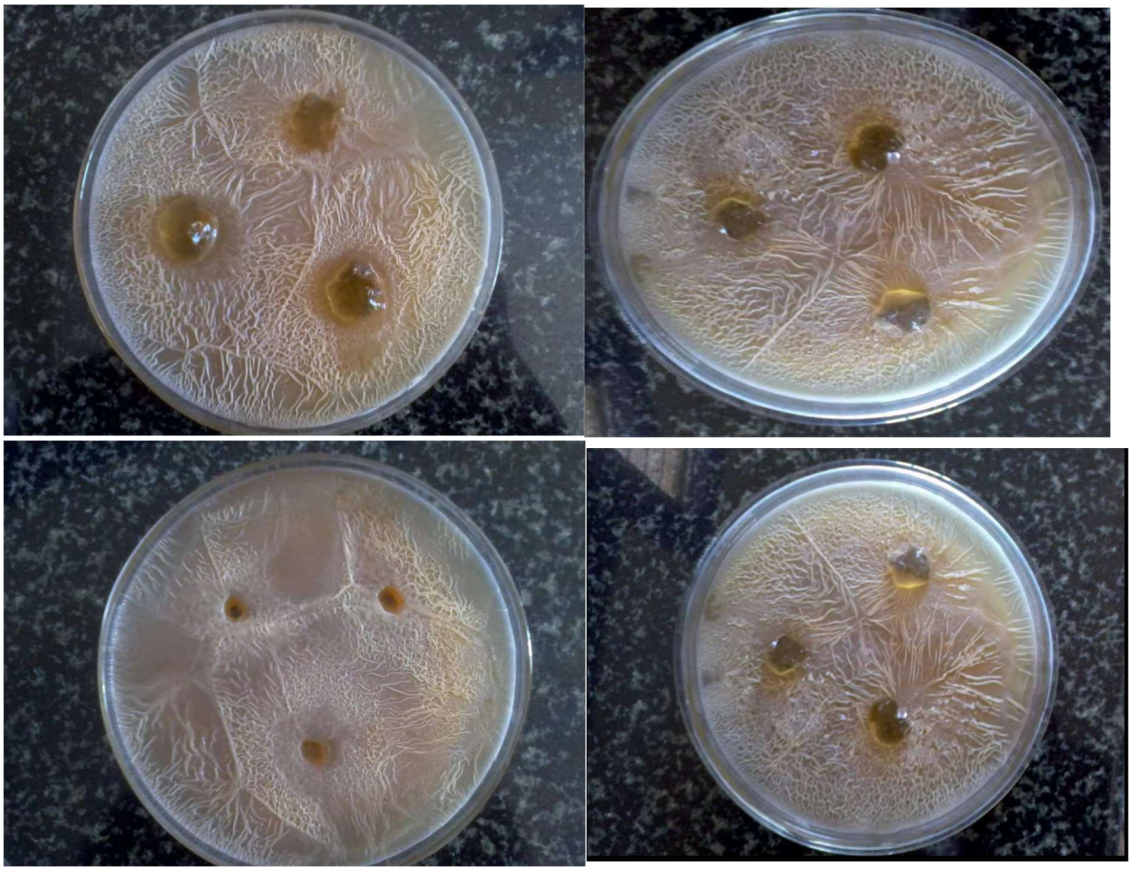
[Table :- 8] Viscosity

Formulation	Viscosity (cps)
F1	3,20,000
F2	1,92,000
F3	2,40,000
F4	3,10,000

[Table 9] : Drug Content (%)

Formulation	1	2	3	Average Drug Content (%)	S.D
F1	98.45	98.53	98.61	98.53	±0.21
F2	96.95	97.25	97.43	97.21	±0.18
F3	98.75	98.95	99.06	98.92	±0.27
F4	100.67	101.55	101.68	101.3	±0.2

Diffusion test:



Conclusion:

The development of a topical antifungal gel containing crisaborole demonstrates considerable promise for managing atopic dermatitis (AD) complicated by fungal infections. Our study indicates that this crisaborole-based gel formulation exhibits strong antifungal activity against *Candida albicans* and *Malassezia furfur*, organisms often implicated in secondary infections among AD patients. The gel was shown to be stable, with suitable physicochemical properties, including optimal pH, viscosity, and spreadability, enhancing both its therapeutic efficacy and patient acceptability.

Furthermore, skin compatibility tests confirmed that the gel is non-irritant, supporting its potential for safe application in chronic inflammatory skin conditions such as AD. The high drug content and effective release profile suggest that this formulation is reliable and effective in delivering the active ingredient to targeted sites. These findings collectively suggest that the crisaborole antifungal gel could be a valuable addition to the treatment options for AD, particularly in cases where fungal complications are present.

Future studies should focus on clinical trials to further evaluate the therapeutic efficacy and safety of this formulation in human subjects. Additionally, exploring the synergistic effects of crisaborole with other anti-inflammatory and antifungal agents may enhance the treatment outcomes for AD patients with recurrent infections.

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