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Development and Evaluation of Crisaborole Topical Cubosomal Gel

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ABSTRACT: The present research aims to develop a topical Cubosomal gel formulation of Crisaborole, CRB topical gel is an anti-inflammatory, non-steroidal phosphodiesterase 4 inhibitor which is currently under investigation for its potential role in the treatment of atopic dermatitis. Crisaborole The pre-formulation Studie to melting point, DSC and FT-IR spectroscopic analysis, determination of wavelength, calibration curve and drug excipient compatibility study. Top-down techniques were used for the preparation of cubosomes. Different formulations (C1-C13) were prepared for better performance in terms of Determination pf particle size, Size Distribution, Zeta potential, entrapmentefficiency.The physical parameters like appearance, pH, viscosity, spreadability, Transmission electron microscope, In-vitro drug release. In this study for formulae (CRB-C1) of crisaborole-loaded cubosomal gel were developed using Glyceryl monooleate as an lipid, Poloxamer 407 as a Stabilizer and Then it is formulated into gel using Carbopol 934 as gel base. Based on particle size (135.70 ± 0.58 nm) polydispersity index (PDI) (0.249 ± 0.01), Zeta potential (ZP -21.50 ± 4.25) %Entrapment efficiency (91.95 ± 0.50) was optimized and further incorporated into topical cubosomal gel. Thecubosomal gel formulation (C1) was found to be clear without any aggregate indicating excellent homogeneity. The In-vitro drug release study shows that the formulation (C1) has a good release rate.

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

I. INTRODUCTION

Atopic dermatitis:

Atopic dermatitis one of the most common skin disorders seen in infants and children, usually has its onset during the first 6 months of life. The prevalence of Atopic dermatitis is similar in the United States, Europe, and Japan and is increasing, similar to that of other atopic disorders, particularly asthma. Atopic dermatitis has been classified into 3 sequential phases: infantile, childhood, and adult, each with characteristic physical findings.

Atopic dermatitis one of the most common skin disorders seen in infants and children, has its onset during the first 6 months of life in 45% of children, the first year of life in 60% of affected individuals, and before 5 years of age in at least 85%of affected individuals.[1] Although the term eczema is frequently used, Atopic dermatitis is a more precise term to describe this subset of dermatitis.

The prevalence of Atopic dermatitis in the US childhood population is 17.2% [2] and is similar to the 15.6% prevalence described in European children [3] and the 24% prevalence in 5- to 6-year-old children in Japan.[4]

Phases of atopic dermatitis:

The infantile phase of Atopic dermatitis reflects the manifestations of Atopic dermatitis from birth to 2 years of age (Fig 1). The erythematous papules and vesicles typically begin on the cheeks, forehead, or scalp and are intensely pruritic. Lesions might remain localized to the face or might extend to the trunk or particularly the extensor aspects of the extremities in scattered, ill-defined, often symmetrical patches.

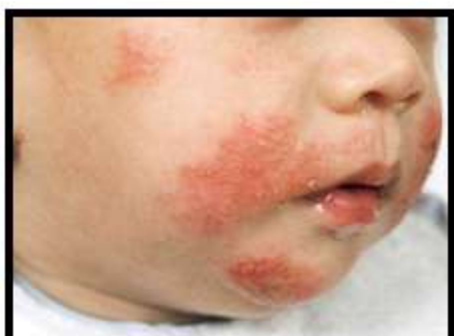

Figure 1: Atopic dermatitis phase 1

The childhood phase of AD might follow the infantile stage without interruption and usually occurs during the period from 2 years of age to puberty. Children are less likely to have the exudative lesions of infancy and instead exhibit more lichenified papules and plaques representing involvement of extensor areas.

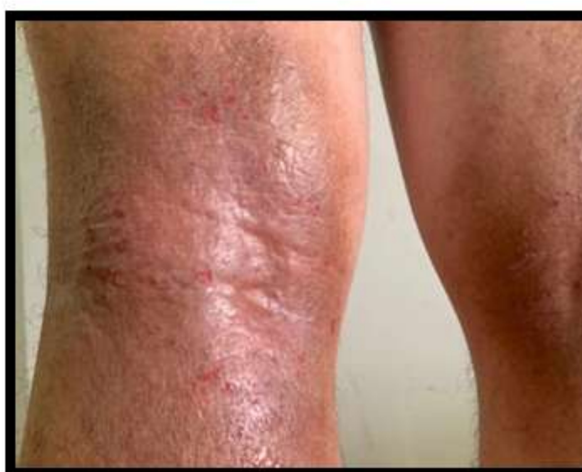

Figure2: Atopic dermatitis phase 2

The adult phase of AD begins at puberty and frequently continues into adulthood. Predominant areas of involvement include the flexural folds, the face and neck, the upper arms and back, and the dorsa of the hands, feet, fingers, and toes. The eruption is characterized by dry scaling erythematous papules and plaques and the formation of large lichenified plaques from lesional chronicity. Weeping, crusting, and exudation might occur but usually as the result of superimposed staphylococcal infection.[5]

more chronic disease. The classic areas of involvement in children are the hands, feet, wrists, ankles, and antecubital and popliteal regions (Fig 2). Although localization at flexural areas is more common, some children show an “inverse” pattern with primarily

Figure3: Atopic dermatitis phase 3

II. INTRODUCTION OF CUBOSOMES:

Surfactant and polymers are generally used in the controlled drug delivery systems. Surfactant and polymer systems form supra-assemblies, which are extensively exploited as active delivery vehicles. These systems include cross-linked gel networks (hydrogels) or liquid crystalline aggregates (liposomes and cubosomes), which load, stabilize, and ultimately transport active components.

Bicontinuous cubic phase liquid crystals known as cubosomes have a number of characteristics that make them an attractive option for use as a generic medication delivery vehicle.

Cubosome particles are first prepared by mechanical fragmentation of the cubic lipid-water phase in a three-phase region containing a liposomal dispersion and to differentiate from liposomes, these particles have been termed as cubosomes.Its structure differs from liposomes in

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that it may hold molecules that are amphiphilic, lipid-soluble, and water-soluble all at the same time.[7][8][9][10][11]

III. STRUCTURE OF CUBOSOMES:

Cubosomes were characterized by a wide interfacial area and honeycombed features that separated the two internal aqueous channels.Cubosomes are nanoparticle more accurately nanostructure particles of a liquid crystalline phase with cubic crystallographic symmetry formed by the self-assembly of amphiphilic or surfactant like molecules.

The cubosomes having high internal surface area along with cubic crystalline structures.

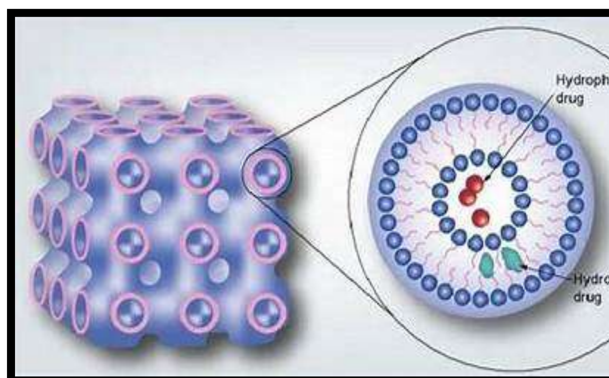

Figure 4: Structure of cubosome

IV. PREPARATION OF CUBOSOMES:

Cubosomes can be prepared by two distinct methods:
1. Top-down technique
2. Bottom-up technique

1.TOP-DOWN TECHNIQUE:

It is the most widely used technique initially reported in 1996 by LjusbergWahren.After being originally manufactured in bulk cubic phase, it is processed into cubosome nanoparticles using high energy methods such high-pressure homogenization. Bulk cubic phase mimics a clear rigid gel formed by water-swollen crosslinked polymer chains. The cubic phases differ in that they are a single thermodynamic phase and have periodic liquid crystalline structure.

Cubic phases break in a direction parallel to the shear direction, the energy required is equivalent to the number of tubular network branches that breaks.It is most commonly employed in research areas where the bulk cubic phase is manufactured first and then splits into

The cubic phases possess a very high solid like viscosity, which is a unique property because of their intriguing bi-continuous structures which enclose two distinct regions of water separated by a continuous water and oil channels, where “bi-continuous” refers to two distinct hydrophilic regions separated by the bilayer.

The structure's interconnectivity produces a transparent viscous gel with a rheology and look akin to cross-linked polymer hydrogels.However, monoglyceride based cubic gels possess significantly more long-range order than hydrogels and because of their composition, excellent biocompatibility.[12]

nanoparticles called cubosomes using high-energy processing.

Bulk cubic phase is mimic a clear rigid gel formed by water swollen cross Linked polymer chains whereas cubic phases are like liquid crystalline shapes.

Yield stress is shown by the cubic phases to rise with the concentration of oils and surfactants that form bilayers. According to Warr and Chen, dispersed liquid crystalline particles develop at transitional shear rates, then the dominant free bulk phase reforms at higher shear rates. Cubic phases are shown to behave as lamellar phases during dispersion with increasing shear.

Based on most existing studies similar to dispersion produced by sonication and high-pressure homogenization suggests the formation of complex dispersions containing vesicles and cubosomes with time dependent ratios of each particle.

The D-surface structure of course cubosomes on a micron scale is identical to that of their developing bulk cubic phase; but, due to the addition of polymers, the P-surface becomes dominant following homogenization.[14]

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 procedure is also developed to produce the cubosomes from powdered precursors by spray drying method. Spray dried powders including monoolein coated with starch or dextran form cubosomes on simple hydration.

Colloidal stabilization of cubosomes is spontaneously provided by the polymers.Cubosomes are permitted to develop or crystallize from precursors in this way. The bottom-up approach first forms the nanostructure building blocks and then gather them into the final material.

It is more recently developed method of cubosome formation, allowing cubosomes to form and crystallize from precursors on the molecular length scale.

The key factor of this method is hydro trope that can dissolve water insoluble lipids into liquid precursors. This is a dilution-based approach that produces cubosomes with less energy input when compared top-down technique. [15]

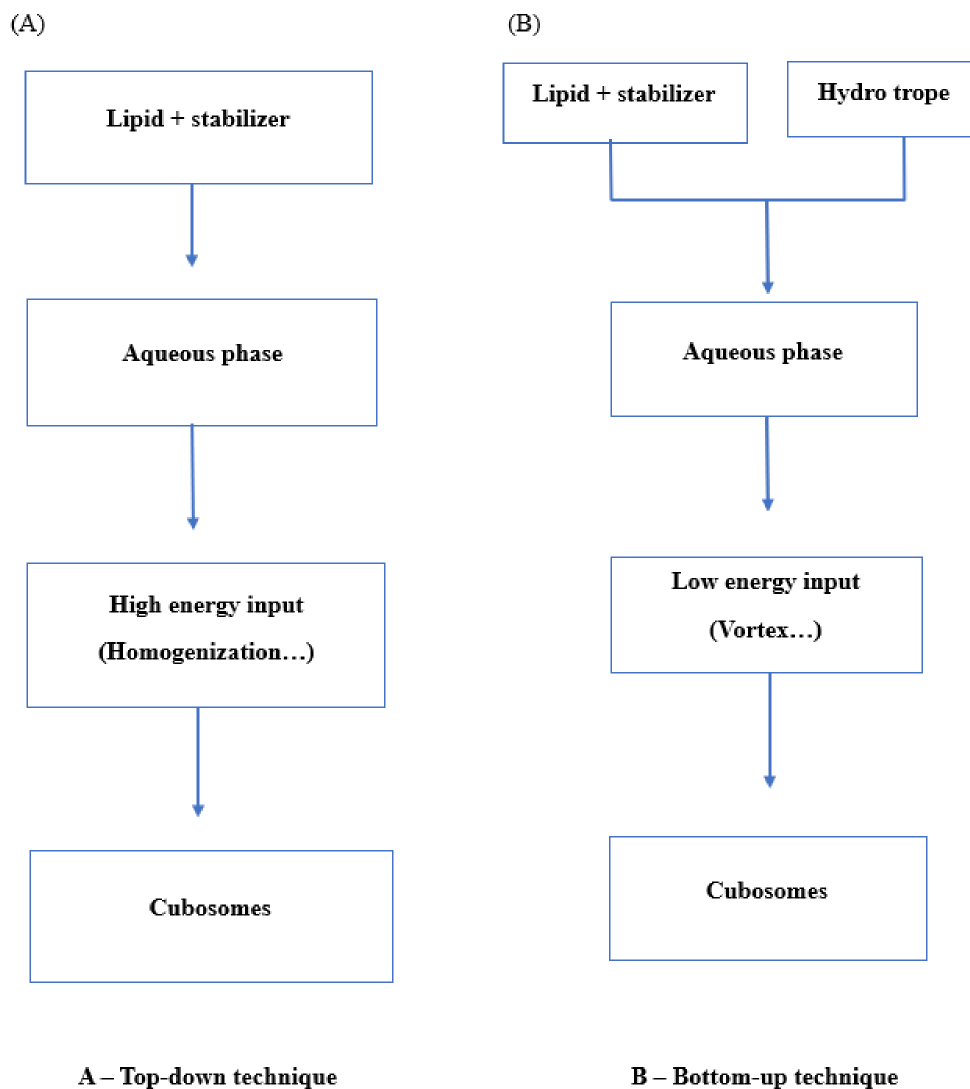

Figure 5. Preparation of Cubosomes

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V. APPLICATION OF CUBOSOMES:

•High internal surface area and cubic crystalline formations result in high pharmacological payloads.
• Relatively simple method of preparation
• Biodegrability of lipids
• Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.
• Targeted release and controlled release of bioactive ingredients.
• It acts as a penetration enhancer allowing the drug to penetrate the stratum corneum and ever deeper skin layers to some extent.
• The cubic phases of cubosomes can be fractured and dispersed to form particulate dispersions that are colloidally and thermodynamically stable for long time.

VI.. MATERIALS AND METHOD:

1. MATERIALS:

Crisaborole was gifted by Virupaksa Organic Limited Telangana. Glyceryl monooleate (GMO) was gifted by Mohini Organics Pvt. Limited, Mumbai, India. Poloxamer 407 was a kind gift from Daewoong Pharmaceuticals, Hyderabad. Crisaborole was a gift sample from Virupaksa organic Pvt. Limited, Hyderabad, A.P, India. Carbopol 934, Carbopol 940, were gift samples from Loba Chemie, Mumbai, India. HPMC K4M and HPMC K15M were of commercial grade. All other reagents used were of analytical grade.
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2. METHOD:

Preparation for Crisaborole Loaded Cubosomes:

The cubosome of Glyceryl monooleate (GMO)/poloxamer 407 was prepared using the top-down method. Poloxamer407 GMO (F127) and GMO were melted at 60°Cover a water bath, then the Crisaborole was added to the above molten mass with continuous stirring until it completely dissolved. 3 ml of Deionized water was gradually added with vortex mixing, until homogenous state was achieved. The cubic phase was obtained, after equilibration for (24 h) at ambient temperature. Cubic phase was disrupted by adding the 10 ml of deionized water with stirring on magnetic stirrer. Coarse dispersion was fragmented by intermittent probe sonication was for 15 min. The specified number of cycles of homogenization was carried out using the high-pressure homogenizer to obtain cubosomes. Cubosomes were then stored in a refrigerator (4–8°C) until required. The composition of prepared cubosomal formulation as per table no.01.[16]

Preliminary Trial Batches of Crisaborole Cubosomes:

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

Table:1: Preliminary Trial Batches of Crisaborole Cubosomes

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

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VII. FORMULATION OF GEL:

Formulation of Cubosomal Loaded Gel:

CRB cubosomes loaded topical cubosomal gel will be by the cold mechanical method as described previously. The Carbopol 934 in a specific quantity will be added into 50 ml of Milli Q water under constant stirring at 500 rpm for about 2h until clear dispersion of gel will be obtained. The cubosomes equivalent to 2% CRB will be added into the above mixture and under constant stirring. The specific amount of TEA will be slowly added into the above mixture drop by drop to attain neutral pH. The prepared CRB cubosomal gel formulation will be kept for 24h ,which finally led to the formation of a white Cubosomal Gel.[17][18]

VIII. RESULT AND DISCUSSION:

1. Organoleptic Properties of Crisaborole:

Table:2:Organoleptic Characterization

Colour	White
Odour	Odourless
Appearance	White Solid

Figure 5: Chemical Structure of Crisaborole

2. Melting Point of Crisaborole:

Table:3: Melting Point Determination

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

3. FT-IR STUDY of Crisaborole:

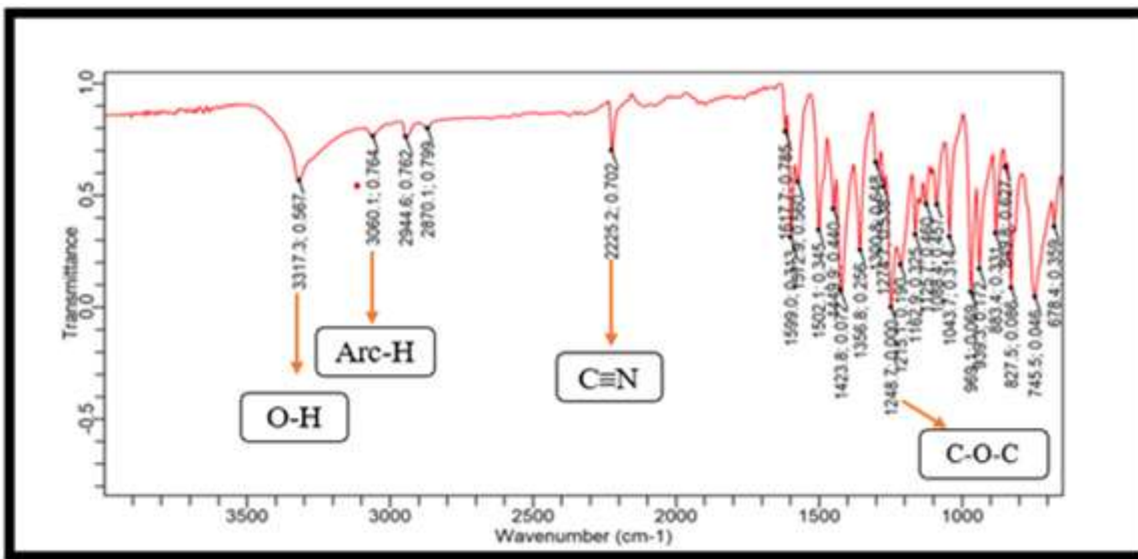

Figure:6: Identification of Crisaborole by FT-IR:

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4. Determination of λmax by UV Visible spectroscopy:

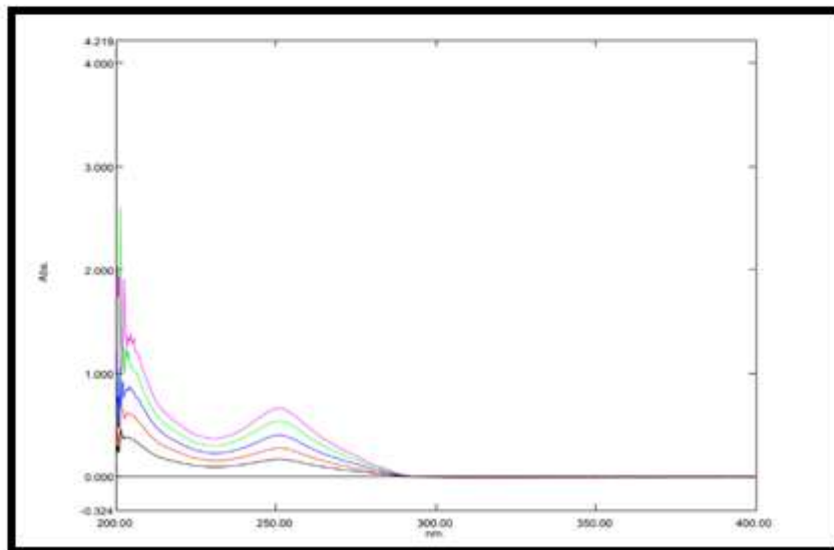

Figure:7: Linearity plot of Crisaborole

5. Linearity plot of Crisaborole:

Table:4: Standard Calibration Curve of Crisaborole

Sr.no	Conc. µg/ml	Mean Absorbance (nm) n=3; mean(±SD)
1	2	0.164 (±0.002)
2	4	0.273 (±0.001)
3	6	0.398 (±0.0005)
4	8	0.53 (±0.01)
5	10	0.65 (±0.005)

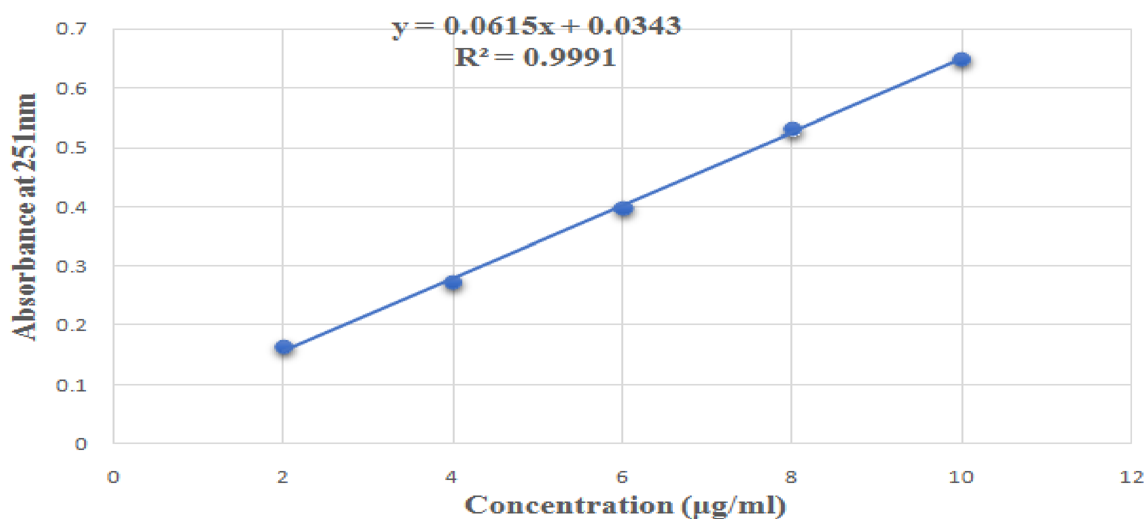

Figure:8: Standard Calibration Curve of Crisaborole summary

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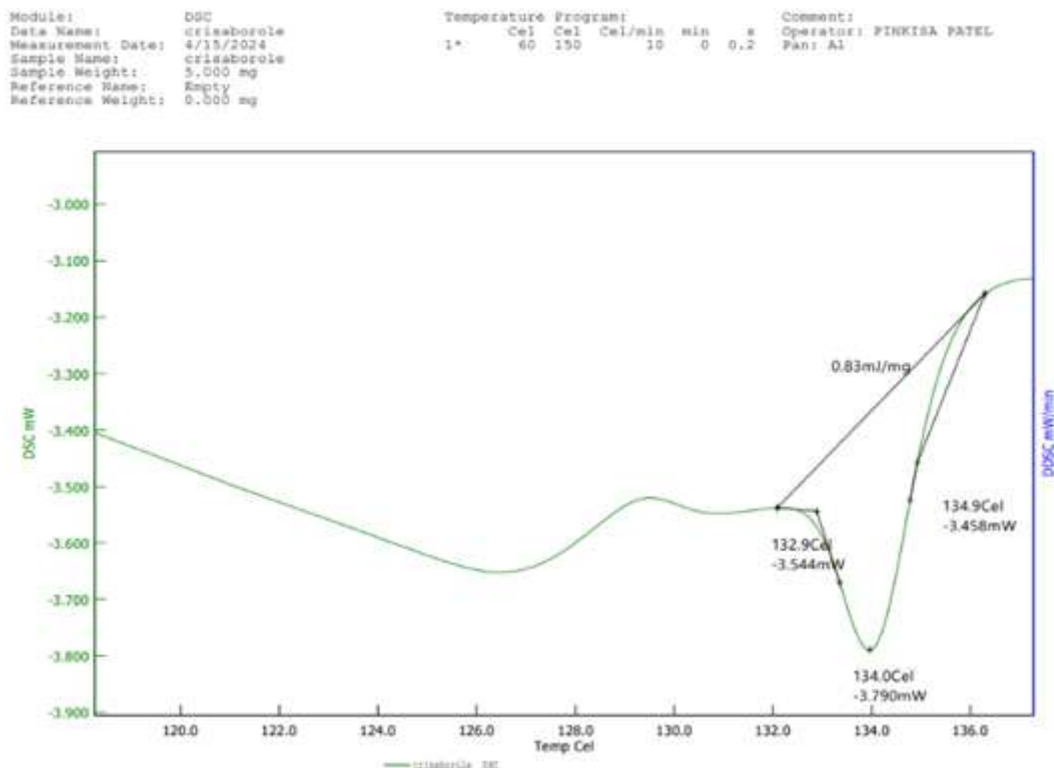

Figure no:9:DSC Thermal Analysis Result of Crisaborole

6. Characterization pf Cubosomes:

Table:5: Particle size, PDI, Zeta potential, % Entrapment Efficiency

Formulation number	Particle size (nm)	PDI	Zeta potential	EE%
C1	135.70 ± 0.58	0.249 ± 0.01	-21.50 ± 4.25	91.95 ± 0.50
C2	141.84 ± 0.63	0.22 ± 0.00	-21.40 ± 2.66	73.20 ± 0.42
C3	182.50 ± 0.24	0.31 ± 0.08	-23.20 ± 1.15	63.50 ± 1.41
C4	091.80 ± 1.10	0.21 ± 0.01	-11.40 ± 2.37	82.40 ± 1.55
C5	110.85 ± 1.34	0.19 ± 0.01	-14.65 ± 2.05	82.00 ± 1.41
C6	183.75 ± 3.61	0.30 ± 0.01	-15.20 ± 0.42	81.13 ± 1.62
C7	082.67 ± 2.68	0.25 ± 0.01	-08.20 ± 0.42	73.25 ± 0.92
C8	094.48 ± 1.16	0.22 ± 0.01	-14.55 ± 0.35	88.90 ± 2.40
C9	143.75 ± 33.16	0.31 ± 0.09	-13.85 ± 2.19	87.48 ± 1.15
C10	117.55 ± 7.74	0.19 ± 0.03	-17.40 ± 1.58	81.10 ± 2.61
C11	111.70 ± 2.74	0.18 ± 0.01	-20.05 ± 3.30	79.00 ± 1.67
C12	172.00 ± 3.54	0.34 ± 0.02	-24.65 ± 3.60	84.50 ± 1.73
C13	151.10 ± 2.28	0.24 ± 0.10	-25.10 ± 2.26	87.36 ± 5.69

The concentration Poloxamer 407 and GMO have the significant impact on the average particle size shown in the table. The particle size of the crisaborole loaded cubosomes were found between the 82.67±2.68 nm (C7) to 183.75±3. nm (C6). As the concentration of the GMO increases, particle size of the cubosomes increases. Increasing in the GMO concentration may lead to increase in

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the viscosity, which may oppose the emulsification process of cubosomes.[19] As the poloxamer concentration increases the particle size of the cubosomes decreases as the poloxamer may reduce the surface tension during the emulsification process. As in the result, increase in the Poloxamer 407 concentration from 0.5% Poloxamer 407 (C1) to 1.5 % Poloxamer 407 (C7) formulation the particle size decreases 110.90 ± 0.58nm to 082.67 ± 2.68nm respectively.[20]

Homogenization cycle have significant impact on the particle size of the cubosomes. Upon increasing the homogenization cycle from one cycle to the two cycle the significant decrease in the particle size was observed. This occurs due to the increase in the mechanical shear.[21] while the carryout another 3rd cycle of the homogenization., the particle size was found to be increase (C13) 151.10 ± 2.28nm this is caused because of the aggregation of the small particle may lead to the formation of the bigger particle.

Sonication time does not have much impact on the particle size of the cubosomes. Upon increasing the sonication time from the 10 minutes, 15 minutes and 20 minutes slight reduction in the particle size was found.

PDI values were obtained between the 0.13 ± 0.01 to 0.34 ± 0.02, which indicated the acceptable size distribution of all cubosomal formulation.

The result of zeta potential of all the formulation was found to be negative this may be due to the ionization of free oleic acid in GMO which may observed on the surface of the GMO.[22][23].

Entrapment efficiency also affected by the polymer concentration as the poloxamer407 concentration increases, decrease in the entrapment efficiency.[24].

As the sonication time increases from the 15 minutes (C1 formulation) to 20 minutes (C11 formulation), increase in the shear stress which may lead to reduction in the entrapment efficiency. So, it was concluded that optimum sonication time was 15 minutes.

Homogenization speed; one cycle, two cycle and 3 cycles has not much impact on the entrapment efficiency.[25]

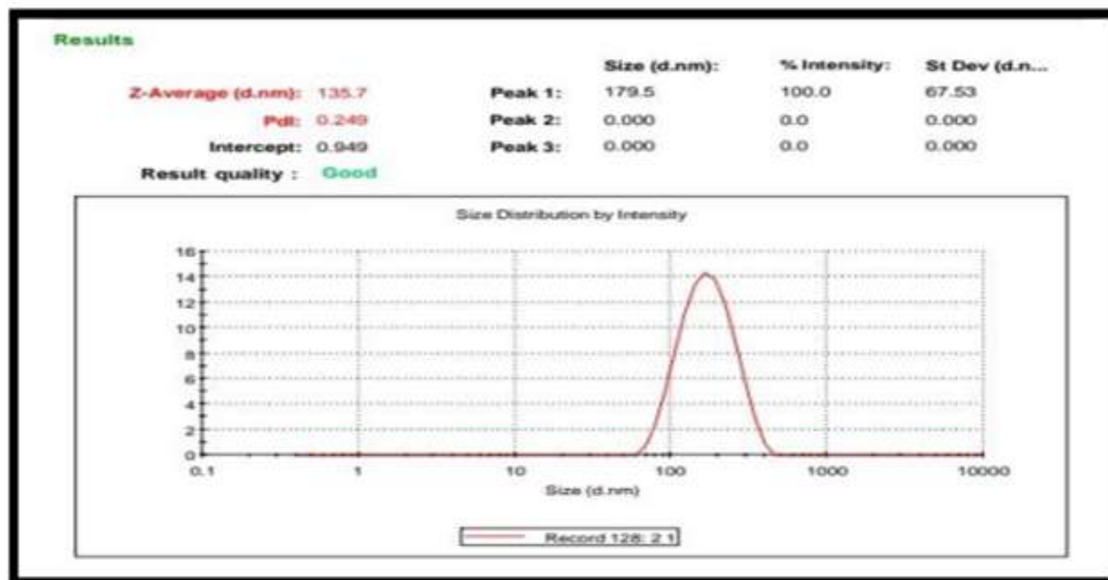

Figure:10: DLS interpretation of formulation C1

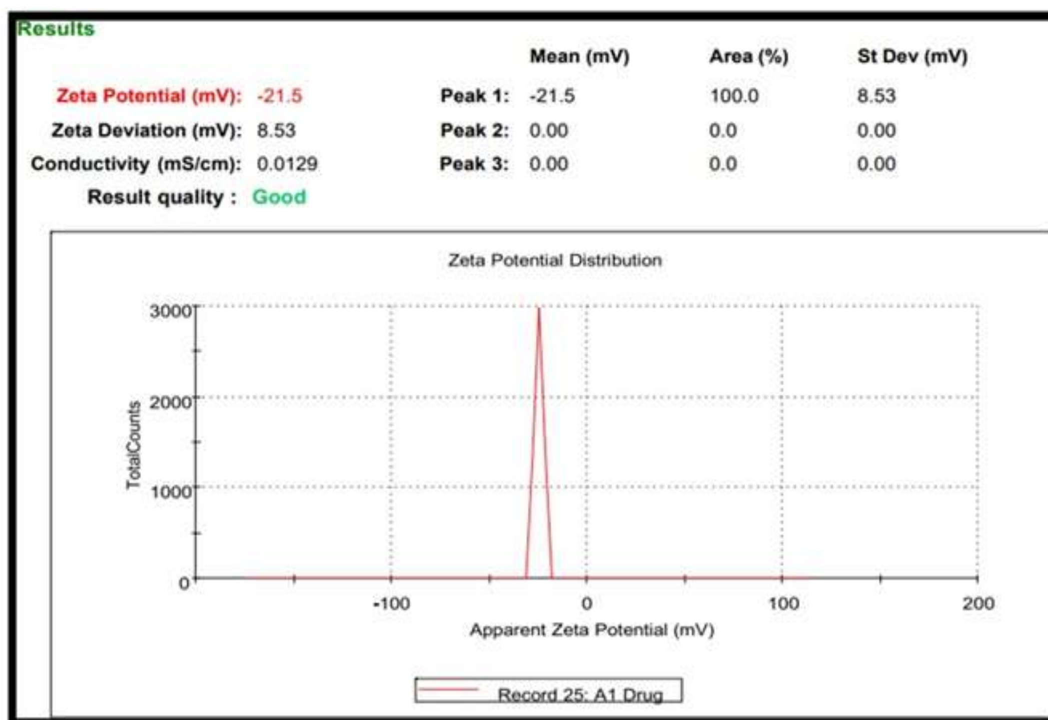

Figure:11: Zeta potential of drug loaded Cubosomes

IX. CHARACTERIZATION OF THE CRISABOROLE LOADED CUBOSOMAL GEL:

1. Visual appearance:

The cubosomal gel was white and homogeneous with no evidence of separation according to the visual inspection.

Figure:12: Visual appearance Cubosomes batches C1 to C6

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Figure:13: Visual appearance Cubosomes batches C7 to C13

Figure:14: Optimized formulation of Cubosomal Gel

2. pH Measurement:
The pH was measured using digital pH meter. The pH of the optimized Cubosomal loaded gel was found to be 6.2. which is similar to pH of human skin (4.5 to 6.5).

3. Viscosity of the cubosomal Gel:
The viscosity studies were done in Brookfield viscometer using a T bar spindle which was rotated at a speed of 30 rpm. The results showed that the optimized Cubosomal loaded gel had good viscosity properties.

Table:6: Viscosity of Cubosomal Gel

Time (min)	Spindle	RPM	Viscosity (csp) (±SD)
5	T bar spindle	30	38434 (±0.08)

4. Spreadability:
The spreadability was found to be **4.45 (±0.12) gm .cm/sec** which indicated easy application of gel to the skin surface.

Figure:15: Spreadability Test

5. Transmission electron microscope:
Morphological appearance of the cubosomal dispersion was carried out using the Transmission electron microscopy. The shape was found to be cubic and cubosomes were found to be well isolated.

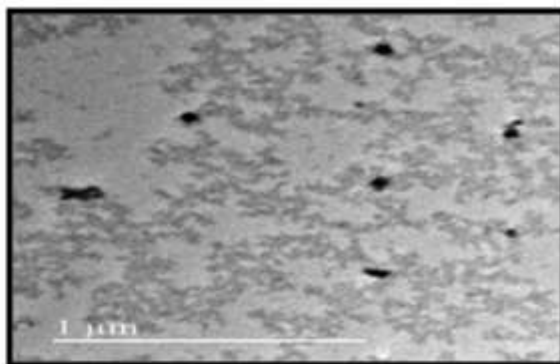

Figure:16: Drug Loaded Cubosomes 1µm

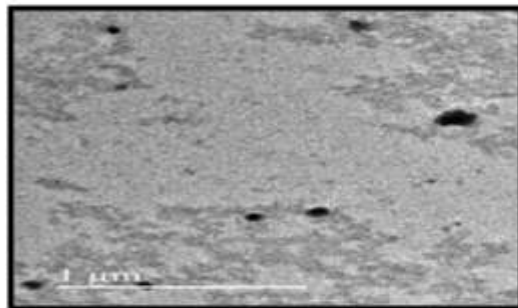

Figure:17: Cubosomal Gel 1 µm

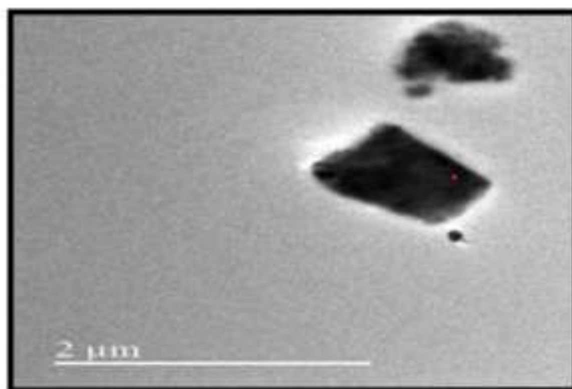

Figure:18: Drug Loaded Cubosomes 2 µm

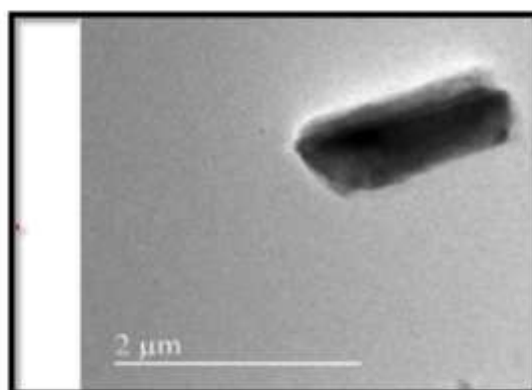

Figure:19: Plain Cubosomes 2 µm

6.In-vitrodrug release studies:

Table:7: %CDR of Pure drug suspension and optimized Cubosomal Gel

Sr.no	Time(h)	% CDR of Pure drug suspension	% CDR of optimized Cubosomal formulation	% CDR of Cubosomal Gel
1	0.5	15.37	3.51	1.51
2	1	40.1	14.78	11.20
3	3	68.59	33.11	30.26
4	6	97.95	56.5	47.68
5	9	-	80.03	73.75
6	12	-	88.8	83.52

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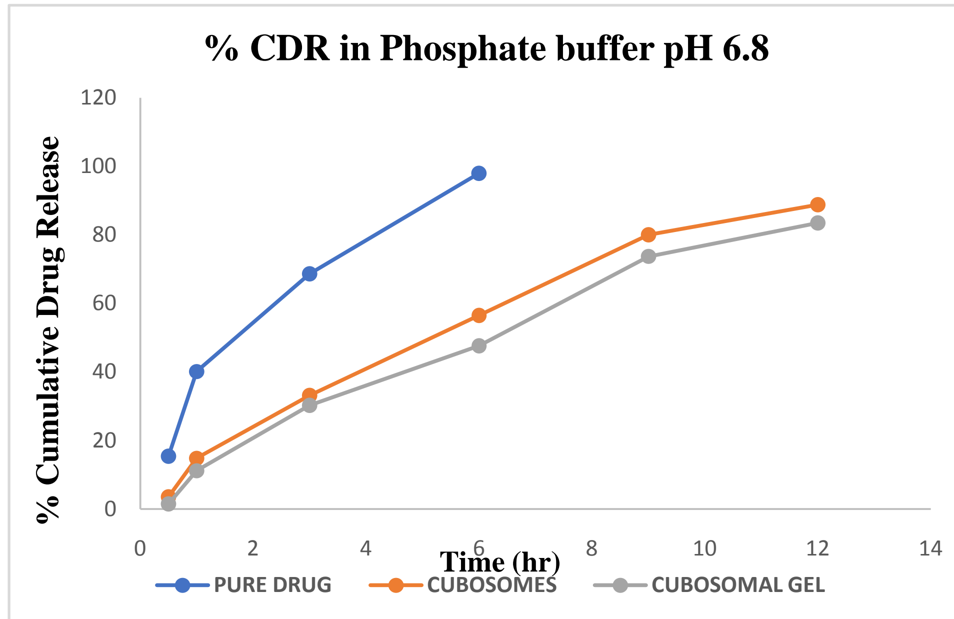

Figure:20: Plot of CDR of optimized Cubosomal Gel and pure drug suspension vs time

7. Stability study:

Cubosomal formulation remained white and homogeneous with no evidence of separation according to the visual inspection. The percentage drug release was found to be 82.24%. there is no significant change after 30 days.

Table:8: Stability study by % Cumulative drug release

Time (h)	% Cumulative drug release	
	Initial	After 30 Days
0.5	1.51	1.48
1	11.2	10.98
3	30.26	29.33
6	47.68	44.66
9	73.75	70.23
12	83.52	82.24

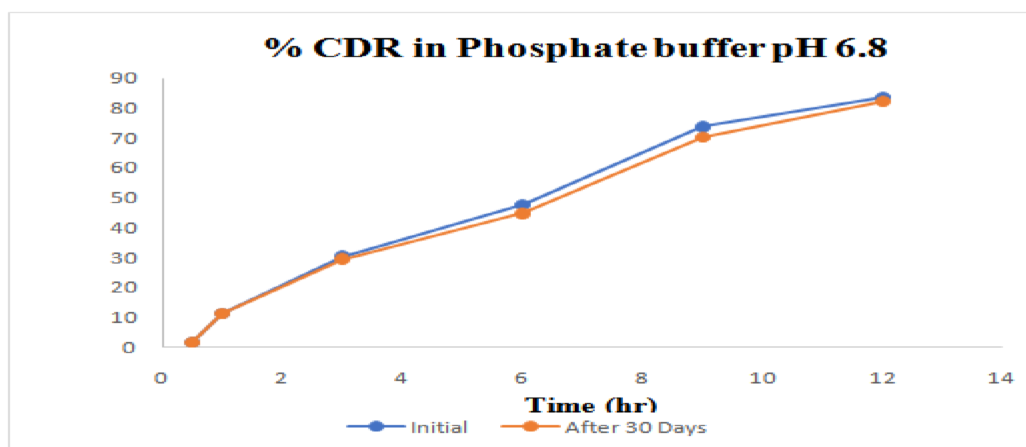

Figure:21: Comparative in-vitro drug release

IX. CONCLUSION:

The topical cubosomal gel gain the importance due to the unique 3D structure and ease of formulation. Cubosomes can be prepared using the combination of biocompatible lipid (GMO), Poloxamer 407 Stabilizer and water as a vehicle. Biocompatible GMO use as lipid having the capability of accommodating both hydrophilic and hydrophobic drug. Poloxamer 407 is use as a stabilizer to prevent aggregation crisaborole is a BCS class II drug and formulated to cubosomes in order to sustain release. Cubosomes formulation prepared using GMO (2%), Poloxamer 407 (1%) so good entrapment efficiency and drug constant release (91.95 ± 0.50). To sustained release C1 formulation of cubosomes are in corporated in to gel using Carbopol 934. The above Research explore the cubosome utility as prolong release drug carrier due to the topical gel formulation.

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