"FABRICATION AND CHARACTERIZATION OF CRISABOROLE LIPID NANO PARTICULATE SYSTEM FOR THE TREATMENT OF ATOPIC DERMATITIS"

A Thesis Submitted to

NIRMA UNIVERSITY

in Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

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May 2020

CERTIFICATE

This is to certify that the dissertation work entitled "Fabrication and Characterization of Crisaborole Lipid Nanoparticulate System for The Treatment of Atopic Dermatitis" submitted by Mr. Mayur Chaudhary with Regn. No. (18MPH106) in partial fulfillment for the award of Master of Pharmacy in "Name of a Department" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University under my/our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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CERTIFICATE OF ORIGINALITY OF WORK

This is to undertake that the dissertation work entitled "Fabrication and Characterization of Crisaborole Lipid Nanoparticulate System for The Treatment Of Atopic Dermatitis" Submitted by Mayur Chaudhary (18mph106) in partial fulfillment for the award of Master of Pharmacy in "Name of M.Pharm. Programme" is a bonafide research work carried out by me at the "Name of Department", Institute of Pharmacy, Nirma University under the guidance of "Name of a Guide and Co-guide". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, this work is original and not reported anywhere as per best of my Knowledge.

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DECLARATION

I hereby declare that the dissertation entitled "Fabrication and Characterization of Crisaborole Lipid Nanoparticulate System for The Treatment Of Atopic Dermatitis", is based on the original work carried out by me under the guidance of Dr. Mayur Patel, Associate Professor, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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Regards
Mayur Chaudhary

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ABSTRACT

Dermatitis is known as skin inflammation having symptoms like dry, swollen, and red skin. Generally long contact with a surfactant, heavy metals, detergent, etc causes dermatitis. Dermatitis is a very common skin disorder. The objective of this study was to formulate and characterize Crisaborole loaded Nanostructured lipid carriers (NLCs). Crisaborole is an anti-inflammatory agent That acts as a phosphodiester-4 inhibitor and use for the treatment of atopic dermatitis. Crisaborole loaded NLCs will be incorporated in gel because of ease in topical administration. Crisaborole NLCs were due to its small size and lipidic nature showing better penetration Precirol ATO 5 as a solid lipid and Glyceryl monooleate as a liquid lipid was selected based on the highest solubility of Crisaborole. While Tween 20 was selected as a surfactant was selected based On minimum solubility of crisaborole and T20 ability stabilization. Hot melt homogenization technique used to formulate NLCs and effects of different factors like surfactant type and its concentration, co-surfactant type, and its concentration, effect of homogenization speed was studied on the formulation characteristics. NLCs were characterized by Particle size, Entrapment Efficiency. The particle size of Crisaborole loaded NLCs was 100nm to 150nm; which is optimum for topical delivery and observing PDI-0.251. %EE is also 82% that shows good entrapment of Crisaborole.

1. INTRODUCTION

1.1 INTRODUCTION TO ATOPIC DERMATITIS

Around a total of 20% of people in this world suffers from Atopic Dermatitis (AD), The main symptoms associated with Ad are skin eruptions and itching thus resulting it into very chronic skin disease. It is estimated that about 40 million patients are suffering from atopic dermatitis. (1) This disease is ignored in its starting stages and then develops into asthma and atopic rhinitis in the future. (2) But, the problem of increasing in cost of healthcare and deteriorating quality of life is increases, a rapidly spreading atopic dermatitis is the major contributor in developing countries. The most common signs and symptoms associated with this chronic disorder are sleep loss, dietary restrictions, eczematous lesions, pruritus, etc. (1)

Skin eruptions (Pruritis) being the most common characteristic of atopic dermatitis. It can be intense and, at times, be disturbing to the sleep. It results in skin scratching and turns, leads to changes in secondary skin changes such as disrupted skin barrier. Depending on the severity of the inflammation, secondary infections, and age, skin abrasions vary greatly. Eczematous lesions around the areas of flexure, the neck, wrist, and ankles are common in children. (1)

1.1.1 PATHOPHYSIOLOGY (3)

Barrier dysfunction:

Various kinds of abnormalities in the barrier dysfunction is the primary reason associated with the early development and early onset of action of atopic dermatitis. Various factors are responsible and attribute to atopic dermatitis; some of them are modulation caused by several processes the modifications into the SC PH. Mutations into the fillarin gene and the overexpression into the proteases leads to

barrier dysfunction. Profilaggrin, a protein consisting of a molecular weight of 400KDa is cleaved when the differentiation of keratinocytes takes place. The protein is cleaved into 11-12 different FLG molecules which are placed into the layers of the epidermis, mainly the granular layer.

Proteases enzyme then cleaves the FLg molecule into the natural moisturizing factors (NMFs). This NMF is mainly responsible for the low Ph and maintenance of moisture into the skin. NMF production is directly affected by the mutation into the FLG gene, and thus the production of the FLG gene gets affected by it.

The PAR 2 enzyme is activated by the kallikreins, which is a skin pH-sensitive protease, and thus this PAR2 enzyme induces the NFKB controlled upregulation of the TSLP. Thus, this process leads to the aggravation of AD skin lesions. Barrier dysfunction because of inhibition of S100/A11 protein.

The more enhanced intercellular adhesion molecule 1 (ICAM-1), E-selectin, and also vascular cell adhesion molecule 1 (VCAM-1) is done by the proliferation of keratinocytes. This is mainly responsible for the increase in the epidermal cytokines.

1. The Itch–Scratch Cycle:

Many symptoms are associated with AD, but the most common symptom related to the Ad is the Itching sensation. Although Histamine is the most vital pruritogen, research has shown that antihistaminic is not so effective in the treatment of AD. The plasma nerve growth factor NGF that is produced by the keratinocytes is now elevated into the patients suffering from the Atopic dermatitis. This leads to an increase in the number of epidermal nerve fibers. Thus, all factors contribute to the itchy skin caused due to mechanical stimulation. The pruritis and the barrier status are closely linked to each other. Scratching on to the skin surface leads to the

disruption of the skin and its surface and the Results into constant increase into the epidermal nerve fibers and thus results in enhanced susceptibility of the skin surface to pruritis. Another factor that contributes to the predisposition to the skin and results in pruritis is the dry skin. Also, this dry skin is responsible for the barrier disruption.

This scratching then results in the induction of the eosinophil infiltration and thus attracts the Th2 cells mainly by the eosinophil derived chemokine CCR4. The process of colonization of the S. aureus and the exposure to the superantigens is responsible for the induction and up-regulation of IL-31 mRNA and then contributes to the inflammatory responses & thus leads to pruritis.

Thus, Atopic dermatitis is a common disorder today faced by a number of patients today in the world. Atopic dermatitis is associated with a number of symptoms but is mainly associated with the Dry skin, Scratching, and thus, in turn, it leads to pruritis. As a number of patients are increasing day by day research is now enhanced, and researchers have gained interest today in the novel treatment and various newer methods to treat AD.

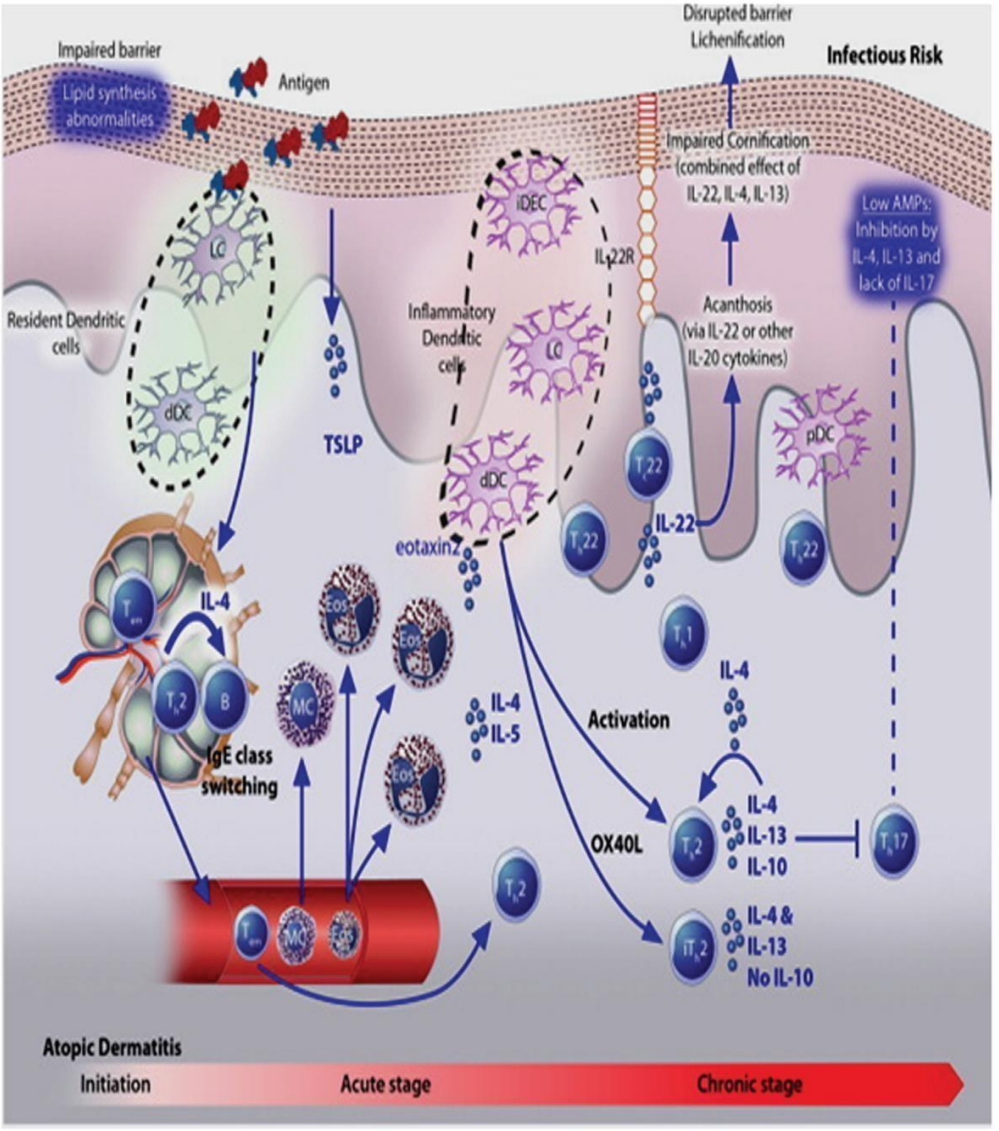


Figure:1.1- Pathophysiology of Atopic Dermatitis (3)

1.1.2 CURRENTLY AVAILABLE TREATMENT OF ATOPIC DERMATITIS *(4)(5)*

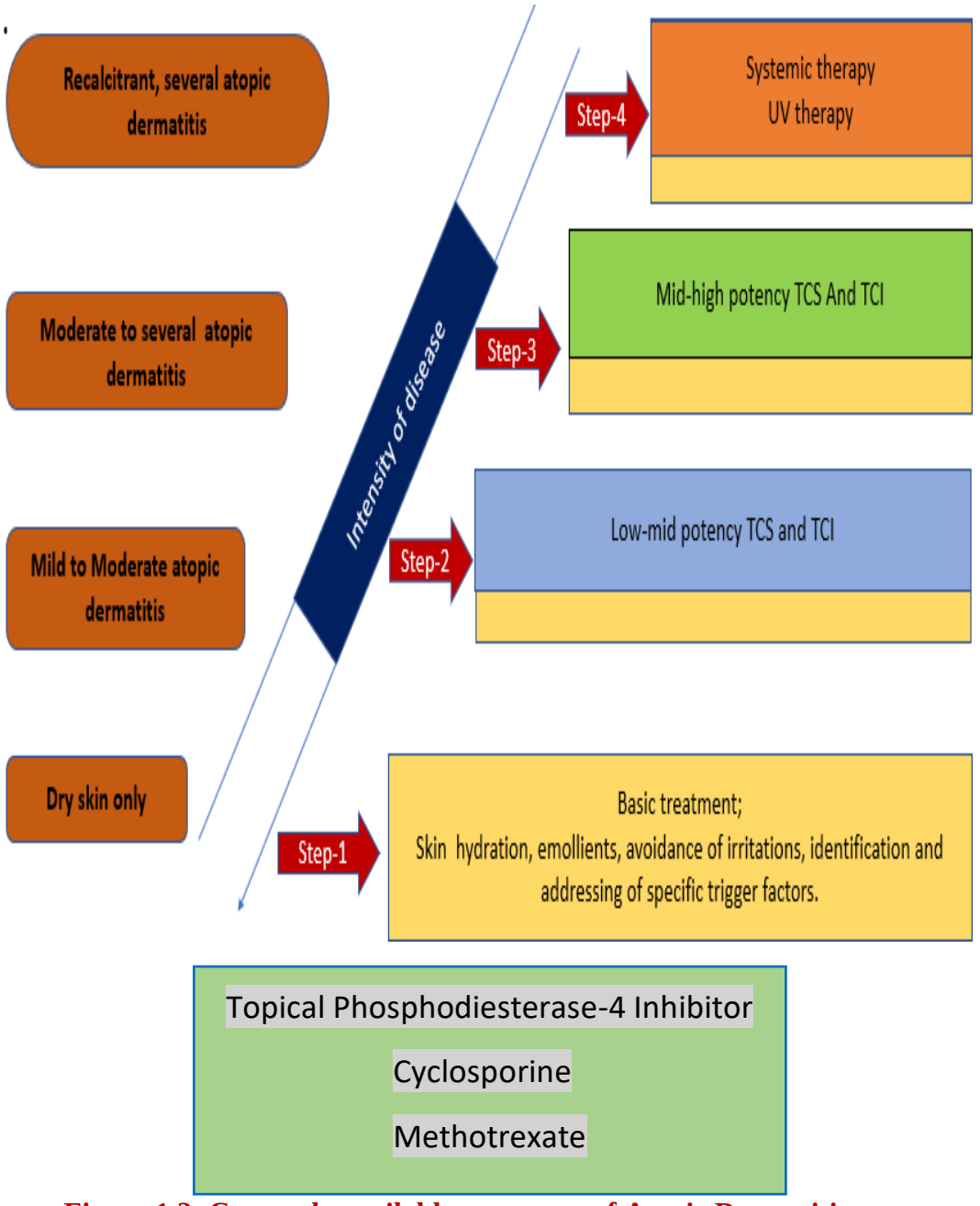


Figure 1.2: Currently available treatment of Atopic Dermatitis (4)(5)

Emollient

Emollient use foundation of topical atopic dermatitis therapy. The emollient product uses atopic dermatitis patients to decrease the risk of sensitization, and daily use emollient helps stabilize the skin barrier

And help prevent atopic dermatitis. Urea is generally emollient because the area acts exfoliating agents.

Topical corticosteroids

Atopic dermatitis for topical anti-inflammatory therapy cornerstone is a topical corticosteroid. Cornerstone act in host DNA binding glucocorticoid. This affect with antigen processing of numerous immune cell and release of pro-inflammatory cytokines. First-line treatment for atopic dermatitis uses topical corticosteroid. This treatment for the once a day and twice a day and this treatment continues daily for up to 28 days (high effectiveness corticosteroid) And supper high effectiveness corticosteroid up to 14 days.

Topical calcineurin inhibitor

The activity of the transcription factor is necessary for cell division to decrease because the inhibition of calcineurin selectivity provides anti-inflammatory and prevents T-cell activation. TCI is used for the treatment of AD (children 2-14 years old). Applied twice a day to face up to 14days. Side effects for burning and site pain.

Topical Phosphodiesterase-4 Inhibitor

Crisaborole has approved Food and drug administration in 2016 approved first phosphodiester-4 inhibitor use atopic dermatitis. Use 2 to 17 years old children. Apply for skin twice a day up to 28 days.

Methotrexate

Methotrexate is for first-line systemic therapy. It is a severe erythrodermic and low-cost API and oral formulation.

Cyclosporine

Cyclosporine potent immunosuppressant that inhibits interleukin-2 production and disrupts T-cell mediated function. Generally, it uses for short time courses during the atopic dermatitis therapy, and this treatment Usually uses 4-5 mg/day and for severe atopic dermatitis up to 28 days.

1.2 INTRODUCTION TO DRUG USED IN ATOPIC DERMATITIS TREATMENT:

1.2.1 MECHANISM OF ACTION PHOSPHODIESTER 4 INHIBITOR (6)(7)

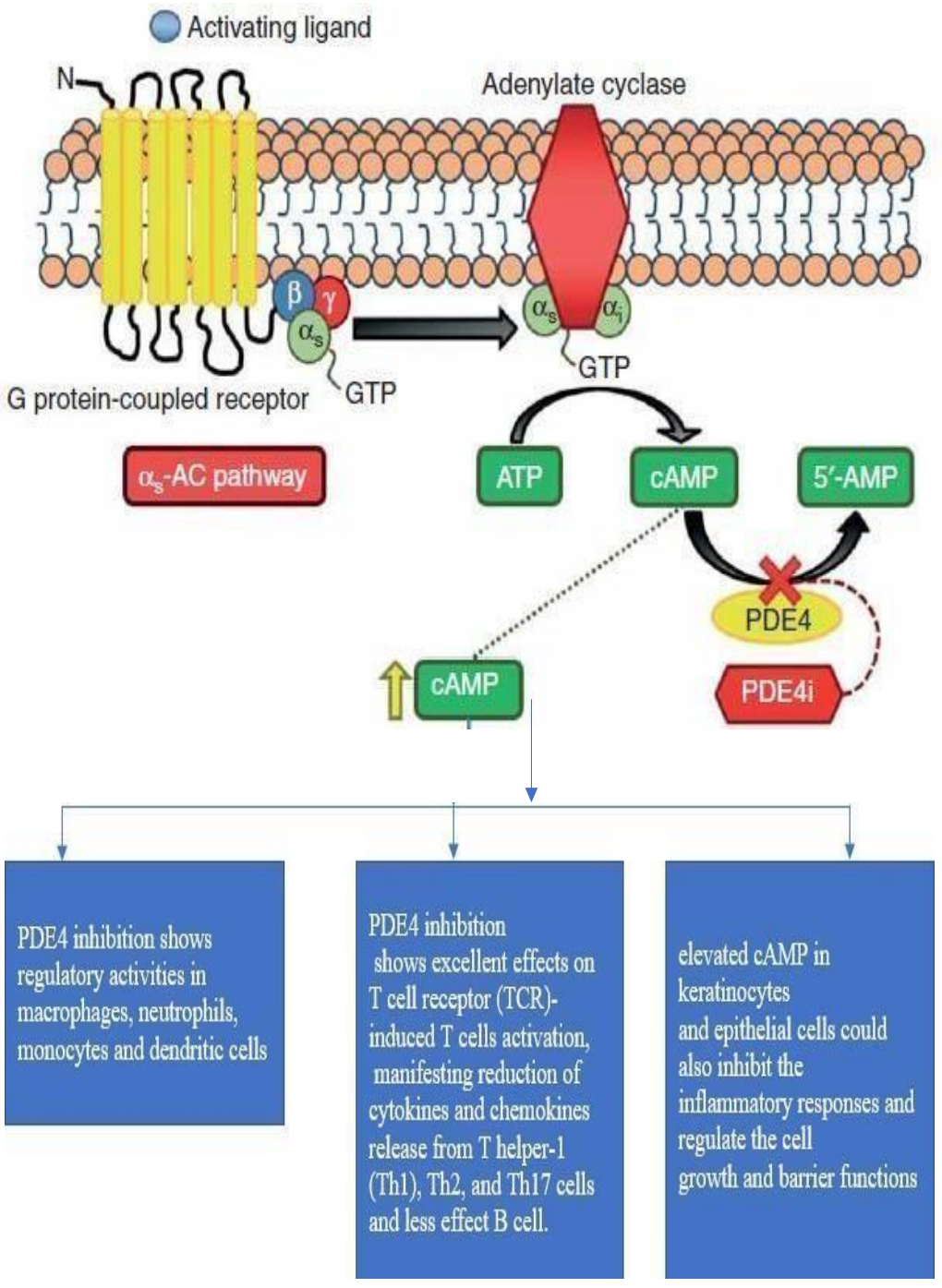


Figure 1.3: Mechanism of Action Phosphodiester 4 Inhibitor (6)

1.2.1 CLASSIFICATION FOR TREATMENT FOR ATOPIC DERMATITIS

Table -1.1 classification for treatment of atopic dermatitis. (5)

Sr no.	Class	Example of drug
1.	**Emollient**	• Cocoa butter • Shea butter • Mineral oil • Lanolin • Petrolatum • Paraffin
2.	**Topical Corticosteroids**	• Triamcinolone • Mometasone furoate • Flurandrenolide • Clobetasol propionate • Halobitasole propionate • Fluocinolone acetonide
3.	**Topical Calcineurin Inhibitors**	• Pimecrolimus • Tacrolimus
4.	**Phototherapy**	• Uv light
5.	**Phosphodiesterase-4 Inhibition**	• Crisaborole
6.	**IL-4 And IL-13 Inhibition**	• Dupilumab
7.	**Il-31 Inhibition**	• Nemolizumab

1.2.3 LIST OF MARKETED FORMULATION:

Table -1.2 marketed formulation (8)

Brand name	Generic name	Dosage form
Protopic	**Tacrolimus**	Ointment
Kenalog	**Triamcinolone**	Aerosol Solution
Embeline and Temovate/Clobex	**Clobetasol**	Cream/lotion
Elidel Pimecrolimus Cream	**Pimecrolimus**	Cream
Elocon	**Mometasone**	Cream
Diprolene	**Betamethasone dipropionate**	Cream
Cortizone	**Hydrocortisone**	Cream/ Ointment
Topicort and Topicort LP	**Desoximetasone**	Cream
Verdeso	**Desonide**	Foam
Cutivate	**Fluticasone**	Cream
Eucrisa	**Crisaborole**	Ointment

1.2.4 DRAWBACK FOR CONVENTIONAL FORMULATION (9)

- Many formulations of alcohol bases that can be irritated and lack of smoothness.
- Less penetration powers.
- Some formulation water-insoluble, so difficulty to wash because of the greasy formulation.
- Its Side effects in itching, irritation, and redness of the skin.
- Bulkier than solid formulation.
- Bioavailability less compares to nanoparticles.
- Less residency time in skin.

1.2.5 ADVANTAGE FOR NANOPARTICLES (10)

- More Half-life of a drug.
- Controlled release and Prolong release.
- Biocompatible and Biodegradable.
- Drug Dissolution and absorption are increases. Bioavailability becomes good.
- Nanoparticles based formulation drug targeting.
- Sterilization of nanoparticle easy feasibility.
- Large scale production is possible.
- Drug payload increases.

1.3 INTRODUCTION TO LIPID NANOCARRIER

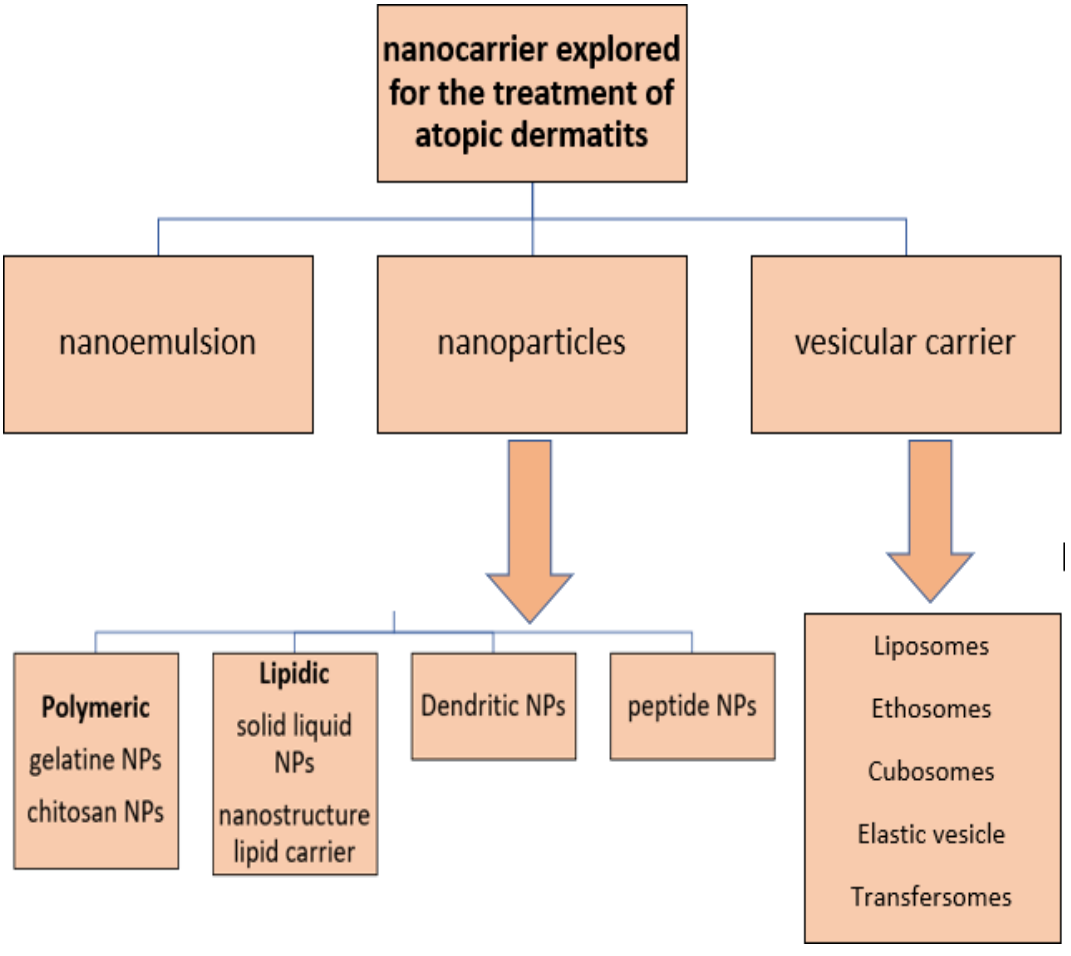


Figure 1.4: Nanocarrier explored for the treatment of atopic dermatitis - (8) (11)

1.3.1 INTRODUCTION FOR SLNs

SLN is the 1st generation of lipidic nanoparticles and This lipidic system colloidal drug delivery. Its range up to 40-1000nm. This system provides a controlled and sustained release effect because the solid lipid incorporates. The SLN is made up of solid lipids about 0.5-40% which is dispersed in the water phase and this was stabilized by using different surfactants in 0.1-5%. Solid lipids like Precirol ATO 5, compritol 888 ATO, GMS, stearic acid, glyceryl palmitostearate, etc. and for Surfactant like Poloxamer 188, polysorbate 20, polysorbate 80, solutol, etc. SLN is divided into three types. (10) (12)

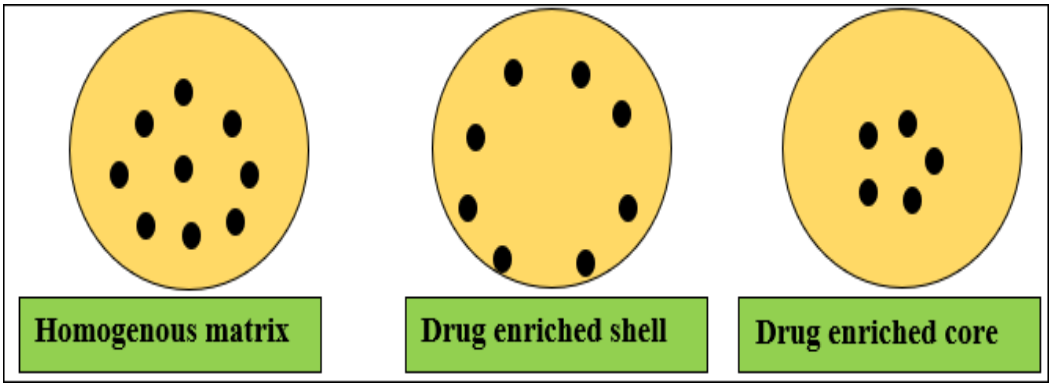


Figure 1.5: Types of SLNs (10)

ADVANTAGE OF SLNs (13)

- Controlled and sustained-release effect.
- Easy large-scale manufacturing.
- Biocompatible and bio degradable lipid use.
- Drug targeting.
- It is used for iv, oral and topical routes.
- Possible for the specific sites of action.

Disadvantages of SLN (13)

- Drug loading problem because of the crystalline structure of solid lipids.
- Sometimes stability problems.
- On storage time, drug expulsion.
- Gelation tendency.

- **EXCIPIENTS USE SLNS AND NLCS**

Table -1.3 Excipient use SLNs and NLCs (10)

Surfactant	Lipid
Non-ionic surfactants	**Fatty acids**
Tween 20,80	Dodecanoic acid
Span 20,80,85	Myristic acid
Tyloxapol	Palmitic acid
Poloxamer 188, 408	**Monoglycerides**
Poloxamine 908	Glyceryl monostearate
Solutol HS15	Diglycerides
Amphoteric surfactants	Glyceryl palmitostearate
Egg phosphatidylcholine (Lipoid E PC S)	**Liquid lipids**
Soy phosphatidylcholine	Glyceryl monooleate
Hydrogenated egg phosphatidylcholine	Soya bean oil
Phospholipon 90 G, Phospholipon 90 H)	Oleic acid
Egg phospholipid (Lipoid E 80, Lipoid E 80	Castor oil
S)	α-tocopherol/Vitamin E
Soy phospholipid (Lipoid S 75)	**Triglycerides**
Ionic surfactants	Caprylate triglyceride
Sodium cholate	Caprate triglyceride
Sodium glycocholate	
Sodium taurocholate	
Sodium taurodeoxycholate	

1.3.1 INTRODUCTION FOR NLCs (10) (12)

In the Second generation nanoparticulate system are overcome to less the drug loading problem of solid lipid nanoparticles, NLCs composed solid lipid-like Precirol ATO 5, Stearic acid, GMS, and liquid lipid-like GMO, olive oil, croconate oil, castor oil and this both mixtures are used. The drug is more soluble in liquid lipid as compare to solid lipid, and it's resulting in high drug loading. Each lipid leads to imperfect crystal formation. Compare to solid lipid

nanoparticles, more stable. And excellent compatibility and NLCs are divided into three types.

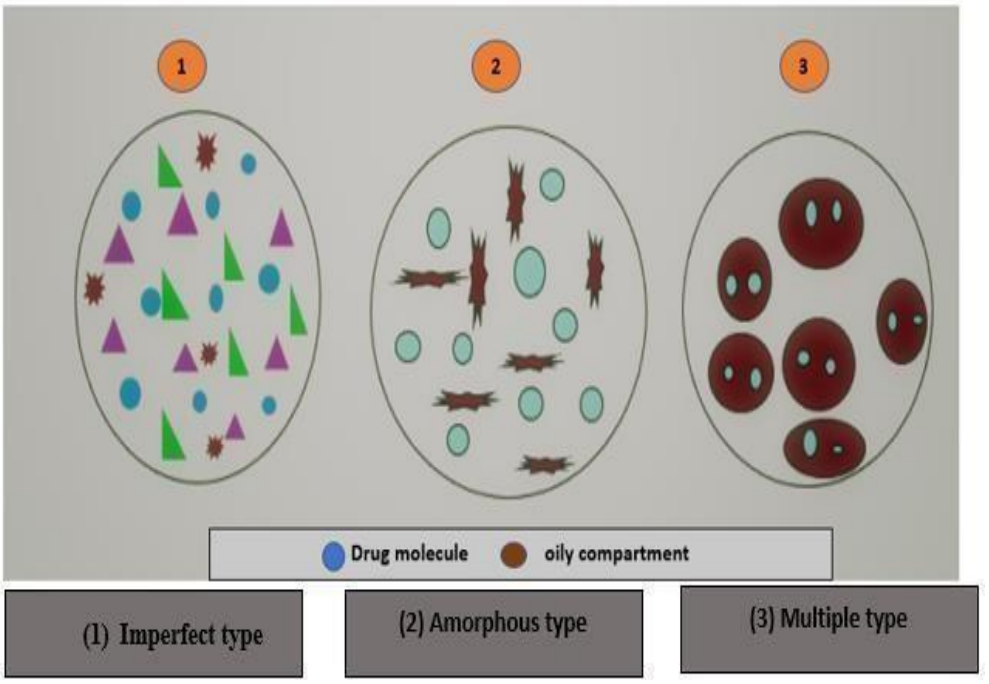


Figure 1.6: Types of NLCs (10)

(1) "Imperfect Crystal" Type

This type of nanostructured lipid carrier imperfectly solid matrix. Such inadequacies can be more useful for glycerides compose to dissimilar fatty acids. To achieving more imperfection rather than using solid lipid. This type of NLC prepared by using a different type of lipids and observing the result in imperfection in the crystal matrix. Further, increase the drug loading use a Liquid lipid small quantity of add.

(2) "Multiple" Type

Oil-in-lipid-water type NLC. The solubility of a drug (Lipophilic) in solid lipid is lesser than the liquid lipid. In multiple types, more amount of oil was mixed adequately in solid lipid. Less amount of concentration, oily particles are simply dispersed into the lipid matrix. This type of NLC is help to lipophilic drug solubilize, and The NLC are formed during the (hot) homogenization process.

(3) "Amorphous" Type

The manufacture of NLC is a proper mixture of solid lipids with liquid lipids. The lipid core is solidified in amorphous nature. Amorphous type NLC lesser drug expulsion of nature maintain by polymorphic of the lipid matrix.

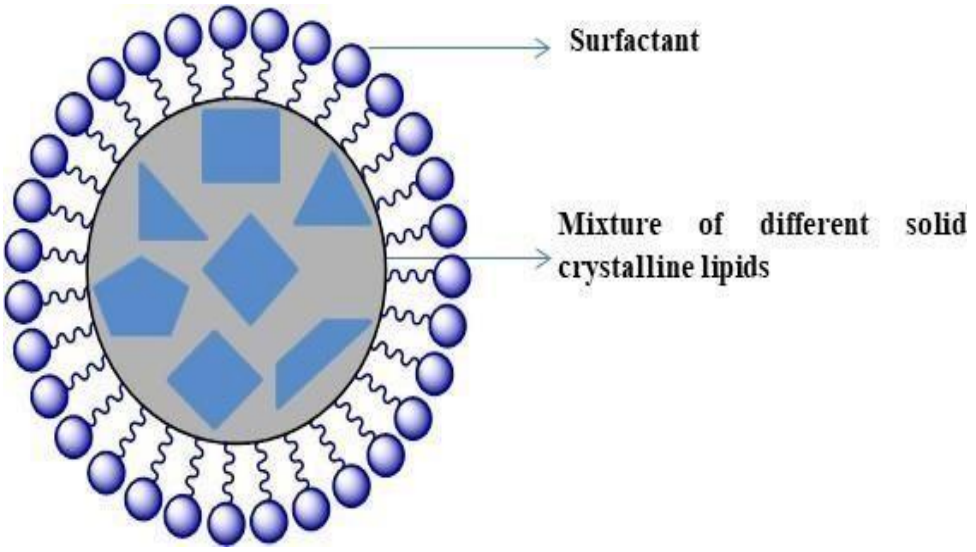


Figure 1.7: Structure for NLCs (10)

1.3.2 FORMULATION TECHNIQUE (10)

SLNs and NLCs prepare this technique:

1. High Shear Homogenization and Ultra-Sonification
2. Double Emulsion Technique
3. High-Pressure Homogenization (HPH)

- Hot HPH
- Cold HPH

4. Microemulsion Technique
5. Solvent Evaporation Technique

- **High-Pressure Homogenization Technique** (15)

HPH is most commonly used to formulate SLNs and NLCs, here in these techniques pressure is 150-2000 bar by high shear stress. This technique further divided into two-part.

(1) Hot homogenization

(2) cold homogenization

Hot homogenization technique raised temperature, and cold homogenization performs less than the room temperature**.**

➢ **Hot Homogenization** (15)

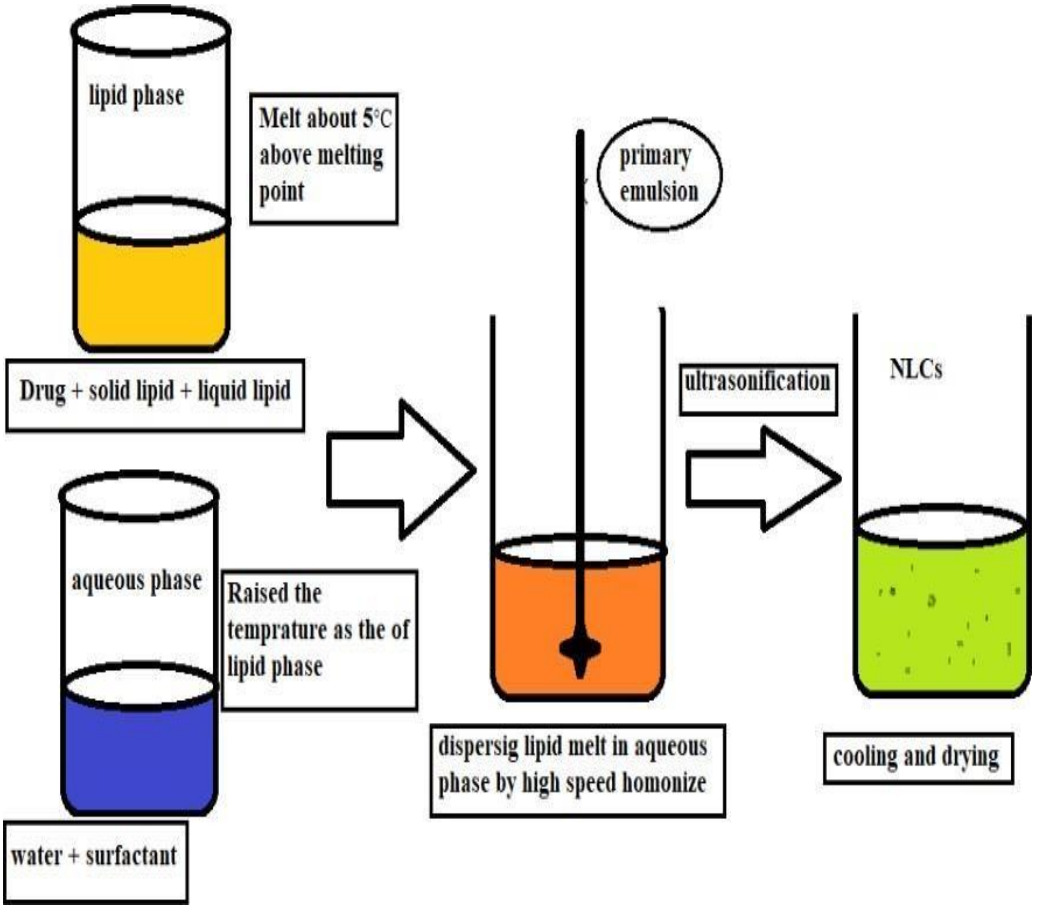


Figure 1.8: Diagrammatic illustration of Hot High-pressure homogenization technique. (15)

- **Cold Homogenization (15)**

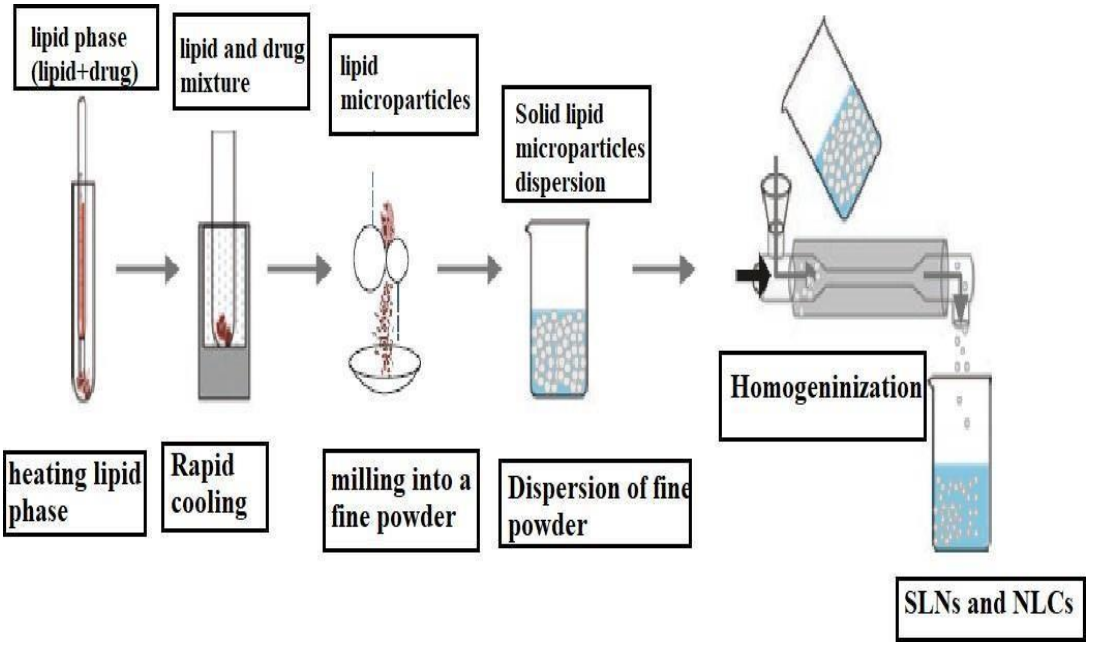


Figure 1.9: Diagrammatic illustration of Cold High-pressure homogenization technique. (15)

- **High Shear Homogenization and Ultra-Sonification** (15)

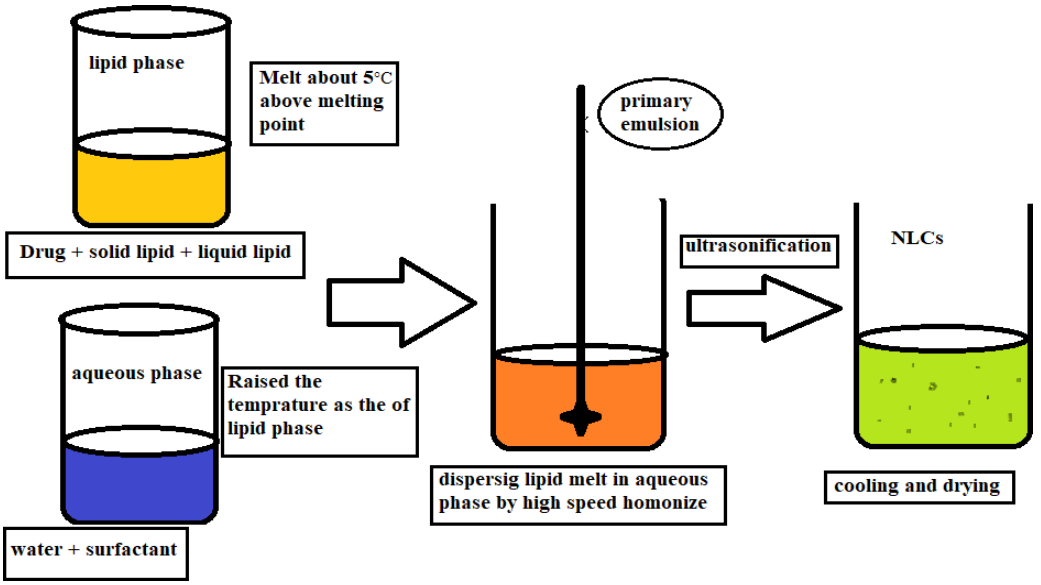


Figure 1.10: Diagrammatic illustration of High shear homogenization and ultra- sonification technique. (15)

- **Microemulsion Technique (10)**

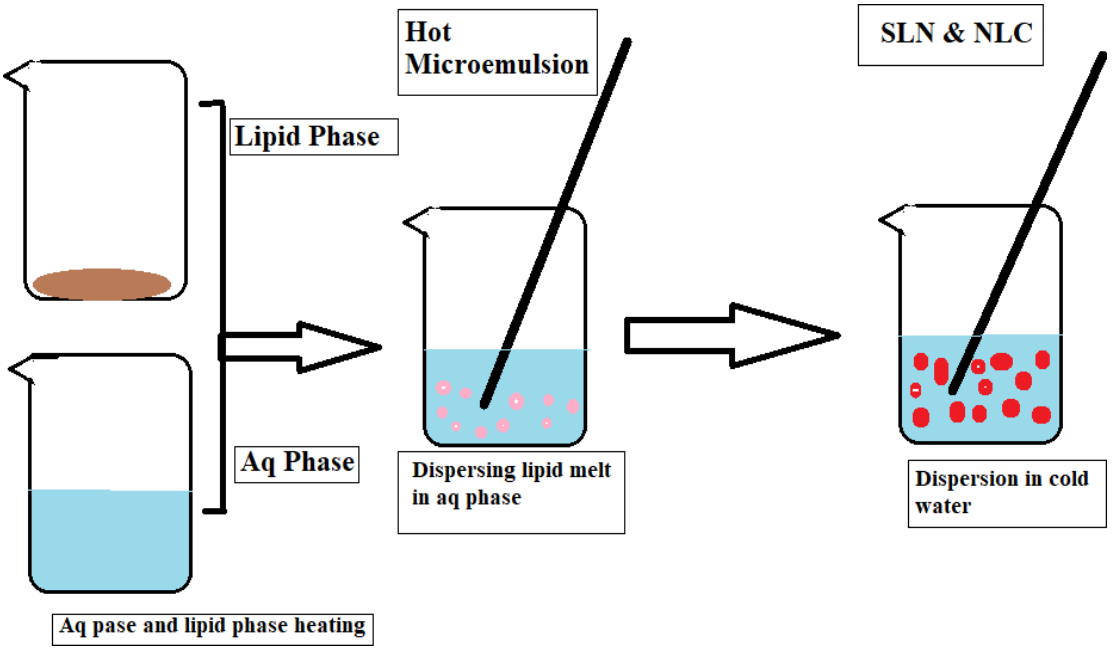


Figure 1.11: Schematic depiction of Microemulsion technique (10)

- **Solvent Injection Technique (15)**

Generally, DMSO and ethanol solvent used in this technique because this solvent is rapidly distributed in the water.

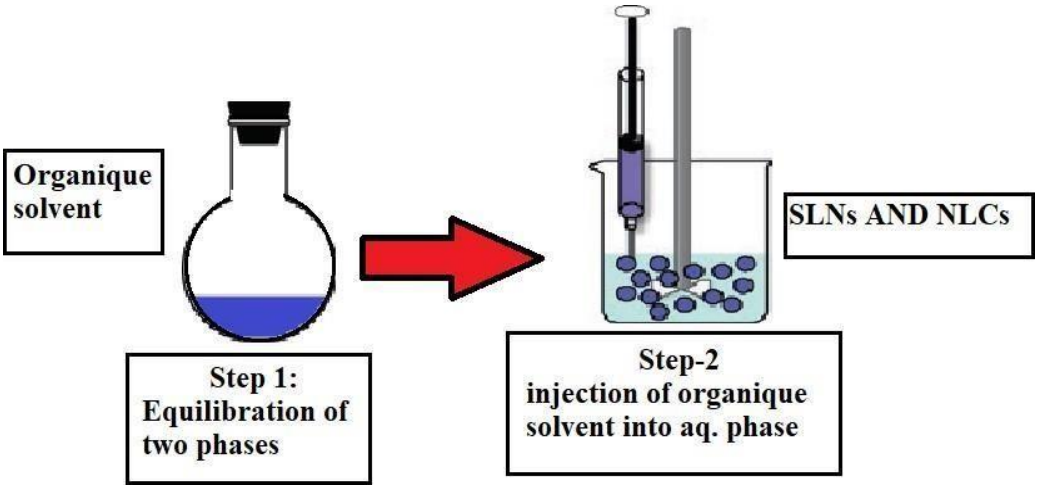


Figure 1.12: Diagrammatic representation of the solvent injection technique (15)

1.3.3 CHARACTERIZATION FOR NANOPARTICLES (10)(16)(17)

❖ **Particle Size (Dynamic Light scattering)**

Principle for photon correlation spectroscopy, intensity varies with time and too quick and move too slight to be evident to the human eye. The step of movement of a particle is inversely proportional to the particle size and can be detected by evaluating time depends on light intensity varies particles from dispersed when they are lighting with the laser beam. The varies in intensity correlated to the rate of diffusion of a particle in out of the Brownian motion; This data can be evaluated to give diffusion coefficient of a particle doing scattering and also this data provides particle size, which bases on the relationship among Brownian motion and particle size.

PI (Polydispersity is the breadth of particle size) is very small in size distribution, a range for polydispersity index among 0.1 to 0.3 (But not more than 0.3) and usually found with the colloidal drug carrier.

❖ **Zeta Potential Determination**

It is a technical measurement of surface potential. A Zeta potential measures stability for formulation and other colloidal dispersion of nanoparticle. The Range of zeta potential is more than 25 mv. The Number of factors determines zeta potential like (surface charge and density of nanoparticle, affect sample concentrate ion of counterions, temperature, and solvent polarity). Zeta potential determines electrophoretic light scattering.

❖ **Stability Study**

Stability study means to stable formulation data is formulated formulation and store different conditions (Room Temperature and 2-8°C) at a different time (1month, 3month,6month) after to check physical and chemical stability and after evaluated different parameters.

❖ **Crystallinity and Polymorphism**

Characterization of nanoparticle Structure is crystallinity and polymorphism. These two techniques are DSC and XRD. Crystalline material characterizes by DSC, and this technique varies a sensitive

technique and Polymorphic detected only by the indirect study of melting enthalpies and transition temperature. XRD is a more dependable method, and it provides deep and structural data.

❖ **Morphology**

Two technique sample for Evaluated morphology is TEM and SEM. This Transmission Electron Microscopy Characterize morphology for nanoparticles like (size, shape, structure, and colloidal structure presence within the dispersion). The scanning electron microscopy commonly use small imaging particles, and this technique is rarely used for surface structure and take shape for particle

❖ **Drug Release**

The drug release profile depends on the different delivery systems as soon as the various conditions where the experimental is carried out, such as different release medium, like a sink or non-sink condition. The different types of drug release evaluated by a technique like UV Spectroscopy and (HPLC) High-Performance Cometographic. Lipid nanoparticle like SLN and NLC are drug release which can be affected by the site where the drug incorporated in the system. Nanoparticle drug release identifies for dialysis method.

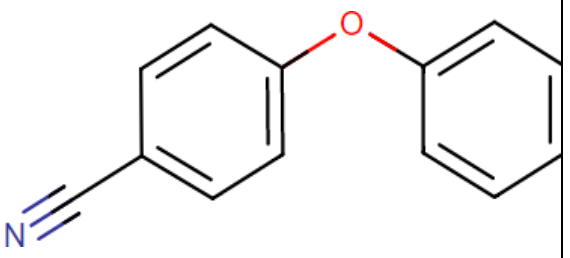
❖ **Entrapment Efficiency**

% EE defines as identify for a concentration of incorporate material (Drug) determined this equation.

$$\%EE = \frac{\text{Total drug- free drug}}{\text{Total drug Where}} \times 100$$

1.4 DRUG INFORMATION:

Table -1.4 Drug Information (18)(19)

Drug name	**Crisaborole**
Structure	
IUPAC name	4- [(1-hydroxy. -1,3-dihydro-2,1-benzoxaborol. -5-yl) oxy] benzonitrile.
Molecular weight	251.05g/mol
Melting point	230-235°C
Solubility	Freely soluble in propylene glycol and IPA soluble in ethanol dimethylformamide
BCS class	4
Log p	2.6

1.4.1 INTRODUCTION TO EXCIPIENTS PROFILE (20)

Table -1.5 Excipient Profile (Precirol ATO 5) (21)

Excipients Name	Precirol ATO 5
USP NF name	Glycerin palmitostearate, glycerol
Chemical description	a mixture of monoglycerides, diglycerides and triglycerides of palmitic acid (C_{16}) and stearic acid (C_{18});(8%–22% monoglycerides, 40%–60% diglyceride, 25%–35% triglycerides
Melting range	50–60°C
Appearance	fine white powder
HLB value	2

Table no-1.6: Excipient Profile (glyceryl monooleate)(22)

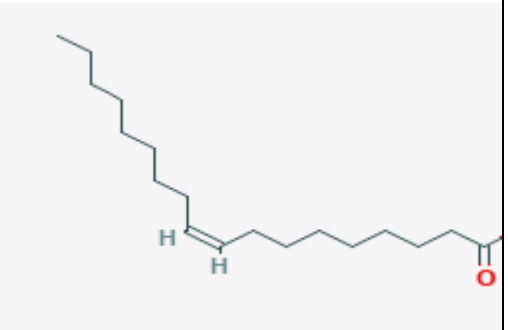
GMO, Structure	
Molecular Weight	356.5 gram/mol
Melting Point	35.0 ℃
IUPAC Name	2,3-dihydroxypropyl (*Z*)- octadec-9 -enoate
Molecular Formula	$C_{21}H_{40}O_4$
Solubility	Ethanol and Alcohol (Hot)
Log p-Value	5.97
GMO Colour	Yellowish white OIL
Odor of GMO	Sweet
Taste (GMO)	Fatty Taste

Table1.7: Excipient Profile (Tween 20) (23)

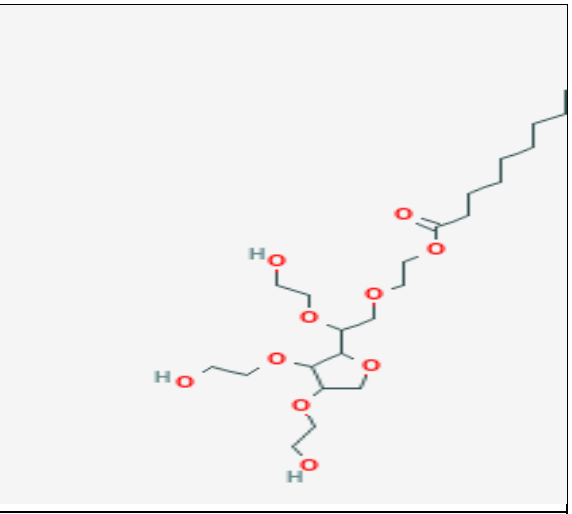
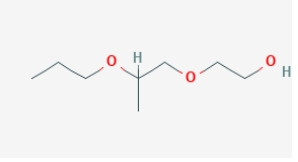
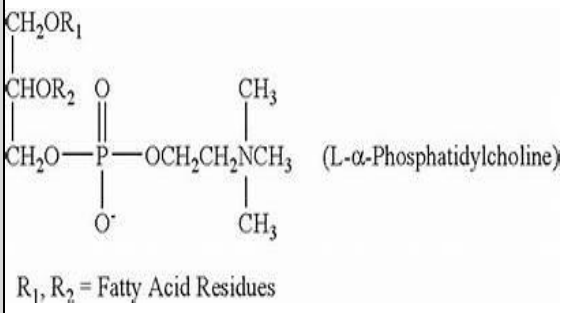
Structure	
IUPAC name	2-[2-[3,4-bis(2-hydroxyethoxy oxolan-2-yl]-2-(2-hydroxyethoxy)ethoxy]ethyl dodecanoat
Molecular formula	$C_{26}H_{50}O_{10}$
Melting point	110 °C
Molecular weight	522.7 g/mol
Solubility	water, ethanol, methanol, ethyl acetate, and dioxane.
Use	foods and cosmetics.
HLB value	16.7

Table -1.8 Excipient Profile (POLOXAMER 188)(20)

Structure	
IUPAC name	2-(2-propoxypropoxy ethanol)
Molecular formula	$C_8H_{18}O_3$
Melting point	52-57°C
Molecular weight	162.23 g/mol
Appearance	white, waxy powder

Solubility	Soluble in water and ethanol
Use	Poloxamer 188 is emulsifier agent and food and cosmetics.
HLB value	More than 24

Table -1.9 **Excipient Profile (Excipient Profile (phospholipon 90 g)**

Structure	
Molecular formula	$C_{44}H_{80}NO_8P$
Melting point	>145°C
Molecular weight	782.08gm/mol
Appearance	White to Off-White Solid
Solubility	Methanol (Sparingly, Sonicated)

2.AIM AND OBJECTIVE

2.1 AIM AND OBJECTIVE

- Fabrication & characterization of Crisaborole lipid nanoparticulate system for the treatment of Atopic Dermatitis.
- To formulate NLC base novel formulation to achieving sustained release of Crisaborole and for improvement of the topical permeation.
- The Problem of conventional formulation of Crisaborole ointment will Overcome.
- To evaluate the effect of formulation parameters on the formulation of Crisaborole, loaded nanostructured lipid carrier.

3.LITERATURE REVIEW

3.1 Literature review on the treatment of Atopic Dermatitis and lipid nanoparticles:

Manisha Lalan, in this review article, has described its necessary information of atopic dermatitis, to establish the management strategies and also the pathophysiology for atopic dermatitis and This article information is useful for different treatment in atopic dermatitis-like, topical corticosteroid, a topical calcineurin inhibitor, phosphodiester four inhibitor, methotrexate, Cyclosporine and also pathophysiology Barrier Dysfunction, Immune Dysregulation and the Itch–Scratch Cycle. (3)

Rohan Shah was written a book for lipidic nanoparticles. In this book, there is information about lipids nanoparticles SLNs, NLCs types and lipidic nanoparticle composition details which type of material and surfactant use, also the different types of preparation technique, and The characterization of lipid nanoparticle, e.g., Particle size, morphology for nanoparticle (SEM, TEM), DSC, Entrapment efficient, Drug loading, etc. this book information about lipidic nanoparticles. (10)

3.2 Literature review of SLN/NLCs on the topical formulation:

E.B. Souto, prepared clotrimazole to load solid lipid nanoparticle and nanostructure lipid carrier both prepared by Hot HPH technique, and characterization stability study (stored in both samples 4°C,20-25°C 40°C), entrapment efficiency and drug release. Concluded for a 3-month stability study for the same result, the drug release profile and entrapment efficiency depend on lipid mixture concentration. Nanostructure lipid carrier more %EE because of the use of liquid lipid in the formulation. And NLCs drug release fast profile as compare to Solid Lipid Nanoparticle with a similar lipid mixture. In finally, SLNs for occlusive capacity higher as compare to NLCs.(24)

M. Joshi and V. Patravale formulated valdecoxib loaded nanostructured lipid carrier on-base gel. These NLCs were firstly screening for different lipid solubility studies, and finally, it selected an excipient base solubility study like Solid Lipid: Glyceryl Dilaurate, liquid lipid: Caproyl 90, Surfactant: Cremophor RH 40. And after preparing NLCs microemulsion technique and after evaluated by photon correlation spectroscopy for particle size. Nanosep centrifugal instrument use to identifies for Drug entrapment efficiency. For gel base, NLCs estimated PH, separability, rheology

and release stud. Pharmacodynamic study in rat paw edema model recognizes skin irritation, efficacy, and lastly, concluded faster onset yet sustained release action for the treatment of inflammation and allied condition. (25)

3.3 Literature review SLN/NLCs use Atopic dermatitis*:*

Navjot Kaur was prepared Mometasone Furoate drug-loaded NLCs microemulsion technique by use of ternary phase diagram was using different combination co-surfactant and surfactant to study microemulsion range. And after optimized formulation was evaluated for Particle size, eta potential, %EE, and morphology, Ex skin permeation studies using rat skin, the result for improving viscosity for topical use. This formulation is less side effects. And sustained drug release showed drug permeation study of NLCs gel as compared to the market formulation. (26)

Mahesh L. Bikkad prepared Halobetasol Propionate loaded nanoparticles formulation. This solid lipid nanoparticle prepare by solvent injection technique and formulation was finally selected to apply 3^2 factorial design. HP loaded NLCs characterization particle size, entrapment efficiency, DSC, SEM, Xray diffraction, and lastly incorporate into Carbopol gel. And SLN base gel was characterized as compare with marketed formulation Ex vivo skin permeation study in final skin irritation test (Draize patch test on rabbit). HP loaded SLNs particle size 200nm and 85-95% EE, ex vivo study sustained-release effect up to 12hr and skin irritation studies which avoid systemic uptake, non-irritant to the skin compared to marketed formulation. And in final result indicate HP loaded nanoparticle local (skin) targeting effect, controlled release, and no skin irritation. (27)

Upendra Nagaich formulated Clobetasol propionate NLCs for the treatment of Atopic Dermatitis. And evaluate for NLCs, and finally optimize batch result was (Particle size 138.9nm, with -20.5mV zeta potential, and PI (polydispersity index) – 0.225 and good stability) of nanostructured lipid carrier. And formulation %EE around 80% and Vitro release up to 85% in 24 hr. NLCs for incorporated in gel and evaluated rheology, Vivo drug permeation study, drug release kinetic study. NLCS base gel compares the marketed gel of clobetasol propionate. In vivo anti-inflammatory studies. In rat paw edema method is used. In final concluded sustained release effect and drug targeting, which can be achieved with immense prospective in dermal delivery. (28)

3.4 Literature Review on Solid Lipid Nanoparticle Skin Penetration for Different Formulation:

Abid et al. evaluated the skin penetration effect size. Solid lipid nanoparticle prepares precirol ATO 5 to use solid lipid and hot melt Homogenize technique to use. Rhodamine B loaded SLN to way penetration by use of (fluorescent microscopy) It was SLN particle size determine to play an important role in skin permeation. Above 100nm particle size gave good skin penetration. Thus, conclude that SLN permeation for skin particle size is an essential role. (29)

Jensen et al. were prepared SLN and characterize in skin permeation study, and in skin permeation study is divided into two types, Normal intact skin and impaired skin might by different penetration. In skin permeation study porcine ear is selected for the skin. SLN were compare marketed ointment. Affected for penetration profile, use different types of lipids, the polarity of lipid, the drug solubility. The result for both types of skin SLN sustained release effect of beneficial. (30)

4.MATERIALS

&

METHODOLOGY

4.1 MATERIALS

Table no – 4.1 MATERIALS LIST

Material	**Company**
Crisaborole	Intas pharmaceuticals (Gift sample)
Precirol ATO 5	Gattefosse India Pvt Ltd (gift sample)
Glyceryl mono-oleate	Gattefosse India Pvt Ltd
Tween 20	Sicso Research Laboratories Pvt Ltd

4.2 EQUIPMENT

Table no – 4.2 EQUIPMENT LIST

Equipment	**Company**
UV visible Spectroscopy	Shimadzu, Japan
Optical Microscope	Olympus CXZ1ILED, India
High-Speed Homogenizer	IKA ® T25 Digital Ultra Turrax®
Franz diffusion apparatus	Orchid, India
Centrifuge	Remi R24, India
TEM	-

4.3 METHODOLOGY

4.3.1 Preformulation Studies

(1) Melting Point

The melting point was measured by filling solid powder into a glass capillary. To measure the melting point of powder, previously one-sided sealed capillary was used. Carefully fill the small amount of powder into it. To fill the powder in a capillary invert capillary tube and tapped gently as powder filled. Put the API filled capillary in the paraffin oil containing beaker. Heat the entire system and measure the temperature by using a thermometer.

(2) UV VISIBLE SPECTROSCOPY (31)

- **A standard curve in Ethanol**

Prepared 50ppm stock solution, dissolving 5mg of crisaborole in 100ml ethanol. And after further dilution prepare were of 1ppm,2ppm,3ppm,4ppm,5ppm,6ppm,7ppm,8ppm. This prepared solution was evaluated by UV visible spectroscopy at λmax-251.

- **A standard curve in Ethanol: Chloroform mixture**

Prepared 50ppm stock solution by dissolving 5 mg crisaborole in 100ml mixture for chloroform: ethanol (1:1). And further dilution (Ethanol) 1.5ppm,5ppm,2.5ppm,3ppm,3.5ppm,4ppm,4.5ppm,5ppm. Were evaluated in ultra-violate visible spectroscopy at λmax-251.

- **A Standard curve in Phosphate Buffer pH-7.4**

Prepared 7.4ph Phosphate buffer. Firstly, 50ppm stock solution prepared 5mg crisaborole dissolved in 100ml ethanol. And further dilution phosphate buffer ph-7.4, 1ppm,2ppm3ppm,4ppm,5ppm,6ppm,7ppm,8ppm after evaluate in UV visible spectroscopy at λmax-251.

4.3.2 Excipient Screening (25)

1. Selection of Solid lipid:

The selection of solid lipid is based on solubility study. A lipid that can solubilize the maximum amount of Crisaborole was selected for further study. 1 gm of solid lipid wastaking and dissolve on magnetic stirrer than gradually add predetermined quantity (4 mg) of crisaborole in it until particle stop to dissolve.

2. Selection of Liquid lipid:

Same as solid lipids, liquid lipid was also selected by finding maximum solubility of crisaborole. The same method was applied to find suitable liquid lipid.

3. Selection of Solid lipid and Liquid lipid Ratio:

Proper selection of solid lipid and liquid lipids in a suitable concentration is very important for formulating stable nanostructured lipid carriers. Both lipids are mixed by vertexing mixture for the 60 minutes followed by heating. Their samples were stored for 1 Day and then checked for blotting with the help of tissue paper. Finally, the ratio which does not show any stain was selected for the formulation development process.

4. Selection of surfactant

The selected surfactant must have minimum solubility for crisaborole. Different types of surfactants (same concentration) in which 4 mg crisaborole was added and it steering for 1 hour and after the 24 hours it was observed and by these, it become the least soluble drug in which these surfactants were selected.

4.3.3 Formulation technique (28)

(1) NLCs (nanostructure lipid carrier)

NLCs were formulated by a high-speed homogenization method. These methods two-phase lipid phase and aqueous phase. Firstly, the lipid phase melted, lipid phase included lipid mixture ratio and added co-surfactant, completely mixed after dissolving drug. surfactant added aqueous phase. Both phases were heated to the same temperature (temperature 5-10 º C above lipid melting point) add lipid phase and the aqueous phase was done under high-speed homogenizer and formed NLCs

(2) Formulate gel

Gel preparation for a different gelling agent was selected. NLCs dispersion for1% w/v gelling and steering 400-500 rpm until it dissolves. And after evaluated for which gelling agent more preferable in these formulations.

4.3.4 CHARACTERIZATION (10)(16)

1. **Particle size**

   Particle size was evaluated by using Horiba's particle size analyzer. Firstly, prepared NLC base formulation and dilution sample with triple distilled water and evaluated. This system analyzed D10,50,90, Z average, Zeta potential, polydispersity index.

2. **%EE (Entrapment efficiency)**

   %EE was determined for NLCs in ethanol: chloroform (1:1) mixture, (break NLCs) and further dilution were prepared in ethanol and after that analyzed it by UV visible spectroscopy. This formula calculated %EE.

$$\%EE = \frac{\text{TOTAL DRUG} - \text{FREE DRUG}}{\text{TOTAL DRUG}}$$

3. **Different scanning calorimetry**

   DSC-60 series equipment was used for analyzing the sample in a temperature range of 101- 400 ºC. DSC thermogram shows each possible interaction between API and excipient.

4. TEM (Transmission Electron Microscopy)

TEM was analyzed the size and morphology of NLCs. This method of evaluating particle shape and size is more precise and accurate.

5. In Vitro Drug Release

In vitro drug release was two type

(A) "Diffusion bag method" by dispersion NLCs

(B) "Franz diffusion cell" by NLCs incorporate gel

(A) Diffusion bag method

This method is also known as the dialysis bag method, and this method was prepared by dialysis membrane tying edges. Dialysis membrane was uses and this membrane molecular weight between 12000 – 14000. Nano Structure lipid carrier (NLC) dispersion was added to deep in release media at150-200 rpm stirring speed & 32 ºC temperature. The sample was taken at different times and analyzed by UV spectroscopy.

(B) Franz diffusion method

The donor compartment was added crisaborole loaded gel and release media was selected receptor compartment. 150 rpm stirring speed 32 ºC temperature maintained and taken a different time sample and analyzed by UV spectroscopy.

5. EXPERIMENTAL WORK

5.1.1 PREFORMULATION

(1) Melting Point

MP was determined using the capillary method.

Table no-5.1 Determination of Melting Point

Theoretical	Practical
128-135°C	132.5

Concluded melting point nearby theoretical value.

(1) Ultra-violate Visible spectroscopy

Estimation of Wavelength in Ethanol

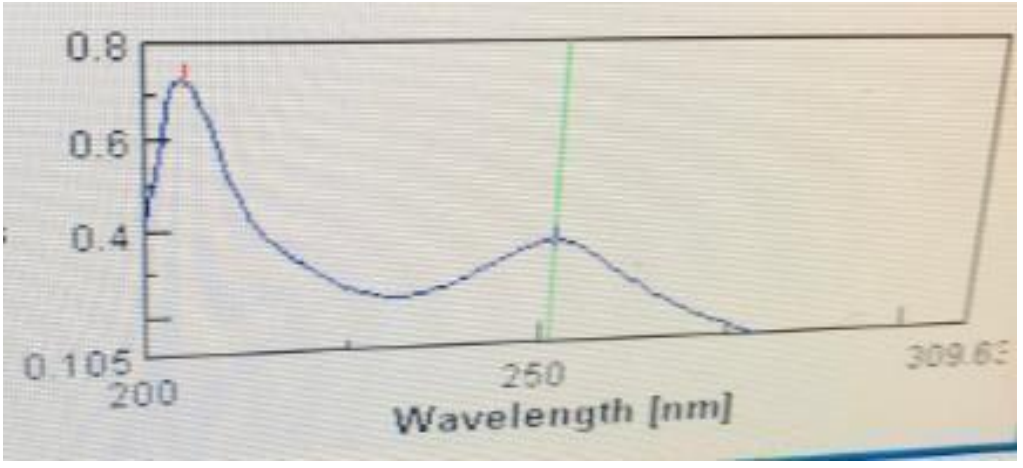


Figure 5.1 Estimation of Wavelength in Ethanol

- **A standard curve in Ethanol**

Table no-5.2 standard curve (Ethanol)

Conc.	Absorbance 1	Absorbance 2	Absorbance 3	Total absorbance
0PPM	0	0	0	0
1PPM	0.149	0.152	0.151	0.150667
2PPM	0.303	0.298	0.277	0.292667
3PPM	0.351	0.377	0.372	0.366667
4PPM	0.453	0.473	0.453	0.459667
5PPM	0.578	0.561	0.548	0.562333
6PPM	0.665	0.66	0.696	0.673667
7PPM	0.821	0.854	0.823	0.832667

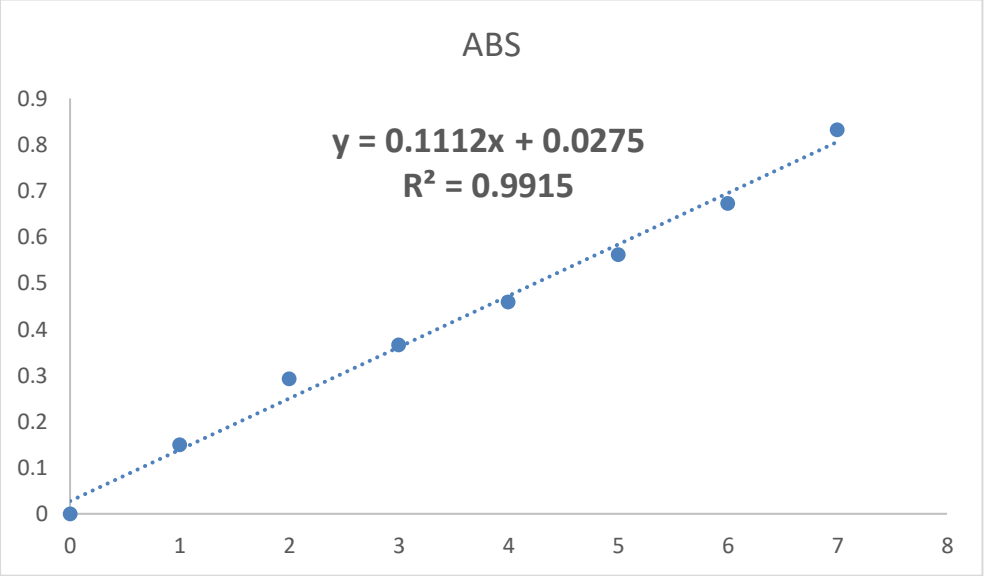


Figure 5.2 Standard curve of Crisaborole in Ethanol

Table no-5.3 (Ethanol) Regression analysis data

Parameter	Value
Slop	0.111
Correlation coefficient	0.991
Intercept	0.0275

A standard curve in Ethanol: chloroform mixture

Table no-5.4 standard curve (Ethanol: Chloroform)

Conc. Ppm	Absorbance 1	Absorbance 2	Absorbance 3	Absorbance Average
0	0	0	0	0
1.5	0.132	0.152	0.139	0.141
2	0.204	0.204	0.185	0.197667
2.5	0.255	0.254	0.239	0.249333
3	0.298	0.298	0.287	0.294333
3.5	0.324	0.34	0.34	0.334667
4	0.353	0.381	0.375	0.369667
4.5	0.405	0.427	0.432	0.421333
5	0.48	0.474	0.495	0.483

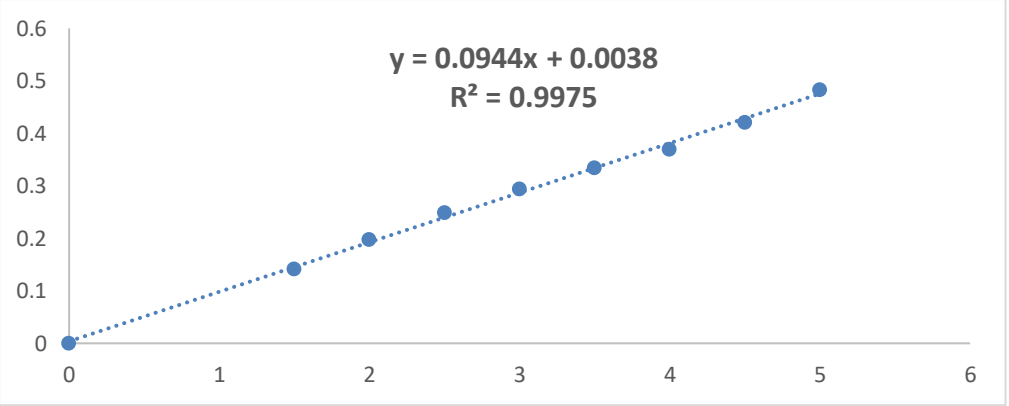


Figure 5.3 Standard curve of Crisaborole in Ethanol: chloroform

Table no-5.5(Ethanol: chloroform) Regression analysis data

Parameter	Value
Slop	0.094
Correlation coefficient	0997
Intercept	0.0038

- **A standard curve in Phosphate buffer pH-7.4**

Table no-5.6 standard curve (Phosphate Buffer-7.4)

Conc. Ppm	Absorbance 1	Absorbance 2	Absorbance 3	Absorbance average
0	0	0	0	0
1	0.086	0.078	0.091	0.085
2	0.163	0.166	0.182	0.170333
3	0.297	0.262	0.284	0.281
4	0.352	0.337	0.325	0.338
5	0.428	0.442	0.457	0.442333
6	0.507	0.511	0.524	0.514
7	0.639	0.617	0.623	0.626333
8	0.737	0.697	0.741	0.725
9	0.787	0.748	0.791	0.775333

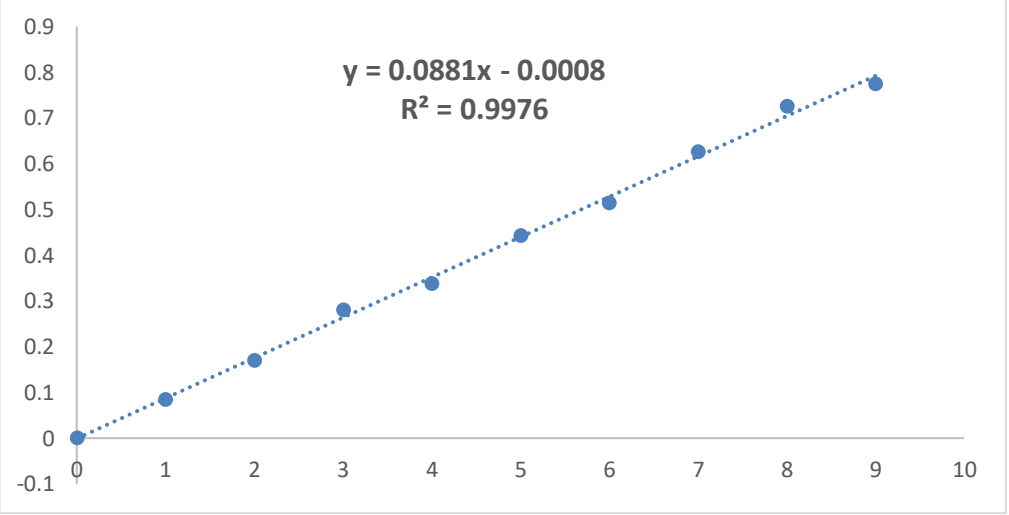


Figure 5.4 Standard curve: Crisaborole in Phosphate Buffer ph-7.4

Table no-5.7 (Phosphate Buffer) Regression

Parameter	Value
Slop	0.0881
Correlation coefficient	0.997
Intercept	-0.0008

5.1.2 EXCIPIENT SCREENING

Solubility study for Solid Lipid

Selected solid lipid had maximum solubility for crisaborole.

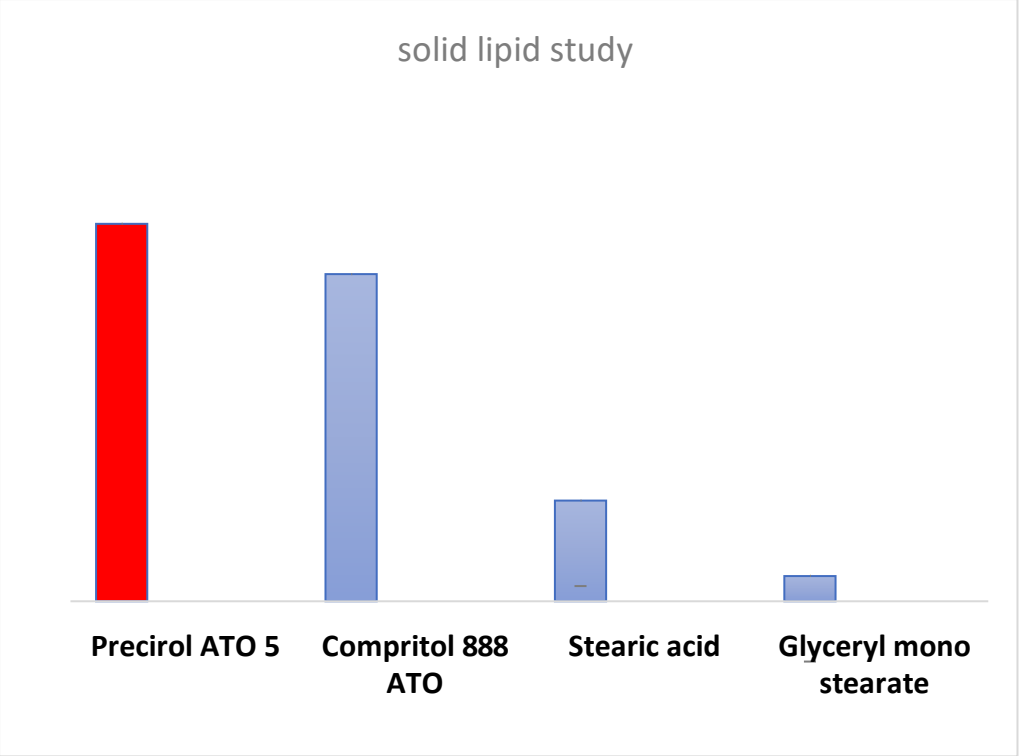


Figure no-5.5 Diagrammatic representation of solubility of a drug in solid lipid

- Precirol ATO 5 solid lipid was selected because my drug was maximum soluble in this lipid.

Liquid lipid

Selected liquid lipids had maximum solubility for crisaborole.

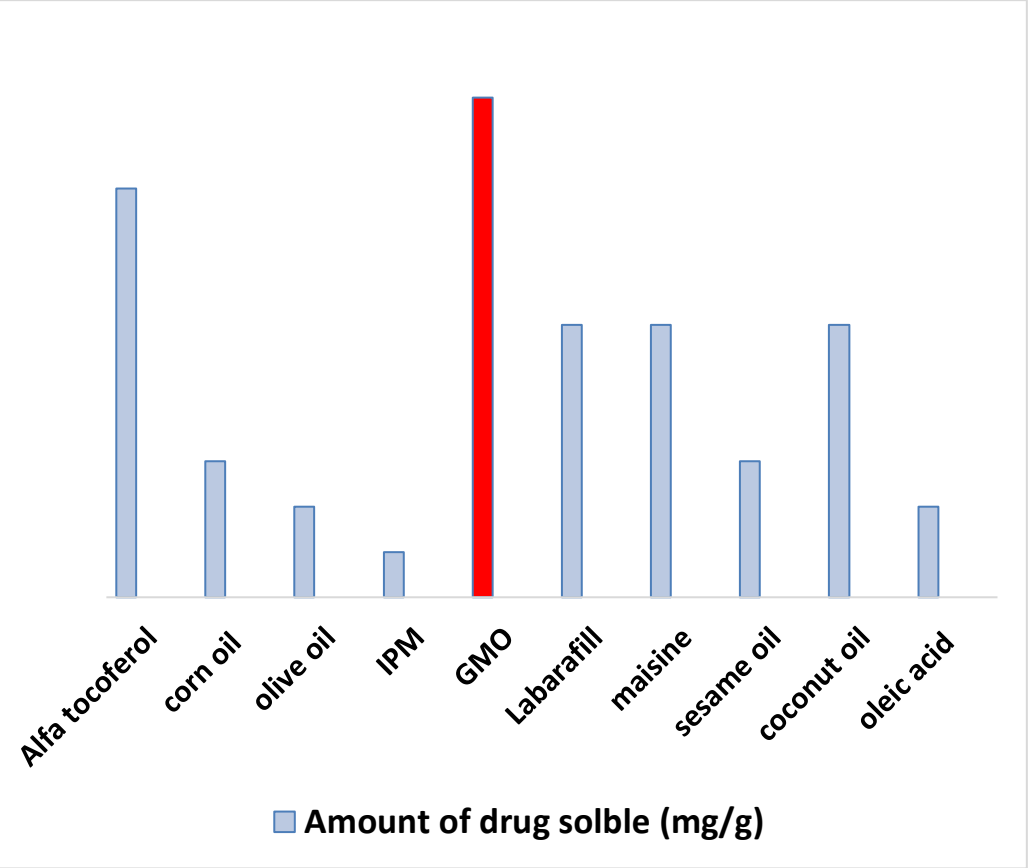


Figure no-5.6 Diagrammatic representation of solubility of a drug in Liquid lipid

- Glyceryl Mono Oleate liquid lipid was selected because my drug (crisaborole) was maximum soluble in this lipid.

- **Binary selection for solid: liquid lipid mixture**

Table no- 5.8 Binary selection for solid: liquid mixture

Solid lipid: liquid lipid ratio	Staining intensity
95:5	No stain
90:10	No stain
85:15	No stain
80:20	Slightly stain
70:30	Intense
60:40	Intense
50:50	Intense

- Precirol ATO 5: Glyceryl Mono Oleate 85:15 was selected because observed no stain in it

❖ **Surfactant solubility study**

- Selected surfactant had minimum solubility for crisaborole.

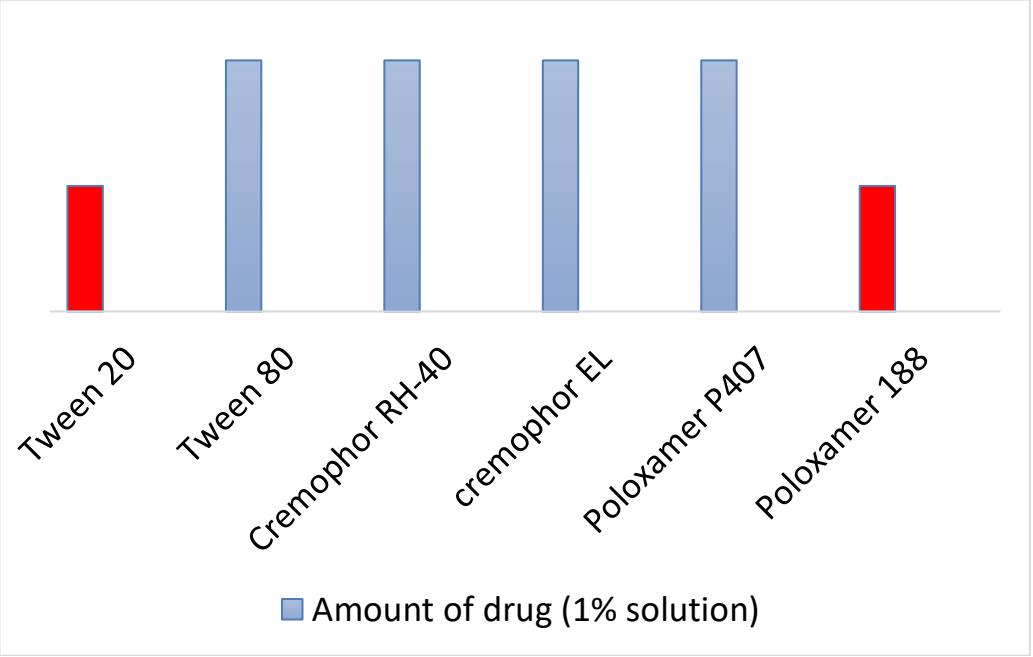


Figure no-5.7 Diagrammatic representation of solubility of surfactant study

- Tween 20 and Poloxamer 188 were selected because drug solubility lowest on it

5.3.4 EXPERIMENTAL TRIAL

❖ **Effect of Surfactant Type**

Batch No.	Surfactant type	Conc. of surfactant (%)	Stability	Microscopic Observation
ST 1	Poloxamer 188	1	Stable for 1 day	Drug crystal and Particle Observed
ST 2	Tween 20	1	Stable	Spiracle particle and no drug crystal Observe

Procedure: - lipid mixture (500 mg) of Solid lipid: liquid lipid (85:15), drug loading 20mg, Hot high shear homogenization.

- Finally, Tween 20 was selected for future trials because of the T20 particle spiracle and stable.

❖ **Effect of cosurfactant type**

- All batch take tween 20 concentration 3%, rpm speed 11000, 5 min. and solid lipid: liquid lipid 85:15, hot high-speed homogenization.
- PLG was Finally selected co-surfactant in future batches.

❖ **Effect for Surfactant concentration**

- Homogenization time – 5min
- Homogenization speed-11000

- At 5min stirring, 11000 rpm and increase tween 20 concentration D90 and Z-average decreases, PDI also increases and %EE and % LOD increases.
- 3% tween 20 selected for surfactant concentration.

❖ **Effect for cosurfactant concentration**

- Surfactant Concentration – 3%
- Homogenization speed – 11000
- Homogenization time – 5min

- At 11000 rpm for 5 min, surfactant concentration. 3% variation for co-surfactant.
- Increases PLG amount PDI and %EE good and finally 150mg PLG concentration. was selected in further batches.

❖ **Effect for speed**

- Tween 20 –3%
- PLG -150mg
- Homogenization time- 5min

- Increases rpm speed D90 and PDI decreases but %EE poor. 11000 was selected for farther batches.

6.CONCLUSION

- Crisaborole loaded NLCs was successfully formulated and evaluated with different parameter.
- Crisaborole loaded NLCs Microscopic observation particle was spherical monodispersed and stable form.
- The particle size of the optimized batch was 140.1nm with good PDI – 0.251.
- Entrapment Efficiency and %LOD was good crisaborole loaded NLCs was %EE was 82%. And %LOD WAS 2.38%.

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