"FORMULATION, OPTIMIZATION OF SOLID LIPID NANOPARTICLES BASED GEL FOR TREATMENT OF ECZEMA"

A Thesis Submitted to

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MASTER OF PHARMACY

IN

PHARMACEUTICAL TECHNOLOGY &

BIOPHARMACEUTICS

BY

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CERTIFICATE

This is to certify that the dissertation work entitled "Formulation, Optimization of Solid Lipid Nanoparticles based Gel for Treatment of Eczema" submitted by Ms. Bhranti Patel with Regn. No. (13MPH104) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University under 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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DECLARATION

I hereby declare that the dissertation entitled "Formulation, Optimization of Solid Lipid Nanoparticles based Gel for Treatment of Eczema", is based on the original work carried out by me under the guidance of Dr. Shital Butani, Associate Professor, Department of Pharmaceutics, 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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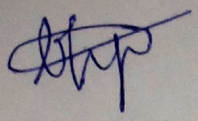

Ms. Bhranti H. Patel

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List of Abbreviations

Short Name	Abbreviation
IP	Indian Pharmacopoeia
UV	Ultra Violet
NaCl	Sodium Chloride
KBr	Potassium Bromide
Conc.	Concentration
ºC	Degree Centipoise
%CDR	Percentage Cumulative Drug Release
µg	Microgram
SD	Standard Deviation
Avg.	Average
cPs	Centipoise
Nm	Nanometer
G	Gram
ml	Mililitre
Cm	Centimeter
Hr	Hour
Mins.	Minutes
w/v	Weight/ Volume
v/v	Volume/ Volume
FTIR	Fourier Transform Infrared Microscopy
λ_{max}	Absorbance maxima
SLN	Solid Lipid Nanoparticles

"Formulation, Optimization of Solid Lipid Nanoparticles Based Gel for Treatment of Eczema"

Abstract

The purpose of the present work was to develop Solid Lipid Nanoparticles based Gel for topical delivery of Dapsone. The main objective was to prepare solid lipid nanoparticles of Dapsone and incorporating them into gel in order to increase the bioavailability by applying suitable design of experiments. Drug solubility studies in lipids and surfactants were performed. The various process parameters like drug : lipid ratio, concentration of surfactant, speed of stirring, time of stirring were studied in order to get to the optimized batch for the further preparation of solid lipid nanoparticles. The 3^2 full factorial designs was adopted to optimize the concentration of surfactant (X_1) and speed of stirring (X_2) in the SLN. The design batches were evaluated for entrapment efficiency (%) (Y_1), drug loading (%) (Y_2) and % CDR after 8 hr (Y_3). Compritol ATO 888 was selected as lipid based on high drug solubility while Span 80 was selected as surfactant due to low drug solubility. The avg. Particle size was found to be 78.15 nm and zeta potential was found to be -28.2 mV and % CDR was 77.42% respectively of the optimized batch. Scanning electron microscopy analysis optimized batch confirmed the size and sphericity of solid lipid nanoparticles. Further, optimized batch was then formulated in gel form using Carbopol 940 as gelling agent. The gel was evaluated for various parameters like pH, drug content, viscosity, peak load and spreadability. In- vitro permeation study of developed gel showed good permeability. Thus, it can be concluded that Dapsone loaded gel could be a promising formulation for effective treatment of eczema as compared to other conventional dosage forms.

Chapter – 1

Aim and Objectives

1. Aim & objective of present work:

- Nanoparticles which are made from solid lipids are gaining major attraction in various applications which have been proposed as an alternative particulate carrier system.
- As SLN are sub-micron colloidal carriers ranging from 50-1000 nm, composed of physiological lipid which are dispersed in water or aqueous surfactant solution.
- Due to its unique properties of SLN like small size, high surface area, high drug loading and its interaction of phases which act as an attractive potential for improvement in pharmaceutical performances.
- To overcome the disadvantages associated with liquid state of oil droplets, the liquid lipid was been replaced by solid lipid which transformed into solid lipid nanoparticles.
- Dapsone, a BCS class-II drug offers both antimicrobial and anti-inflammatory activity. Oral administration of Dapsone leads to several adverse effects like nausea, vomiting and haemolytic anaemia.
- To overcome these problems, Dapsone is been effective using nanotechnology. The therapeutic approach for Dapsone which is still to be explored is the topical route. By utilizing topical applications, it overcomes the strategy in treatment of eczema.
- Hence, the aim of the present work was to develop topical gel containing Dapsone SLN dispersion.
- The main objectives of the present investigation are:
    - Formulation of solid lipid nanoparticles by microemulsification technique.
    - Optimization of the final formulation by applying design of experiments (DOE)
    - Development of gel containing optimized SLN to enhance skin permeability.

Chapter – 2

Introduction

2. Introduction

2.1 Introduction to skin[16]:

- The human skin mostly consists of two mutual distinct dependent tissues, the stratified, avascular, cellular epidermis and an underlying dermis of connective tissue. Hypodermis lies at the bottom of the dermis which is fatty and subcutaneous. A cross-section of the skin is shown in fig.2.1

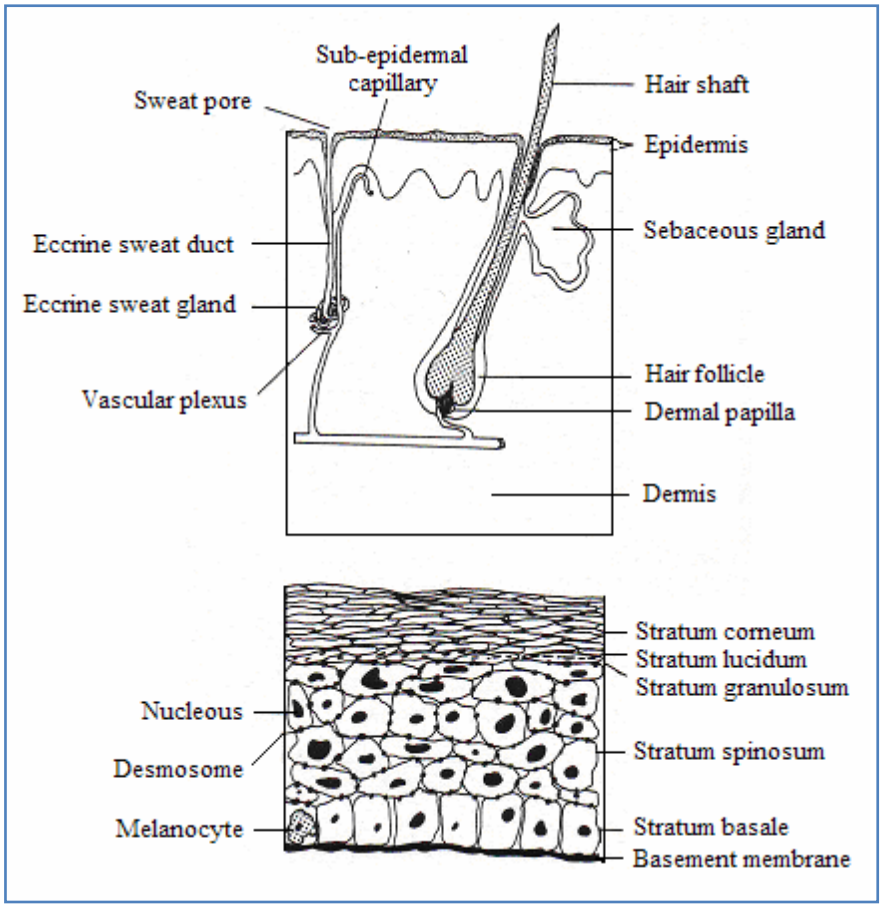

Figure 2.1 Schematic cross-section of the skin. [19]

- The epidermis shifts in thickness, contingent upon cell size and number of cell layers, running from around 0.8 mm on the palms and soles down to 0.06 mm on the eyelids. Cells which give epithelial tissue contrast from those of every single other organ,

once they rise from the proliferative layer of basal cells, changing in a requested manner from metabolically dynamic and partitioning cells to thick, dead, keratinized protein.

- In the thick epidermis of the palms of the hand and soles of the feet, there are five average layers (strata). Beginning with the furthest layer, they include the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale. The strata spinosum and basale together are known as the stratum germinativum once they create new cells. In parts of the body other than the palms and soles, just the stratum corneum and stratum germinativum are routinely introduced. These layers will be quickly portrayed beginning from the deepest layer.

- In the stratum germinativum, the basal layer is made out of basal cells, which are nucleated, columnar and around 6 μm wide, with their long hub at right points to the dermoepidermal intersection, associated by cytoplasmic intercellular scaffolds. Mitoses of the basal cells continually recharge the epidermis and this expansion in sound skin adjusts the loss of dead horny cells from the skin surface, hence the thickness of the epidermis stays steady. Subsequently, the aggregate turnover time, from the basal layer to shedding, midpoints 28 days in healthy skin. The basal cell layer additionally incorporates melanocytes, which deliver and disseminate melanin granules to the keratinocytes in a complex interaction.

- Beneath the basal cell layer lays the complex dermatoepidermal intersection, which constitutes an anatomic capacity unit, where four segments can be recognized, i.e. the basal cell plasma film with its hesmidesmosomes, the lamina lucida, the basal lamina, and the stringy segments underneath the basal lamina, which incorporate tying down fibrils, derma microfibril packs, and collagen fibrils. This storm cellar film relates to the sinewy zone underneath the basal lamina. As the phones delivered by the basal layer move outward, they change both morphologically and histochemically. The cells smooth and their cores shrink. They have a polygonal shape and are

interconnected by fine prickle cells. Every prickle encases an expansion of the cytoplasm, and the restricting tips of the prickles of contiguous cells hold fast to shape intercellular extensions – the desmosomes. These connections keep up the honesty of the epidermis. Between the desmosomes a hairlike space brimming with tissue liquid divides neighboring cells and the void grants supplements and oxygen to pass outward.

- The stratum lucidum seems just in the palms of the hands and soles of the feet, an anatomically particularly, inadequately recoloring hyaline zone frames a thin, translucent layer promptly over the granular layer, going about as a defensive shield against the bright (UV) beams of the sun and averting sunburns.

- At the last phase of separation, epidermal cells build the shallowest layer of the epidermis, the stratum corneum, which is a level, moderately thick layer of dead cells masterminded in parallel lines. The cells lie tangential to the skin surface and interdigitate their sidelong edges with adjoining cells to shape iron laminae. These cells contain keratin, and are additionally the last store of the deciding results of epidermal digestion system. They encase sebaceous and sweat organ emissions in an exceptionally composed structure. This layer assumes a urgent part in controlling the percutaneous absorption of drug molecules.

- The dermis, at 3 to 5 mm thick, is much more extensive that the overlying epidermis and it is considered the bulk of the skin. The dermis comprises basically of a framework of connective tissue woven from fibrous proteins (approximated sythesis: collagen 75%, elastin 4% and reticulin 0.4%), which install in a formless discovered substance of mucopolysacharide giving around 20% of the mass. Veins, nerves and lymphatics cross this framework and skin limbs (eccrine sweat organs, apocrine organs, and pilosebaceous units) enter it. It can be partitioned in two sections, a shallow, slight, papillary layer made out of limited filaments, which shapes a negative picture of the furrowed lower surface of the epidermis, and a thick fundamental

reticular layer made of wide collagen strands. The dermis additionally overflows with flexible strands which extend moderately effortlessly and which return to their unique shape when the anxiety dies down. The flexible strands frame a system in the dermis, so that the mechanical properties of connective tissues rely on upon the of both collagen and elastic filaments.

- The dermis needs a rich blood supply which directs temperature and weight, conveys supplements to the epidermis and evacuates waste items, activates safeguard strengths, and adds to skin shading. Branches from the supply route arrange (the blood vessel plexus) pass on blood to the hair follicles, the sweat organs, the subcutaneous fat, and the dermis itself. The blood supply reaches to inside 0.2 mm of the skin surface, so that it promptly ingests and deliberately weakens most substances which enter past the stratum corneum and the suitable epidermis. The vascular surface accessible for the trading of materials between nearby tissues and the blood is around 1-2 cm2 every cm2 of skin surface with a blood stream rate of around 0.05 ml/min/cm3 of skin. Of specific pertinence to biopharmaceutical studies is the way that this liberal blood volume normally works as a sink regarding the diffusing atoms which achieve it amid the procedure of percutaneous assimilation. This sink condition guarantees that the infiltrate focus in the dermis stays close to zero and subsequently the fixation inclination over the epidermis is maximal. As the focus inclination gives the main thrust to dissemination, and bottomless blood supply helps percutaneous ingestion.

- The hypodermis (subcutaneous fat) spreads everywhere throughout the body as a fibrofatty layer, except for the eyelids and of the male genital locale [218]. The sheet of fat lies between the generally adaptable skin and the unfaltering, profound sash, and its thickness shifts with the age, sex, endocrine, and nutritious status of the person. The cells produce and store lipids in expansive amounts and packs of collagen strands weave between totals of fat cells giving adaptable linkages between the basic structures and the shallow skin layers. The hypodermis is additionally in charge of

warm hindrance and mechanical pad. It is a site of blend and a stop of promptly accessible high vitality chemicals.[19]

Functions of the skin:

1. **Protection:**
   - Physical Barrier: The stratum corneum of the epidermis is moderately impermeable gives the insurance from nature because of the keratinocytes are organized in a platform like grid, bound together by the sinewy protein keratohyalin and a histidine-rich protein involucrin. Furthermore, the intercellular spaces are loaded with a lipid-rich framework masterminded in a laminar manner giving a powerful and waterproofing boundary.

   - Immune capacities: The skin capacities as a first line of safeguard against attacking microorganisms. The instruments by which it has the capacity do this incorporate the creation of hostile to microbial peptides, inhabitant epidermal Langerhans cells, and transient epidermal T-cells. Furthermore, the dryness of the external layer of the epidermis and the persistent shedding of keratinocytes helps in keeping any managed development of creatures on the skin.

   - Ultraviolet Radiation: Ultraviolet radiation is made out of electromagnetic vitality with wavelengths from 400 nm to 200 nm. The skin capacities as a defensive layer for UV radiation in two ways. The stratum corneum reflects radiation, so lessening the presentation dosage. Sun introduction builds the action of melanocytes, the number of melanosomes delivered and the rate of exchange of melanin to the epidermal keratinocytes. This serves to diminishing assimilation of UV radiation by DNA and cell constitutes.

2. Sensation:

- Cutaneous innervation is profoundly unpredictable and is included in impression of outside boosts, thermoregulation and sociosexual correspondence. Tactile afferent modalities incorporate touch, vibration, temperature, weight, agony and tingle. Different receptors recognize and transmit boosts to the focal sensory system.

- For Example, in bare (glabrous) skin, Meissner's corpuscles distinguish changes in light touch and vibration, Merkel cell receptors recognize light touch and maintained weight; In the profound dermis and subcutaneous fat, Pacinian corpuscles recognize weight and vibration changes and Ruffini receptors recognize skin stretch and add to joint position sense.

- Pain receptors are free nerve endings and are polymodal in their capacity, which is they can identify various boosts.

- Itch is a complex impression that is inadequately caught on. It can be characterized as a impression that delivers the desire to scratch and is interceded by c-filaments.

- Thermoreceptors exist for icy and warmth as free nerveendings, sporadically dispersed in the skin.

3. Skin circulation:

- Anangiosomeis a composite square of tissue with overlying skin that is supplied by a fundamental source course and related depleting veins. The body is formed of various angiosomes that fit together like a jigsaw. The angiosomes are connected by conveying vessels (stifle supply routes and swaying veins) that permit blood stream between them in specific situations. The blood supply of the dermis far surpasses that which is needed for its nutritious needs.[56]

2.2 Introduction to eczema:

2.2.1 Introduction:

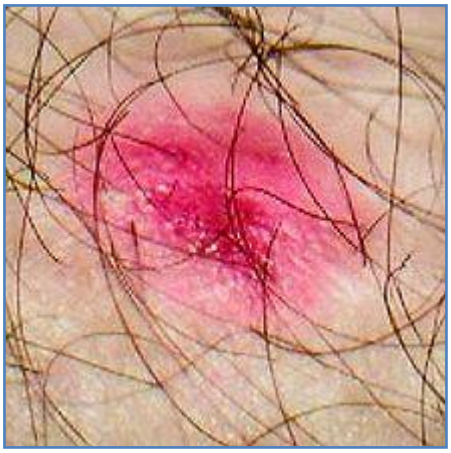

Figure 2.2 A patch of eczema that has been scratched[6]

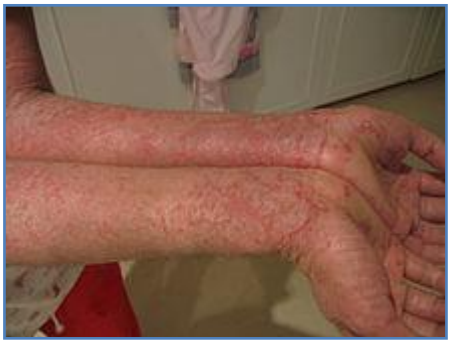

Figure 2.3 More severe eczema[6]

- Dermatitis or eczema is inflammation of the skin. It is described by bothersome, erythematous, vesicular, sobbing, and crusting patches. The term dermatitis is additionally generally used to depict atopic dermatitis or atopic skin inflammation in a few dialects, dermatitis and skin inflammation are equivalent words, while in different dialects dermatitis suggests an intense condition and skin inflammation an interminable one. The reason for dermatitis is unclear. One probability is that the condition is created by a broken exchange between the immune framework and skin.

- The term skin inflammation is comprehensively connected to a scope of relentless skin conditions. These incorporate dryness and repeating skin rashes that are portrayed by one or a greater amount of these indications: redness, skin swelling, tingling and dryness, crusting, chipping, rankling, splitting, overflowing, or dying. Regions of interim skin staining may show up and are some of the time because of mended wounds. Scratching open a recuperating injury may bring about scarring and may expand the rash.

- Treatment is ordinarily with lotions and steroid creams. In the event that these are not successful, creams in view of calcineurin inhibitors may be used. The ailment was assessed starting 2010 to influence 230 million individuals all inclusive (3.5% of the populace). While dermatitis is not life-debilitating, various different sicknesses have been connected to the condition, including osteoporosis, misery, and coronary.[6]

2.2.1.1Classification:

1. Atopic dermatitis:

Atopic dermatitis is not infectious. Individuals with AD can't "offer" it to another person.

Atopic dermatitis aggravation results from an excess of responsive incendiary cells in the skin. Exploration is looking for the motivation behind why these cells over-respond. Patients with AD (asthma or roughage fever) are conceived with these over-receptive cells. At the point when something triggers them, they don't kill as they ought to. We attempt to control AD by controlling the trigger elements that "turn on" aroused skin, or by "damping the flares" with calming treatments.[8]

2. Contact dermatitis:

Contact dermatitis is a response that can happen when the skin interacts with specific substances, which can bring about skin irritation. Aggravations are substances that cause

blazing, tingling or redness. Basic aggravations incorporate solvents, mechanical chemicals, cleansers, exhaust, tobacco smoke, paints, fade, woolen fabrics, acidic sustenances, astringents and other liquor (barring cetyl liquor) containing healthy skin items, and a few cleansers and aromas. Allergens are generally creature or vegetable proteins from nourishments, dusts, or pets. Contact dermatitis is regularly seen around the hands or parts of the body that touched the aggravation/allergen. There are two sorts of contact dermatitis: irritant and allergic.

- **Irritant contact dermatitis:**

  The outcome is a flaky, bothersome, tireless skin rash where the watch touches the skin. Irritant dermatitis is the most well-known sort. It's brought on by contact with acids, basic materials, for example, cleansers and cleansers, cleansing agents, solvents, or different chemicals. The response can resemble a red, dry flaky rash, or can look more like a blaze.

- **Allergic contact dermatitis:**

  Unfavorably susceptible contact dermatitis is brought about by presentation to a substance or material to which you have ended up hypersensitive.

  Despite the fact that you might not have a response to a substance when you are initially presented to it, consistent utilization can in the end cause affectability and a response to the item. A few items cause a response just when the skin is likewise presented to daylight (photosensitivity). These incorporate shaving salves, sunscreens, sulfa treatments, a few scents, coal tar items, and oil from the skin of a lime. A couple of airborne allergens, for example, ragweed or bug spray shower, can bring about contact dermatitis.[9]

3. **Seborrheic dermatitis:**

   Seborrheic dermatitis can influence the upper midsection and have round, red ranges notwithstanding slight scaling.

Seborrheic dermatitis is a typical skin condition that is like skin inflammation and some of the time happens in patients with dermatitis. In infants, it has a tendency to generally influence the scalp and is known as "support top". More seasoned youngsters and grown-ups can create it on the scalp also, which is like dandruff however a tendency to be more irritated and aroused has. It can likewise influence the face and upper midsection now and again, and can cover with psoriasis.

The primary manifestations of seborrheic dermatitis incorporate one or a greater amount of the accompanying:

- Redness (erythema)
- Itching
- Dry and chipping skin

- The reason for seborrheic dermatitis is thought to be because of an anomalous incendiary reaction to yeast regularly found on the skin: Malassezia. Like skin inflammation, numerous components can irritate seborrheic dermatitis including anxiety, change of seasons, ailments, and substantial liquor utilization.[10]

4. Dyshidrotic Eczema:

Dyshidrotic dermatitis is a condition in which little rankles grow on the hands and feet. Rankles are regularly irritated.

- **CAUSES**

Individuals are more inclined to create dyshidrotic skin inflammation when:

- They are under anxiety.
- They have hypersensitivities, for example, hayfever (Allergic Rhinitis).
- Their hands are frequently in water or sodden.
- They do concrete work or other work that opens their hands to chromium, cobalt or nickel.

- **Symptoms:**

  Little liquid filled blisters called vesicles show up on the fingers, hands, and feet. They are most normal along the edges of the fingers, toes, palms, and soles. These rankles can be exceptionally bothersome. They additionally cause flaky patches of skin that drop or get red, split, and agonizing. Scratching prompts skin changes and skin thickening. Huge blisters may bring about agony.[11]

5. Nummular eczema:

Nummular dermatitis (otherwise called discoid skin inflammation and nummular dermatitis) is a typical kind of dermatitis that can happen at any age. It is remarkable in light of the fact that it looks altogether different than the typical atopic dermatitis and can be considerably harder to treat.

"Nummular" originates from the Latin word for "coin" as the spots can look coin-molded on the skin. They have a tendency to be very much characterized, however may be exceptionally bothersome or not irritated by any stretch of the imagination. They can be exceptionally dry and layered or can get to be wet and open.

- The reason for nummular skin inflammation is obscure, yet it has a tendency to be more confined than atopic dermatitis and does not appear to run in families. In some cases there is an activating occasion, for example,
  - A creepy crawly nibble.
  - A response to irritation (counting atopic dermatitis) somewhere else on the body.
  - Dry skin in the winter.

- Since it can look like ringworm (tinea corporis), it is imperative to verify that it is not a contagious contamination, particularly in the event that it is not reacting to treatment. This can typically be finished with a scratching or a parasitic society. Like

atopic dermatitis, nummular skin inflammation can likewise get to be tainted by microscopic organisms for the most part staphylococcus—and should be treated like present.

- **How is Nummular eczema treated?**

- Oral antihistamines can be useful for some, and may lessen a portion of the tingle, particularly around evening time.
- Like atopic dermatitis, nummular skin inflammation advantages from lotions to quiet and secure the harmed skin boundary.

- By and large, you may get a remedy for a corticosteroid pharmaceutical to cool the irritation also. For reasons unknown, the milder and much more direct intensity corticosteroid creams may not be of much help with nummular skin inflammation; all the more intense creams are regularly needed. Luckily, not at all like the perpetual way of atopic dermatitis, nummular skin inflammation has a tendency to vanish totally after satisfactory treatment in numerous people, minimizing the chance for symptoms with these stronger topical corticosteroids.

- In situations where corticosteroids are not suitable, or when they have been utilized for a delayed period, a non-corticosteroid topical pharmaceutical, for example, tacrolimus (Protopic) or pimecrolimus (Elidel) may be recommended. These specialists, topical calcineurin inhibitors , are endorsed for utilization by grown-ups and kids two years old or more established, and they evade a number of the symptoms of corticosteroids.

- Topical or oral anti-infection agents may be utilized when there is confirmation of bacterial disease.[12]

6. Neurodermatitis:

Neurodermatitis, otherwise called lichen simplex chronicus, is a bothersome skin sickness like atopic dermatitis. It has a tendency to result in central fixes one or numerous that are because of successive rubbing or scratching of the same region over the long time.

- These patches have a tendency to be thick and flaky, and have favored zones on the body, including:
  - Nape of the neck
  - Scalp
  - Shoulders
  - Instep of feet/lower legs
  - Wrists
  - Backs of hands

- Like in atopic dermatitis, the irritated regions can get to be thickened with improved skin markings, and are regularly stained. Dissimilar to atopic dermatitis, the particular fixes have a tendency to dependably be available while whatever is left of the skin stays sound.

➢ **How is neurodermatitis treated?**

- Thoroughly abstaining from scratching and rubbing is critical to breaking the cycling and recuperating the skin; then again, this can be extremely troublesome. Gives fingernails extremely the ax, and applying ice or an against tingle readiness as opposed to scratching can be useful.

- In a few circumstances, performing patch testing to search for allergens can be utilized to focus a conceivable hypersensitive reason that can then be dispensed with.

- Like atopic dermatitis, neurodermatitis advantages from lotions to smooth and secure the harmed skin boundary. Oily arrangements might likewise help shield the territory from rubbing and scratching. Occlusive measures, for example, socks, gloves, and even bandage wraps might likewise help the skin mend by upsetting the tingle scratch cycle. Unna boots (cloth impregnated with zinc oxide glue) are especially useful for neurodermatitis.

- Like in different manifestations of skin inflammation, a topical corticosteroid medicine can help smooth the irritation and tingle. Since the skin has a tendency to be thick and layered in neurodermatitis, more powerful creams are as often as possible obliged and must be utilized just as a part of brief blasts (up to 2 weeks) to forestall symptoms. Infrequently covering the corticosteroid with plastic wrap or an Unna boot can significantly help in extreme or safe cases.[13]

7. Stasis dermatitis:

Stasis dermatitis is at times called venous stasis dermatitis on the grounds that it emerges when there is an issue with the veins, for the most part in the lower legs.

- Rather than the typical blood course through the veins back to the heart, varicose veins or an issue with the valves of the veins considers weight to create. This weight brings about liquid spilling out of the veins and into the skin, which then causes: Swelling, Redness, Scaling , Itching

➢ **How is stasis dermatitis treated?**

- Since the reason is known, treating the hidden issue (the veins) is favored. In any case, infrequently the surgery for the veins is impractical, or is not ready to repair the veins totally.

- Weight tights or wraps can be utilized to bail mechanically move the liquid out of the skin and delicate tissues. Raising the feet when conceivable can likewise help thusly.

- Like in different manifestations of skin inflammation, a topical corticosteroid medication can help cool the irritation and tingle. Here and there covering the corticosteroid with plastic wrap or an Unna boot can incredibly aid in extreme or safe cases.[14]

2.2.1.2. Signs and symptoms: [6]

- Dermatitis manifestations fluctuate with every distinctive type of the condition. They extend from skin rashes to rough rashes or including rankles. Albeit each kind of dermatitis has distinctive manifestations, there are sure signs that are basic for every one of them, including redness of the skin, swelling, tingling and skin injuries with once in a while overflowing and scarring. Likewise, the zone of the skin on which the manifestations seem has a tendency to appear as something else with each kind of dermatitis, whether on the neck, wrist, lower arm, thigh or lower leg. Despite the fact that the area may fluctuate, the essential indication of this condition is irritated skin. All the more seldom, it may show up on the genital territory, for example, the vulva or scrotum. Symptoms of this kind of dermatitis may be exceptionally extraordinary and may travel every which way. Aggravation contact dermatitis is generally more excruciating than irritated.[6]

2.2.1.3. Treatment and prevention of eczema: [7]

- There is no general cure for dermatitis. Treatment for the condition intends to recuperate the influenced skin and forestall flaring of the indications. Specialists will propose an arrangement of treatment based around a tolerant age, indications and present condition of wellbeing.

- For a few individuals, dermatitis goes away over the long run and for others it remains a deep rooted condition.

- There are various things that individuals with dermatitis can destroy themselves request to treat their condition, to help the skin and lighten symptoms:

- Standard steaming showers can help ease skin inflammation manifestations.
- Take standard steaming showers
- Immediately apply cream inside 3 min a while later to "secure" dampness
- Moisturize consistently
- Wear cotton and delicate fabrics, maintaining a strategic distance from harsh, scratchy strands and tight-fitting garments
- Use mellow cleanser or a non-cleanser cleaning agent when washing
- After washing, air dry or delicately pat skin with a towel. Try not to rub.
- Avoid fast changes of temperature and exercises that make you sweat (where conceivable)
- Learn your skin inflammation triggers and dodge them
- Use a humidifier in dry or frosty climate
- Keep fingernails short to keep scratching from breaking skin.

There are a few manifestations of prescription that can be endorsed by specialists so as to treat the side effects of eczema:

- Topical corticosteroid creams and balms. These are a kind of mitigating medicine and ought to diminish the fundamental manifestations of dermatitis, for example, skin inflammation and irritation.
- If inadequate, systemic corticosteroids can be endorsed. These are either infused or taken by mouth, and are utilized for brief times of time
- Antibiotics
- Specific solutions are utilized to treat contagious and viral diseases
- Antihistamines that cause languor are regularly prescribed, as these can help to decrease the danger of evening scratching
- Topical calcineurin inhibitors (a kind of medication that smothers the exercises of the insusceptible framework) diminishes aggravation and helps counteract flares

- Barrier repair creams lessen water misfortune and work to repair the skin.
- Phototherapy can be endorsed to treat mellow to direct dermatitis. It includes presentation to bright A or B waves, alone or consolidated, and the skin will be observed precisely on the off chance that they are utilized.

- Despite the fact that the condition itself is not shortly reparable, there ought to be a specific treatment plan to suit every case. Indeed, even after a zone of skin has recuperated it is vital to continue taking care of it, as it may become irritated again.[7]

2.3 Topical dosage forms: [48]

- Topical dosage forms are those which are connected to the skin. These arrangement are connected to the skin either for their physical impacts, that is for their capacity to go about as skin protectants, ointments, emollients, drying specialists, and so on or for their particular impact of therapeutic specialists present. Arrangements sold over the nation often contain mixtures of therapeutic substance utilized as a part of the treatment of such condition as minor skin contamination, tingling, wound, pimple inflammation, psoriasis and dermatitis. Skin application, which oblige a remedy by and large contain a solitary restorative specialists planned to counter a particular diagnosed condition. Topical dose structures have been utilized following extremely antiquated times. The application of restorative substance to skin or to different body holes is an idea as old as mankind. Different balms, creams, gels, salves, glues, powders and mortars have been utilized for numerous years. The essential topical medication conveyance framework (TDDS) is that they could give controlled consistent organization of a medicament by basic application to the skin surface. The topical conveyance has been endeavored and made fruitful utilizing various lipid based frameworks viz., vesicular frameworks, lipid, microsphere, lipid nanoparticles, lipid emulsion and polymeric gels.

2.3.1 Advantages of topical systems:

- They wipe out the variables, which impacts gastrointestinal retention, for example, food intake, stomach exhausting, intestinal motility and travel time.
- Produces managed and controlled level of medication in plasma therefore decreases the possibility of over or under-dosing.
- Reduces recurrence of medication dosing.
- Topical frameworks are effectively retractable along these lines end of medication inaproxenut, if lethal impacts are watched.
- Offers an option course when oral treatment is unrealistic as if there should arise an occurrence of sickness and vomitting.
- Helps in accomplishment of more steady blood levels with lower measurements of medication by ceaseless medication in aproxenut and by-passing hepatic first-pass digestion system and subsequent degradation.
- In specific circumstances, enzymatic change inside epidermis may be utilized to enhance permeability of certain hydrophilic medications when connected to the skin in the form of prodrug.

2.3.2 Limitations of topical systems:

- Drugs with sensible part coefficient and having solubility both in oil and water are most perfect, as medication must diffuse through lipophilic stratum corneum and hydrophilic practical epidermis to achieve the systemic flow. Just medications, which are successfully consumed by the percutaneous courses all things considered or by utilizing entrance promoters, can be considered.
- The course is not suitable for medications that aggravate or sharpen the skin.
- The course is confined by the surface range of conveyance framework and the measurements that needs to be managed in the ceaseless condition of ailment.
- Topical medication conveyance frameworks are moderately lavish contrasted with routine dose shapes. They may contain a lot of medication, of which just a little rate

may be utilized amid the application period. Aside from these impediments different issues incorporate pharmacokinetics and pharmacodynamic confinements. Therefore clinical need must be analyzed precisely before building up.

2.4 Introduction to Solid lipid nanoparticles:

2.4.1 Introduction: [5]

- Nanoparticles produced using strong lipids are pulling in real consideration as novel colloidal medication transporter for intravenous applications as they have been proposed as an option particulate bearer framework. SLN are sub-micron colloidal bearers extending from 50 to 1000 nm, which are made out of physiological lipid, scattered in water or in watery surfactant arrangement. SLN offer novel properties, for example, little size, expansive surface range, high medication stacking and the cooperation of stages at the interface and are alluring for their capability to enhance execution of pharmaceuticals.
- Keeping in mind the end goal to beat the impediments connected with the liquid condition of the oil drops, the liquid lipid was replaced by a solid lipid, which inevitably changed into strong lipid nanoparticles.
- The purposes behind the expanding enthusiasm for lipid based framework are numerous – crease and incorporate.
  - Lipids improve oral bioavailability and decrease plasma profile variability.
  - Better portrayal of lipoid excipients.
  - An enhanced capacity to address the key issues of innovation exchange and production scale-up.

Solid lipid nanoparticles are one of the novel potential colloidal bearer frameworks as option materials to polymers which is indistinguishable to oil in water emulsion for parenteral nourishment, however the fluid lipid of the emulsion has been supplanted by a strong lipid indicated on Fig. They have numerous points of interest, for example, great biocompatibility,

low poisonous quality and lipophilic medications are better conveyed by solid lipid nanoparticles and the framework is physically stable.

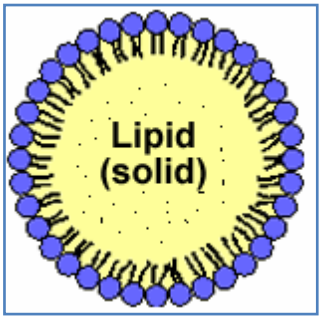

Figure 2.4 Structure of solid lipid nanoparticles[5]

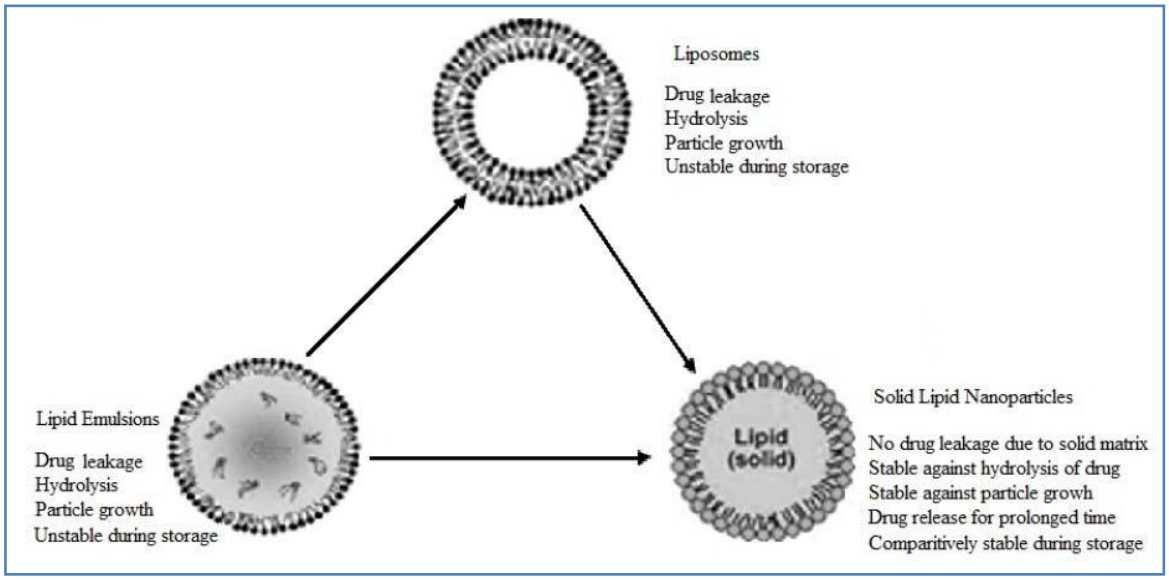

Figure 2.5 A diagrammatic representation on SLN over emulsions and liposomes[5]

- Solid lipid nanoparticles (SLNs) are thought to be the best lipid based colloidal transporters, presented in mid nineties. This is the standout amongst the most prominent ways to deal with enhance the oral bioavailability of the inadequately water solvent medications. SLNs are in the submicron size scope of 50-1000 nm and are made out of physiologically endured lipid segments which are in strong state at room temperature. The schematic representation of diverse particulate medication

transporters, for example, emulsions and liposomes and their points of interest are contrasted and SLNs in Fig. SLNs join all the upsides of polymeric nanoparticles, fat emulsions and liposomes.

2.4.1.1. Advantages of SLN:

- Control and/ or target drug release.
- Excellent biocompatibility.
- Improve stability of pharmaceuticals.
- High and improved drug content.
- Easy proportional up and clean.
- Better control over discharge energy of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.
- Chemical protection of labile fused compounds.
- Much simpler to make than biopolymeric nanoparticles.
- No exceptional solvent needed.
- Conventional emulsion manufacturing methods appropriate.
- Raw materials fundamental the same as in emulsions.
- Very high long term stability.
- Application flexibility.
- Can be subjected to industrial sterilization procedures.

2.4.1.2. Disadvantages of SLN

- Particle development.
- Unpredictable gelation susceptibility.
- Unexpected motion of polymeric transitions.

2.4.1.3. Aims of solid lipid nanoparticles

- Possibility of controlled drug discharge.
- Increased stability of drug.
- High drug pay load.

- Avoidance of organic solvents.
- Incorporation of lipophilic and hydrophilic drugs.

2.4.2. Methods of preparation of solid lipid nanoparticles:

1. High pressure homogenization
   a) Hot homogenization
   b) Cold homogenization
2. Ultrasonication/high speed homogenization
3. Solvent evaporation method
4. Solvent emulsification-diffusion method
5. Supercritical fluid method
6. Microemulsion based method
7. Spray drying method
8. Double emulsion method
9. Precipitation technique
10. Film-ultrasound dispersion

- **High pressure homogenization (HPH):**
  - It is a solid and effective strategy, which is utilized for the creation of SLNs. High weight homogenizers push a liquid with high weight (100–2000 bar) through a limited hole (in the scope of a couple microns). The liquid quickens on a short separation to high speed (more than 1000 Km/h). High shear stress and cavitation strengths disturb the particles down to the submicron range. For the most part 5-10% lipid substance is utilized yet up to 40% lipid substance has likewise been researched.

  - Two general methodologies of HPH are hot homogenization and cold homogenization; deal with the same idea of blending the drug in greater part of lipid melt.

a) Hot homogenization:

- Hot homogenization is completed at temperatures over the melting point of the lipid and can consequently be viewed as the homogenization of an emulsion. A preemulsion of the drug stacked lipid melt and the watery emulsifier stage (same temperature) is acquired by high-shear blending device. HPH of the preemulsion is completed at temperatures over the melting point of the lipid. In general, higher temperatures bring about lower molecule sizes because of the diminished viscosity of the inward stage. Be that as it may, high temperatures expand the degradation rate of the drug and the carrier. Expanding the homogenization weight or the quantity of cycles frequently brings about an increment of the particle estimate because of high kinetic energy of the particles.

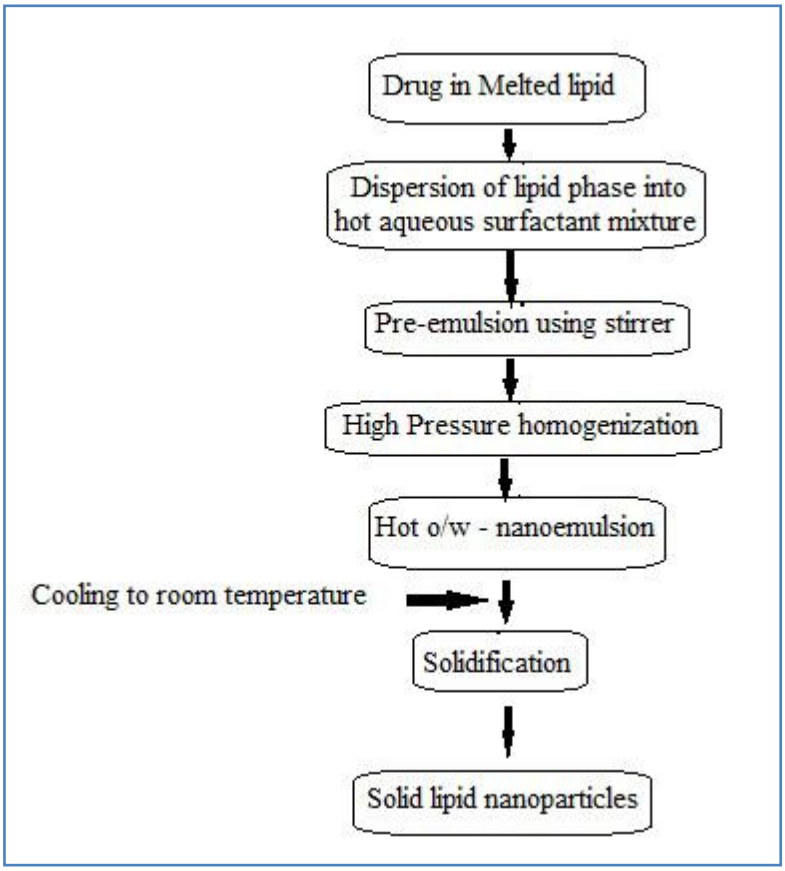

Figure 2.6 Solid lipid nanoparticles preparation by hot homogenization process

b) Cold homogenization:

- Cold homogenization has been produced to overcome different issues connected with hot homogenization, for example, Temperature-prompted drug corruption, drug appropriation into the aqueous stage amid homogenization, Complexity of the crystallization venture of the nanoemulsion prompting a few changes and/or super cooled melts. In this procedure the medication containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are scattered in an cold surfactant arrangement yielding a presuspension. At that point this presuspension is homogenized at or beneath room temperature; the gravitation force is sufficiently hard to break the lipid microparticles straightforwardly to solid lipid nanoparticles.

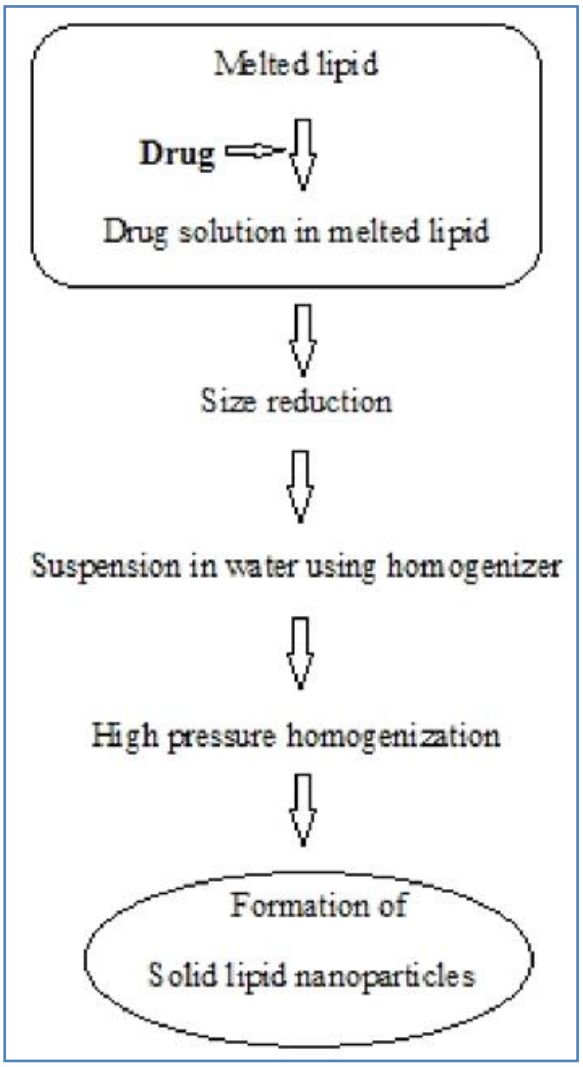

Figure 2.7 Solid lipid nanoparticles preparation by cold homogenization process

Advantages:

- Capital cost is low.
- Demonstration is done at lab scale.

Disadvantages:

- Biomolecule harm is done at lab scale.
- Polydisperse dispersions.

- **Ultrasonication / high speed homogenization:**

- For small size particle size, both ultrasonication and high speed homogenization is used. SLNs are also prepared by this method.

Advantages:

- Shear stress is reduced.

Disadvantages:

- Contamination of metal is possible.
- On storage particle growth is observed.

- **Solvent evaporation:**

- The lipophilic material is broken up in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in a aqueous stage. Endless supply of the solvent, nanoparticles scattering is framed by precipitation of the lipid in the watery medium by giving the nanoparticles of 25 nm mean size. The arrangement was emulsified in a liquid stage by high pressure homogenization. Organic solvent was removed from the emusion by reduced pressure (40- 60 mbar).

Advantages:

- Can lead to large scale production.
- It is continuous process.
- It is demonstrated commercially.

Disadvantages:

- Polydisperse distributions.
- Damage of biomolecule is seen.

➢ **Solvent emulsification-diffusion method:**

- The main advantage of this method is that heat is avoided during the preparation and average particle size is 30-100 nm.

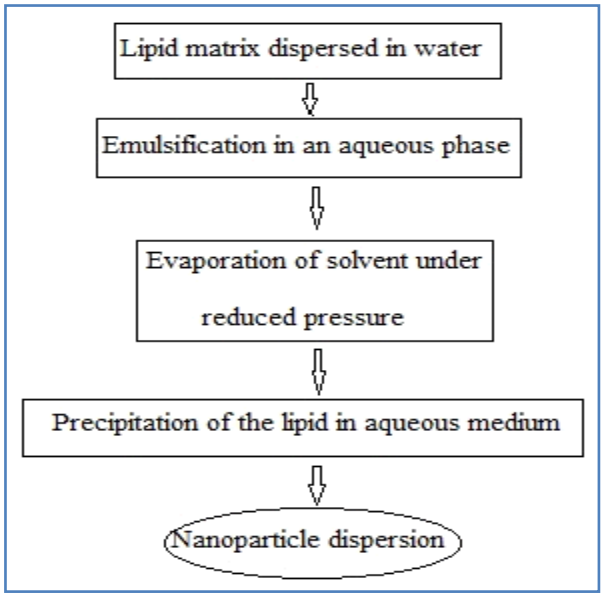

Figure 2.8 Systematic representation for emulsification-diffusion method

➢ **Supercritical fluid method:**

- These are an alternative method for preparation of SLNS by particles from gas saturated solutions.

Advantages:

- Avoidance of solvents.
- Dry powders are formed as particles instead of suspensions.
- Temperature and pressure conditions are low.

➢ **Microemulsion based method:**

- This system is in view of the dilutions of microemulsions. As microemulsions are two-stage frameworks made out of an inward and external stage (e.g. o/w microemulsions). They are made by mixing an optically simple mixture at 65-70°C, which ordinarily made

out of a low dissolving unsaturated fat (e.g. stearic corrosive), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is scattered in cold water (2-3°C) under mixing. SLN dispersion can be utilized as granulation liquid for moving into solid products (tablets, pellets) by granulation process, yet in the event of low molecule content excessively of water needs to be removed. Because of the weakening step; achievable lipid substance are significantly lower as compared to HPH.

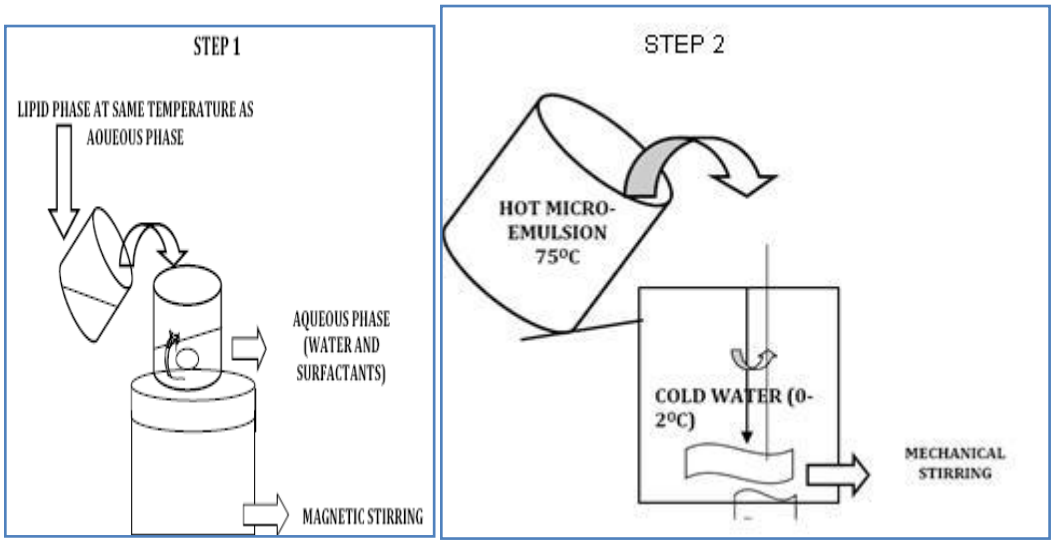

Figure 2.9 Microemulsion method

Advantages:

- Stability is achieved.
- Input of low mechanical energy.

Disadvantages:

- Lower nanoparticles concentration is seen.
- Labor intensive formulation work.

➢ **Spray drying method:**

- Secondary method as compared to lyophilization technique. The use of lipid whose melting point is more than 70ºC is recommended.

➢ **Double emulsion method:**

- Encapsulation of the drug is done with the stabilizer to prevent partitioning of water phase during solvent evaporation.

➢ **Precipitation method:**

- Evaporation of the organic solvent (eg. Chloroform) in which glycerides are dissolved and the solution will be emulsified in aqueous phase leads to precipitation forming nanoparticles.

➢ **Film-ultrasound dispersion:**

- A lipid film is formed when the lipid and drug were put in suitable organic solutions by decompressing, rotating and evaporation of suitable organic solutions after adding the aqueous solution containing emulsions was added. SLN with uniform particle size was formed by using the ultrasound with probe to diffuser.

2.4.3. Applications of SLN:

- **SLN as potential new adjuvant for antibodies:**

  Adjuvants are utilized as a part of inoculation to upgrade the immune response. The more secure new subunit antibodies are less viable in vaccination and accordingly successful adjuvants are needed. New improvements in the adjuvant region are the emulsion frameworks. These are oil-in-water emulsions that corrupt quickly in the body. Being in the strong state, the lipid parts of SLNs will be corrupted all the more gradually giving a more extended enduring introduction to the safe framework.

- **Solid lipid nanoparticles in cancer chemotherapy:**

  From the most recent two decades a few chemotherapeutic agents have been encapsulated in SLN and their in-vitro and in-vivo viability have been assessed.

Results of these studies have been demonstrated to move forward the viability of chemotherapeutic medications, all the while lessening in symptoms connected with them. The quick evacuation of colloidal particles by the macrophages of the RES is a significant hindrance to focusing on tissues somewhere else in the body, for example, bone marrow and strong tumors.

A) SLN as targeted carrier for anticancer drug to solid tumor:

An anticancer drug called Tamoxifen which is incorporated into SLN for prolongation of drug after IV administration in breast cancer.

B) SLN in breast cancer and lymph node metastases:

Safety and bioavailability of drug was improved by formulating Mitoxantrone SLN local injections to reduce its toxicity.

- **Solid lipid nanoparticles for delivering peptides and proteins**:

  Proteins and antigens expected for helpful purposes may be joined or adsorbed onto SLN, and further controlled by parenteral routes or by option routes, for example, oral, nasal and pulmonary. Vital peptides, for example, cyclosporine An, insulin, calcitonin and somatostatin have been joined into solid lipid particles and are as of now under examination. A few neighborhood or systemic therapeutic applications may be predicted, for example, vaccination with protein antigens, irresistible ailment treatment, perpetual infections and disease treatment.

- **Solid lipid nanoparticles for targeted brain drug delivery:**

  The amazingly little molecule size of solid lipid nanoparticles, which are under 50 nm, may be gainful concerning drug targeting. SLNs can enhance the capacity of the drug to infiltrate through the blood-cerebrum barrier and is a promising drug focusing on framework for the treatment of central nervous system issue. Solid lipid nanoparticles physicochemical characteristics are regarded to issues related to brain targeting formulations.

- **Solid lipid nanoparticles for lymphatic targeting:**
  Development and evaluation of solid lipid nanoparticles is done for the lymphatic uptake after intraduodenal administration to rats.

- **SLN for potential agriculture applications**:
  Incorporation of essential oil into SLN reduces the evaporation as compared to emulsions which are used in agriculture as pesticides.
- **SLN in cosmetic and dermatological preparations:**
  SLN are considered as being the up and coming era of conveyance framework after liposomes. Because of the lower danger of systemic symptoms topical treatment of skin infection seems ideal, yet the stratum corneum neutralizes the entrance of xenobiotics into practical skin. Particulate bearer frameworks may mean a choice to enhance dermal entrance. Other than liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been concentrated on seriously. Taking after the evaporation of water from the lipid nanodispersion connected to the skin surface, lipid particles frame an adhesive layer impeding the skin surface. Nanoparticles have turned out 15-overlay more occlusive than microparticles, and particles littler than 400 nm in a dispersion containing no less than 35% lipid of high crystallinity has been generally strong.

2.5 Drug profile[15]

- **Name**: Dapsone
- **Chemical Name: 4**-[(4-aminobenzene)sulfonyl]aniline
- **Structural Formula:**

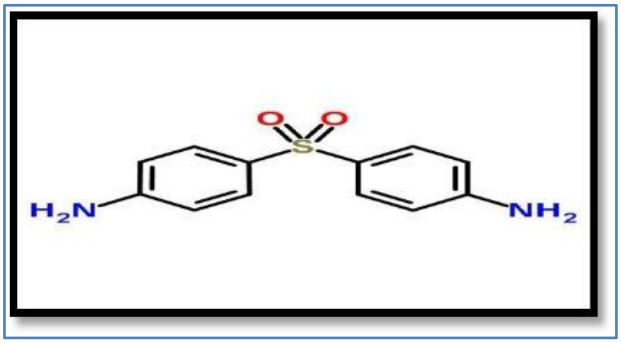

Figure 2.10 Structure of Dapsone[15]

- **Physical and Chemical Properties:**
  - **Melting Point:175.5°C**
  - **pKa:2.41**
- **Mechanism of Action:**

  Dapsone acts against bacteria and protozoa in the same way as sulphonamides, that is by inhibiting the synthesis of dihydrofolic acid through competition with para-amino benzoate for the active site of dihydropteroate synthetase.
- **Uses and Administration:**

➢ In the treatment of leprosy.

➢ In combination with pyrimethamine, dapsone can be used for chloroquine-resistant malaria.

2.6 Polymer profile

➢ **Carbopol 940[24]**

- **Nonproprietary Names:**
  - BP: Carbomers
  - PhEur: Carbomers
  - USP-NF: Carbomer
- **Synonyms:** Acrypol; Acritamer; acrylic acid polymer; carbomera; Carbopol; carboxypolymethylene; polyacrylic acid; carboxyvinyl polymer; Pemulen; Tego Carbomer
- **Chemical Name and CAS Registry Number:**

  Carbomer 940 [9007-17-4]
- **Functional Category:**

  Bioadhesive material; controlled-release agent; emulsifying agent; emulsion stabilizer; rheology modifier; stabilizing agent; suspending agent; tablet binder.

- **Structural Formula:**

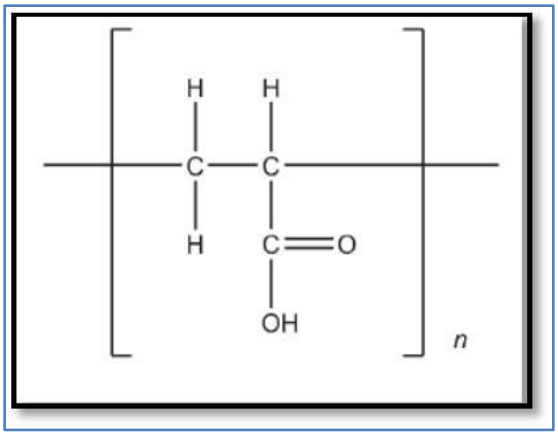

Fig. 2.11 Acrylic Acid monomer unit in carbomer polymer[24]

Carbomer polymers are formed from repeating units of acrylic acid. The monomer unit is shown above. The polymer chains are crosslinked with allyl sucrose or allyl pentaerythritol.

- **Description:** Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a characteristic slight odor.
- **Application:**

  Various uses are described in following table.

Table 2.1 Use of Carbomers

Sr. No.	Use	Concentration (%)
1	Emulsifying agent	0.1-0.5
2	Gelling agent	0.5-1.0
3	Suspending agent	0.5-1.0
4	Tablet binder	0.75-3.0

5	Controlled- release agent	5.0-30.0

- **Stability:**

  Carbomers are stable, hygroscopic materials that may be heated at temperatures below 104°C for up to 2 hours without affecting their thickening efficiency.

- **Storage conditions:**

  Carbomer powder should be stored in an airtight, corrosionresistant container and protected from moisture. The use of glass, plastic, or resin-lined containers is recommended for the storage of formulations containing carbomer.

2.7 Excipient profile

2.7.1 Span 80[25]

- **Nonproprietary Names**
  - BP: Sorbitan oleate
  - PhEur: Sorbitani oleas
  - USP: Sorbitan monooleate
- **Synonyms**

  Ablunol S-80; Arlacel 80; ArmotanMO; Capmul O; Crill 4; Crill 50; Dehymuls SMO; Drewmulse SMO;
- **Chemical Name and CAS Registry Number**

  (Z)-Sorbitan mono-9-octadecenoate [1338-43-8]
- **Functional Category:**

  Emulsifying agent; nonionic surfactant; solubilizing agent; wetting and dispersing/suspending agent
- **Structural Formula:**

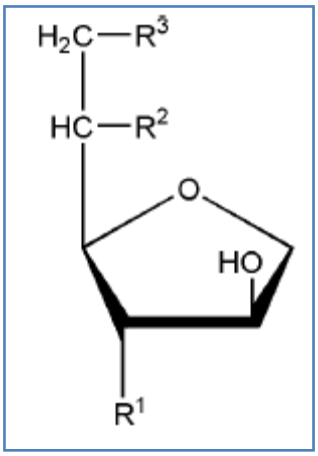

Figure 2.12 General structure of Sorbitan [25]

R1 = R2 = OH, R3 = R (see below) for sorbitan monoesters

R1 = OH, R2 = R3 = R for sorbitan diesters

R1 = R2 = R3 = R for sorbitan triesters

Where R = (C17H35)COO for isostearate

(C11H23)COO for laurate

(C17H33)COO for oleate

(C15H31)COO for palmitate

(C17H35)COO for stearate

The sesquiesters are equimolar mixtures of monoesters and diesters.

- **Description:**

  Sorbitan esters occur as cream- to amber-colored liquids or solids with a distinctive odor and taste. Appearance is yellow viscous liquid.

- **Application:**

  Various uses are described in following table:

Table 2.2 Uses of sorbitan esters

Sr. No.	Use	Concentration (%)
1	Emulsifying agent	

	Used alone in water-in-oil emulsions	1–15
	Used in combination with hydrophilic emulsifiers in oil-in-water emulsions	1–10
	Used to increase the water-holding properties ofointments	1–10
2	Solubilizing agent	
	For poorly soluble, active constituents in lipophilic bases	1–10
3	Wetting agent	
	For insoluble, active constituents in lipophilic bases	0.1–3

- **Stability:**

  Sorbitan esters are stable in weak acids or bases.

- **Storage Conditions**

  Sorbitan esters should be stored in a well-closed container in a cool, dry place.

2.7.2 Compritol ATO 888[26]

- **Nonproprietary Names:**
  - BP: Glycerol dibehenate
  - PhEur: Glyceroli dibehenas
  - USP-NF: Glyceryl behenate
- **Synonyms:**

  Glyceryl Behenate; 2,3-dihydroxypropyl docosanoate; docosanoic acid, 2,3-dihydroxypropyl ester; E471; glycerol behenate; glyceryl monobehenate.

- **Chemical Name and CAS Registry Number:**

  Docosanoic acid, monoester with glycerin [30233-64-8]

- **Functional Category:**

  Coating agent; tablet binder; tablet and capsule lubricant.

- **Description:**

  Glyceryl behenate occurs as a fine white powder or hard waxy mass with a faint odor.

- **Application:**

  Glyceryl behenate is used in cosmetics, foods, and oral pharmaceutical formulations. In cosmetics, it is mainly used as a viscosity-increasing agent in emulsions.

Table 2.3 Uses of glyceryl behenate

Sr. No.	Use	Concentration (%)
1	Lipophilic matrix or coating for sustained-released tablets and capsules	>10.0
2	Tablet and capsule lubricant	1.0-3.0
3	Viscosity-increasing agent in silicon gels (cosmetics)	1.0-15.0
4	Viscosity-increasing agent in w/o or o/w emulsions (cosmetics)	1.0-5.0

- **Storage Conditions**

  Glyceryl behenate should be stored in a tight container, at a temperature less than 35ºC.

2.8 Introduction to 3^2 full factorial design: [20]

Design of experiments should be such that it helps in finding the optimized batch in minimum number of trials which are to be performed. Out of the various designs, the 3^2 full factorial was found for further studies of various parameters in final formulation. These experimental designs consist of 8 runs. Various series of experimental trials were performed and evaluation was based on the setup of experimental runs taken at different combinations of factor levels. All the values of responses were fitted to a linear equation model and the adequacy of this model was checked by various statistical parameters such as ANOVA, lack of fit, and multiple correlation coefficients R^2 tests.

The equation constructed from 3 factorial experiments is in the following form:

$$Y= B_0 + B_1X_1+ B_2X_2 +B_{11}X_1^2+B_{22}X_2^2 + B_{12}X_1X_2$$

Where,

B_0 = intercept

X_1 and X_2 = variables

B_1 and B_2 = Co-efficient of X_1 and X_2 variable

B_{12} = Co- efficient of interaction

B_{11} and B_{22} = Co- efficient of quadratic terms

An optimized formulation can be found out by grid analysis after establishing the linear equation model. The coefficient of responses exemplifies the relative importance of each factor. A grid method has been employed to recognize the optimum region & interpretation of response surfaces with the help of computer which then compute the responses based on the equation at many factor level combinations. The formulation whose response has optimal characteristics based on the experimenter's specification is the chosen.

Advantages:

- In the absence of interaction, factorial designs have maximum efficiency in estimating main effects.
- If interactions exist, factorial designs are necessary to reveal and identify the interactions.
- Since factor effects are measured over varying levels of other factors, conclusions apply to a wide range of conditions.
- Maximum use is made of the data since all main effects and interactions are calculated from all of the data.
- Factorial designs are orthogonal.

Applications:

- It helps in interpretation of the mechanism of experimental system.
- It suggests and implements a practical process or set of experimental condition in the pharmaceutical industries of manufacturing process.
- It helps in providing guidance for further experimentation in minimum number of trials.

Chapter – 3

Literature Review

3. Literature Review:

3.1 Literature review on Dapsone

1. K. Panduranga Rao et al [2] prepared liposomes containing oleic acid and stearic acid sequestered in chitosan gel. Both Dapsone and bromothymol blue were entrapped in liposomes. Here the carboxyl group of sequestered liposomes were then coupled to ammo group of chitosan by carbodiimide. In vitro release studies were carried out of drug from liposomes and liposomes sequestered in chitosan gel using phosphate buffer and mice plasma was also studied. It was concluded that liposomes coupled to chitosan gel showed slower release of Dapsone than uncoupled liposomes.

2. L. M. Monteiro et al [3] prepared Dapsone nanoemulsion using Isopropyl Myristate, Tween 80, Span 80 and propylene glycol for oral delivery and studied permeability and in silico bioavailability. The release profiles of Dapsone nanoemulsion by using different combinations of surfactants and cosolvent which showed higher dissolution rate in simulated gastric and enteric fluid than the dispersed Dapsone powder. The drug release kinetics was compatible with a Higuchi model.

3. N. Kaila et al [4] prepared extemporaneous suspension from tablets using Sodium CMC and Veegum HV and stability was checked. The shelf life for the suspension was reported as 31.67 days at 25℃ and 230.76 days at 4℃ under refrigeration. The energy of activation was found to be -23288.35 J/K/M and zero-order rate of degradation for Dapsone at 25℃ was found to be 0.040845 day^{-1} of the suspension. The analytical stability testing study was carried out of 91 day at 4°, 30°, 50°, 60° and 70℃.

4. V. Borges et al [1] prepared nanoemulsion loaded Dapsone using IPM, ISO, Tween 80 and Span 20 for the topical delivery for treatment of leprosy. Use of N-methyl pyrrolidone provided greater nanoemulsion region and higher solubilization of Dapsone and increase rate

of in-vitro release compare to nanoemulsion using Isopropyl Myristate. Also, by using Isopropyl Myristate increasing in-vitro epidermal permeation was found which followed Higuchi model. They also showed that topical administration of Dapsone can be an alternative route for treatment of leprosy which provides new therapeutic applications for an established drug and also showed that physicochemical characterization demonstrated that formation of nanosystems had uniform droplet distribution and pH which is compatible to skin surface.

3.2 Literature Review on Solid Lipid Nanoparticles:

1. Ehsan Aboutaleb et al [35] prepared solid lipid nanoparticles of Rifampin by modified microemulsion based method and characterization such as particle size, zeta potential, encapsulation efficiency, morphology and antibacterial activity against Mycobacterium fortuitum were evaluated. The obtained SLNs were found to be spherical with diameter of about 100 nm, low zeta potential with 82% entrapment efficiency. The formulations also showed sustained drug release at 72 hr and antimycobacterial efficacy was improved against M. Fortuitum and minimum inhibitory concentration of drug loaded SLNs was eight times less than free RIF. Lastly, it was concluded that solid lipid nanoparticles are promising vehicles for antimycobacterial effect of rifampin.

2. **Surender Verma et al** [32] prepared solid lipid nanoparticles of Cefixime using Compritol ATO 888 as lipid core by solvent-evaporation method. The characterization including mean particle size was observed as 586.3 nm, entrapment efficiency was 72.43% and in vitro drug release in PBS pH 7.4 was 95.37% of the total drug in 10 hr was observed. In-vivo study was also conducted on male rats after oral administration of cefixime and cefixime solid lipid nanoparticles, relative bioavailability of cefixime SLNs was found to be 1.87. It was concluded that cefixime absorption is enhanced by using solid lipid nanoparticles formulations from the results.

3. Abather A. Sadiq et al [36] developed Silibinin loaded solid lipid nanoparticles to increase oral bioavailability and targeting lower part of GI tract by using GMS, TM, TP and TS as

solid lipid matrix and Tween 20, Tween 80, PVA and poloxamer 188 as emulsifier by solvent emulsification-evaporation method with slight modification. The entrapment efficiency, particle size distribution and in-vitro release, TEM, FTIR and DSC were studied. The SLNs prepared were found to be of submicron size. The entrapment efficiency were found to be in range from 64.67±4.51% to 87.00±2.00% of all the prepared SLNs. GMS had lower EE than TS using P188 or PVA as coemulsifier with high EE%. In-vitro drug release showed retardation in the trend TS>TP>TM. FTIR, DSC and TEM studies showed there was no drug- excipient incompatibility and formation of amorphous solid solution. It was concluded that SIL could be incorporated into SLN containing TS and P188 for oral use.

4. **Sacheen Kumar et al** [37] prepared and characterized solid lipid nanoparticles for the possibility entrapment of Paliperidone for the treatment of schizophrenia. Preparation of Paliperidone loaded solid lipid nanoparticles using Capmul GMS 50K as lipid and sodium deoxycholate as surfactant which also act as permeability enhancer. The final size of SLNs produced was found to be 200 nm, entrapment efficiency 55% and drug loading 4.15% was found. SLNs appeared spherical in TEM images and dough nut shape in AFM. By characterization of DSC, FTIR and XRD analysis, it was observed that there is no interaction found between drug and lipid and drug was well dispersed in lipid matrix.

3.3 Literature Review on Solid Lipid Nanoparticles based gel:

1. Tanmay N. Patel et al [38] prepared solid lipid nanoparticles loaded with Imiquimod by solvent diffusion evaporation method and incorporating into gel using Apifil, Precirol ATO 5 and Dynasan 116 as lipid. Other parameters like organic phase, organic solvent, concentration of Tween 20, temperature for secondary phase and drug; lipid ratio were optimized. Characterization of solid lipid nanoparticles dispersions such as particle size, zeta potential, DSC, TEM, FTIR, % entrapment efficiency and in-vitro drug release was studied. Further Carbopol 934 was used as a gelling agent for incorporation of Imiquimod SLN for enhancement of topical delivery. SLN based gel was also evaluated for by following characterization such as spreadability, drug content, diffusion study, viscosity, ex-vivo

studies. It was concluded that by incorporating Carbopol 934 in Imiquinod SLN enhances the topical availability in treatment of actinic keratoses and superficial basal cell carcinoma.

2. Gajanan S Sanap et al [39] prepared solid lipid nanoparticles of Miconazole nitrate for systemic delivery of the active after topical application by hot high pressure homogenization technique. MN-SLN was characterized for particle size, entrapment efficiency and SEM. After incorporating into gel for topical administration was evaluated for texture analysis, in-vitro drug release and ex-vitro skin permeation studies. The mean particle size was less than 250 nm. An initial rapid release was observed in case of marketed gel where MN-SLN gel showed slow initial release with lag time of 0.5 and 1 hr. Ex-vivo studies showed SLN shows control release and release depending upon the lipid content. High amount of MN release was seen through abdominal skin of rats from marketed gel. It was concluded that MN loaded SLN bearing hydrogel provides sustained as wellas topical effect from fungal infection.

3. Laith Hamza Samein et al [40] prepared SLN incorporating Nystatin to study its effect on skin when administered through a suitable semisolid vehicle such as gel by pre-emulsion probe sonication. The optimization was selected by using Box Behnken design and characterization of gel for particle size, % entrapment efficiency, XRD, FTIR and DSC which was formulated as gel containing solid lipid nanoparticles. Different lipids used out of which GMS and PG were selected. The optimized formula ingredients was GMS, Span 60 and Tween 80 were used for formulation. The optimized formulation using different concentration of carbopol 940 with 0.4% was considered as final. The stability study indicated there was no change between parameters before and after stability studies. It was concluded that Ny-SLN was found to be effective against Candida albicans.

4. N. Silpa et al [41] formulated Moxifloxacin loaded solid lipid nanoparticles using palmitic acid as lipid, Tween 80 and poloxamer as surfactant, methanol and butanol as cosolvents by o/w microemulsion using high speed homogenization. SLNs were characterized for particle size, zeta potential, drug content, entrapment efficiency, SEM, DSC and IR studies. The

optimized formulation was incorporated into various gels containing xanthan gum and carbopol. In vitro drug release studies were carried out for moxifloxacin SLN loaded gels. Ex-vivo studies were also carried out of Moxifloxacin SLN loaded gel for 12 hrs. It was concluded that stable formulation without precipitation of drug and showed sustained drug release and moxifloxacin proved to be the better topical delivery to treat bacterial infections.

Chapter – 4

Experimental Work

4. Experimental Work

4.1 Materials and Equipments

Table 4.1 List of materials used

MATERIALS	COMPANY NAME
Dapsone	Thermofischer Scientific Pvt. Ltd
Compritol ATO 888	Gifted by Gattefosse, France
Gelucire 39/01	
Gelucire 43/01	
Labrasol	
Labrafil	
Cremophor EL	BASF, Germany
Glyceryl Monostearate	Central Drug House Pvt. Ltd, India
Stearic Acid	
Carbomer 934	
Propylene Glycol	
Triethanolamine	
Sodium Hydroxide	
Potassium Dihydrogen Orthophosphate	
Tween 20	S.D. Fine- Chem Ltd, India
Tween 80	
Span 80	
Span 20	S.D. Fine- Chem Ltd, India
Methanol AR	
Dichloromethane	

Table 4.2 List of Equipments Used

INSTRUMENTS	MODEL COMPANY NAME
Digital Balance	Citiweigh- Tejas Exports, India
Mechanical Stirrer	Remi Motors Ltd. India
Magnetic Stirrer	
Hot Air Oven	EIE Instruments Pvt. Ltd, India
Ultraviolet Spectrophotometer	Shimadzu UV 1800 Corporation, Japan
Refrigerated Micro Centrifuge	Rajendra Electrical Industries Ltd. India
Ultrasonicator	Trans-O-Sonic D- Compact, India
pH meter	Analab Scientific Instruments, India
Malvern- Zetasizer	Nano ZS90, Malvern Instruments Ltd, UK
Brookfield Viscometer	Brookfield Engineering Laboratories, USA
Texture Analyser	QTS 250, Brookfield Engineering Laboratories, USA
Fourier Transformed Infra Red Spectrophotometer	FTIR 6100 Type A, Jasco, Japan
Multi- Diffusion Cell Apparatus	Orchid Scientific & Innovative India Pvt. Ltd
Incubator Shaker	EIE Instruments Pvt. Ltd, India
Scanning Electron Microscope	JSM- 5610LV; JEOL, Gujarat

4.2 Pre-formulation studies

4.2.1 Identification of dapsone

4.2.1.1 Melting point analysis[23]

The melting point of the Dapsone was determined by thiel's tube method and it was compared with the standard reported melting of Dapsone.

Result:

Table 4.3 Melting point analysis of Dapsone

Sr. No.	Drug	Reported Melting Point (ºC)	Observed Melting Point (ºC)
1	Dapsone	175-177	175

Result and Discussion:

The melting point of Dapsone was found similar with the reported value of melting point which confirms drug sample.

4.2.2 UV spectrophotometric analysis[23]

A 0.0005 % w/v solution in methanol was scanned for 200-400 nm in methanol using UV-Visible spectrophotometer. The wavelength maxima was compared with reported wavelength maxima of Dapsone.

Result:

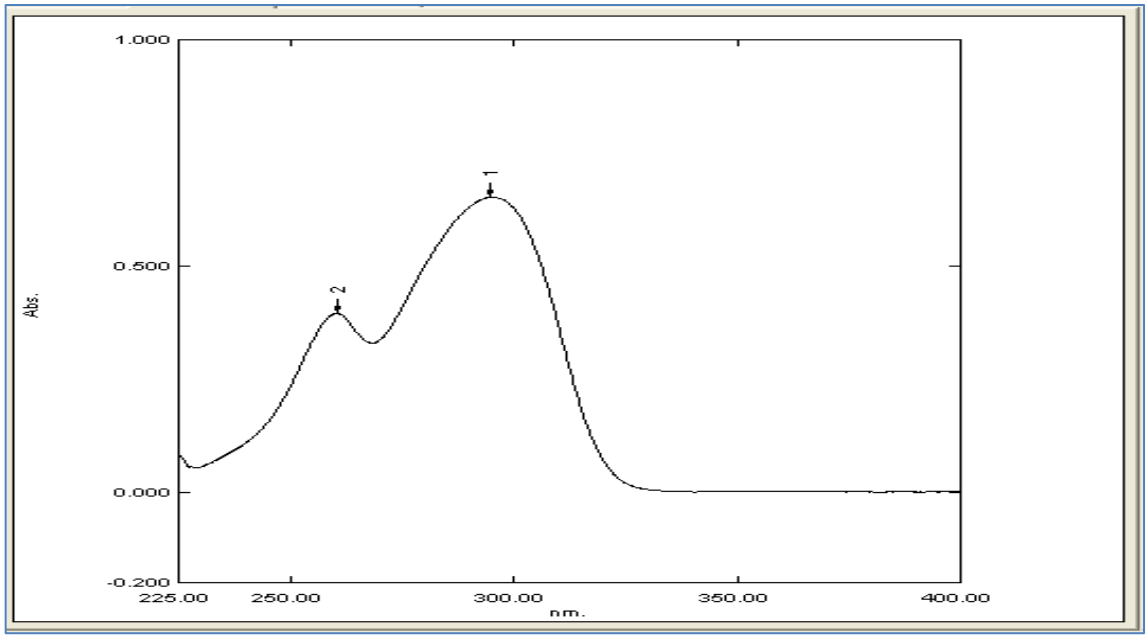

Figure 4.1 UV Spectrum of Dapsone showing maxima at 260 nm[23]

Table 4.4 Wavelength maxima (λ_{max}) of Dapsone

Sr. No.	Drug	Reported wavelength maxima (λ_{max})	Observed wavelength maxima (λ_{max})
1	Dapsone	260	260.65

Result and Discussion:

The UV absorbance of Dapsone was found to be 260.65 nm which was similar to reported value of wavelength maxima (λ_{max}), which confirms identification of drug sample.

4.2.3 FTIR spectra of Dapsone[57]

Identification of drug was done using Infrared spectroscopy. KBr disc was containing the drug was prepared and the spectra was recorded in a range between 2000 and 400 cm^{-1}.

Result

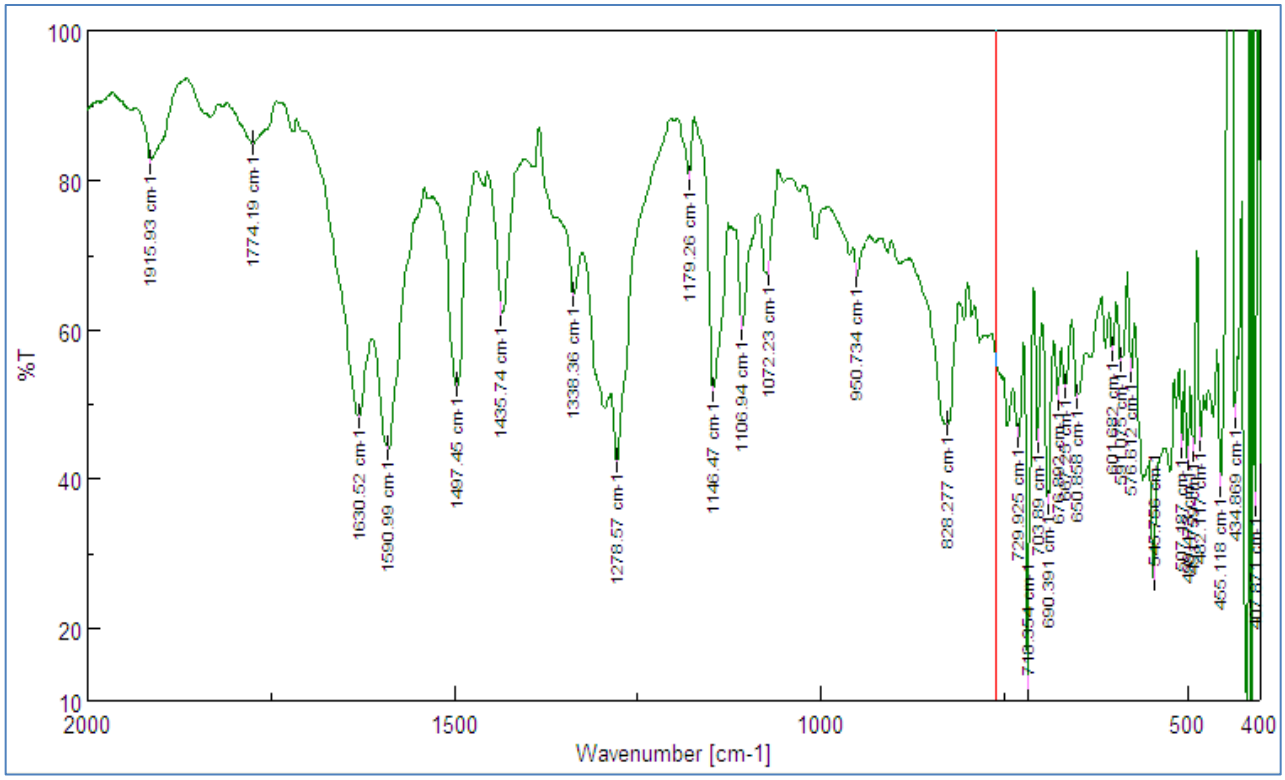

Figure 4.2 FTIR Spectrum of Dapsone

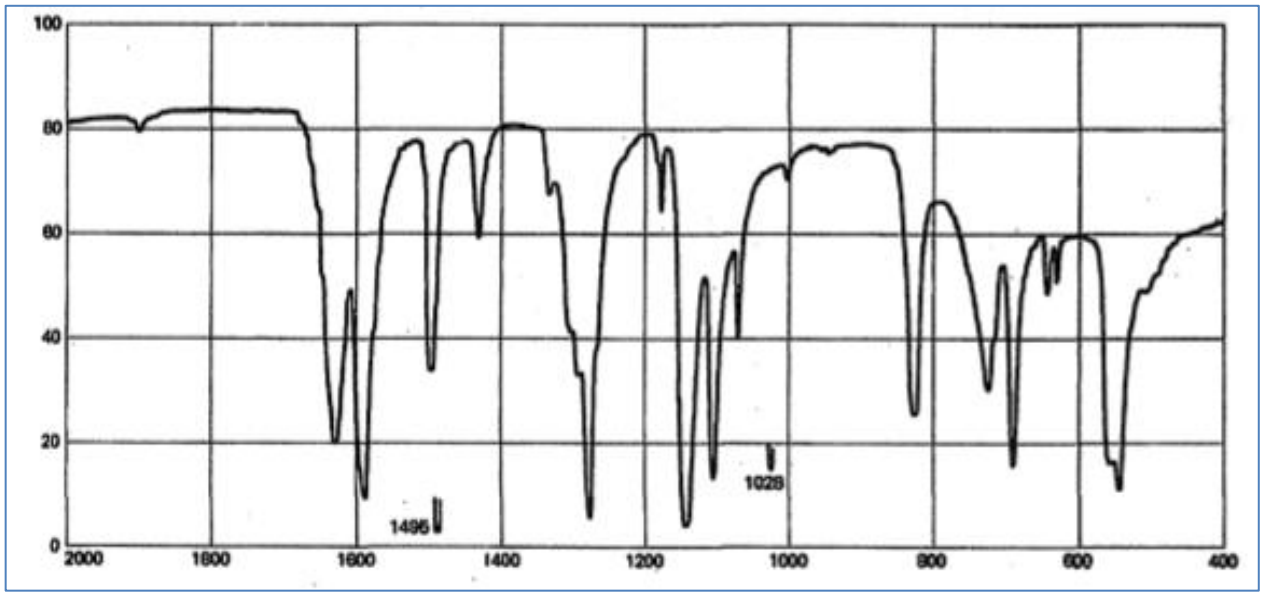

Figure 4.3 Standard FTIR Spectrum of Dapsone [57]

Table 4.5 Interpretation of the FTIR spectra of Dapsone Sample

Sr. No.	Standard Frequency (cm-1)	Observed frequency (cm-1)	Inference
1	1633	1630.52	N-H bending
2	1592	1590.99	C-C stretching
3	1150	1146.47	O=S=O stretching
4	1107	1106.94	C-N stretching
5	685	676.892	C-H bending

Result and Discussion:

The sample spectrum of Dapsone was compared with standard and both spectra were found similar in peak values representing wave numbers. Thus, it was concluded that procured Dapsone sample was a pure drug.

4.2.4 Drug-polymer compatibility study using FTIR spectroscopy

Compatibility study of procured drug & polymer was done by Infrared spectroscopy. KBr disc containing the drug and polymer mixture was prepared and the spectrum was recorded in a range between 4000 & 400 cm^{-1}.

Result

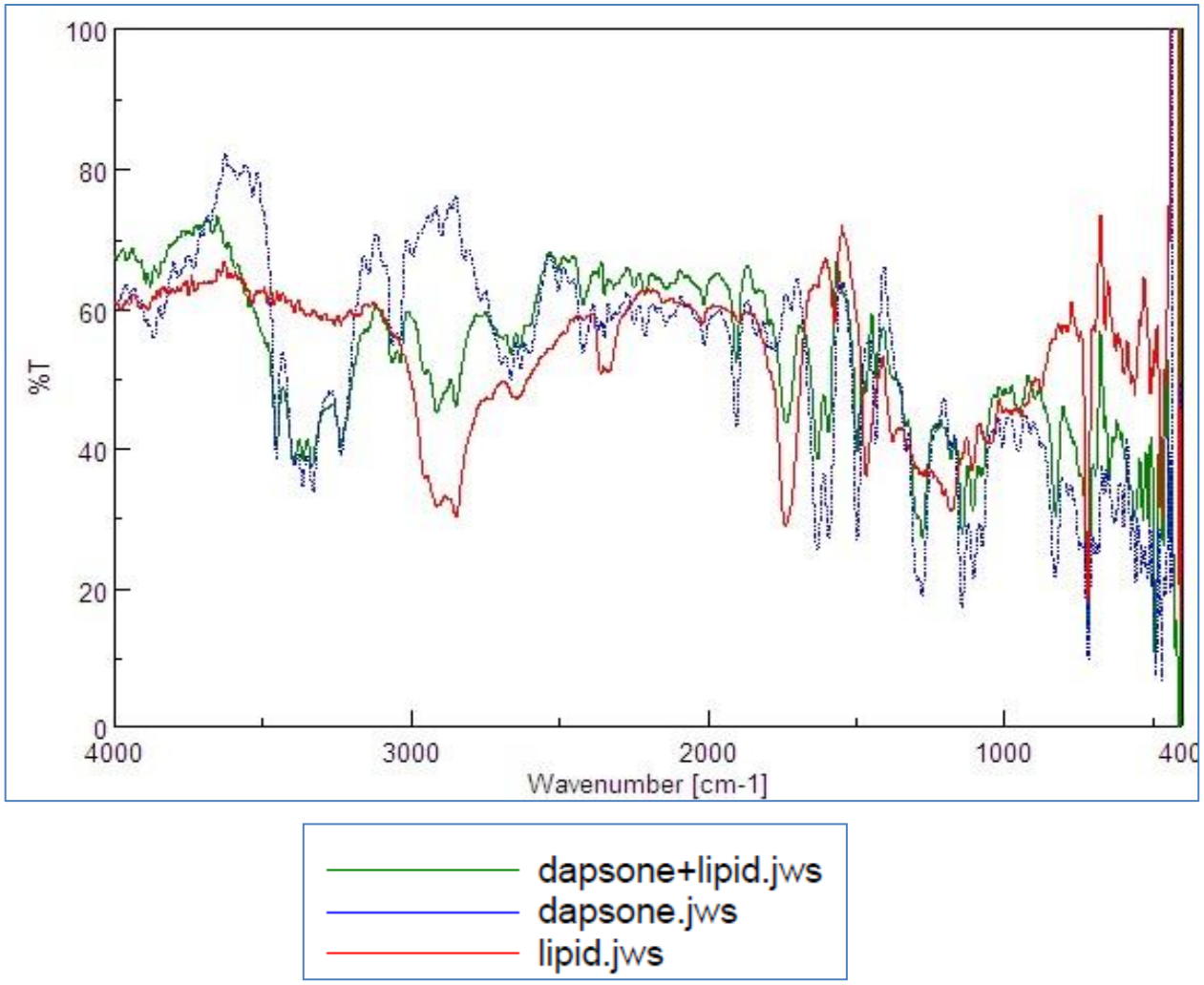

Figure 4.4 Overlay of FTIR Spectra of drug, lipid and drug + lipid

Result and Discussion:

The intensity of characteristic peaks of Dapsone and compritol ATO 888 physical mixture found similar as FTIR spectra of Dapsone, which confirmed drug-polymer compatibility.

4.2.5 Development of spectrophotometric method for estimation of Dapsone

For developing analytical methods which are precise, specific and accurate for having quantitative data on various studies such as purity, evaluation of drug, compatibility studies, in-vitro diffusion studies, etc. Therefore, the following analytical methods were developed

and validated for Dapsone.

4.2.5.1 Calibration curve of Dapsone in methanol

- **Preparation of stock solution:**

A standard stock solution of Dapsone was prepared in methanol by dissolving 100 mg Dapsone in 100 ml of methanol.

- **Preparation of dilutions:**

Suitable dilutions were made from the standard solution to get concentrations in the range of 2-12 µg/ml with interval of 2 µg/ml.

The absorption maxima (λ_{max}) was determined by scanning 12 µg/ml solution against the reagent blank on UV-visible spectrophotometer and the absorbance maxima was found out at 260 nm. The absorption of all the prepared solutions was then measured at the λ_{max}, 260 nm, against blank. The readings were recorded in triplicate. Mean values (n=3) along with the standard deviation were recorded and the regressed calibration curve was developed.

Table 4.6 Calibration plot of Dapsone in Methanol

Conc.(µg/ml)	**Absorbance**			**Average**	**Standard Deviation**
	(1)	(2)	(3)		
0	0.00	0.00	0.00	0.00	0.00
2	0.138	0.140	0.144	0.14	0.00305505
4	0.271	0.272	0.270	0.271	0.001
6	0.403	0.402	0.404	0.403	0.001
8	0.555	0.556	0.558	0.556	0.001527525
10	0.745	0.757	0.763	0.712	0.009165151
12	0.801	0.812	0.818	0.81	0.008621678

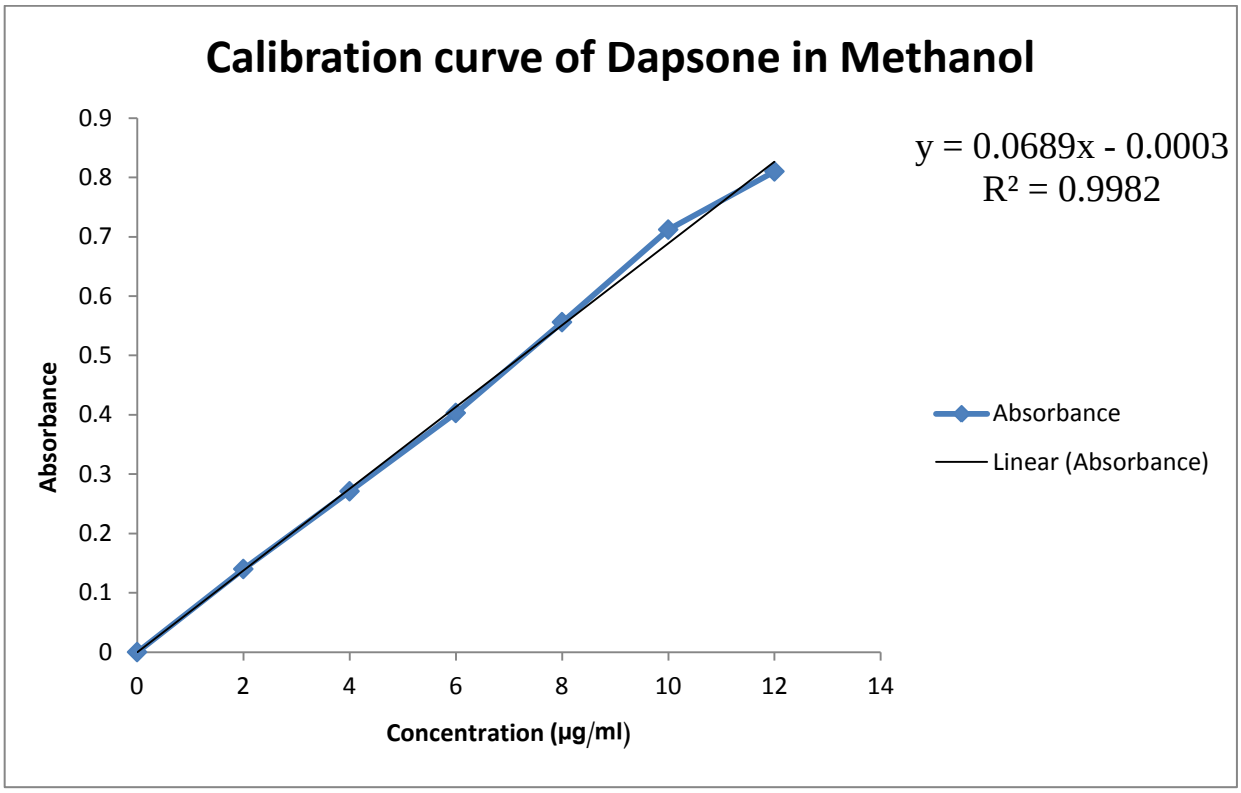

Figure 4.5 Calibration Curve of Dapsone in Methanol

Regression analysis

Table 4.7 Regression Analysis of the calibration plot of Dapsone in methanol

Sr. No.	Regression Parameter	Values
1	Correlation Coefficient	0.9982
2	Slope	0.0689
3	Intercept	0.0003

4.2.5.2 Calibration curve of Dapsone in methanol + Dichloromethane (1:2)

- **Preparation of stock solution:**

10 mg Dapsone was weighed in 10 ml volumetric flask, from that solution 1ml was pipetted out in 10 ml volumetric flask and volume was made upto 10 ml.

- **Preparation of dilutions:**

Suitable dilutions were made from the standard solution to get concentrations in the range of 2-12 µg/ml with interval of 2 µg/ml.

The absorption maxima (λ_{max}) were determined by scanning 12 µg/ml solution against the reagent blank on UV-visible spectrophotometer and the absorbance maxima were 260 nm. The absorption of all the prepared solutions was then measured at the λ_{max}, 260 nm, against blank. The readings were recorded in triplicate. Mean values (n=3) along with the standard deviation were recorded and the regressed calibration curve was developed.

Table 4.8 Calibration plot of Dapsone in Methanol + Dichloromethane (1:2)

Conc.(µg/ml)	**Absorbance**			**Average**	**Standard Deviation**
	(1)	(2)	(3)		
0	0.00	0.00	0.00	0.00	0.00
2	0.189	0.192	0.196	0.192	0.002121
4	0.339	0.342	0.347	0.342	0.002121
6	0.504	0.506	0.509	0.506	0.001414
8	0.688	0.691	0.694	0.691	0.002121
10	0.842	0.845	0.847	0.844	0.002121
12	1.037	1.039	1.043	1.039	0.001414

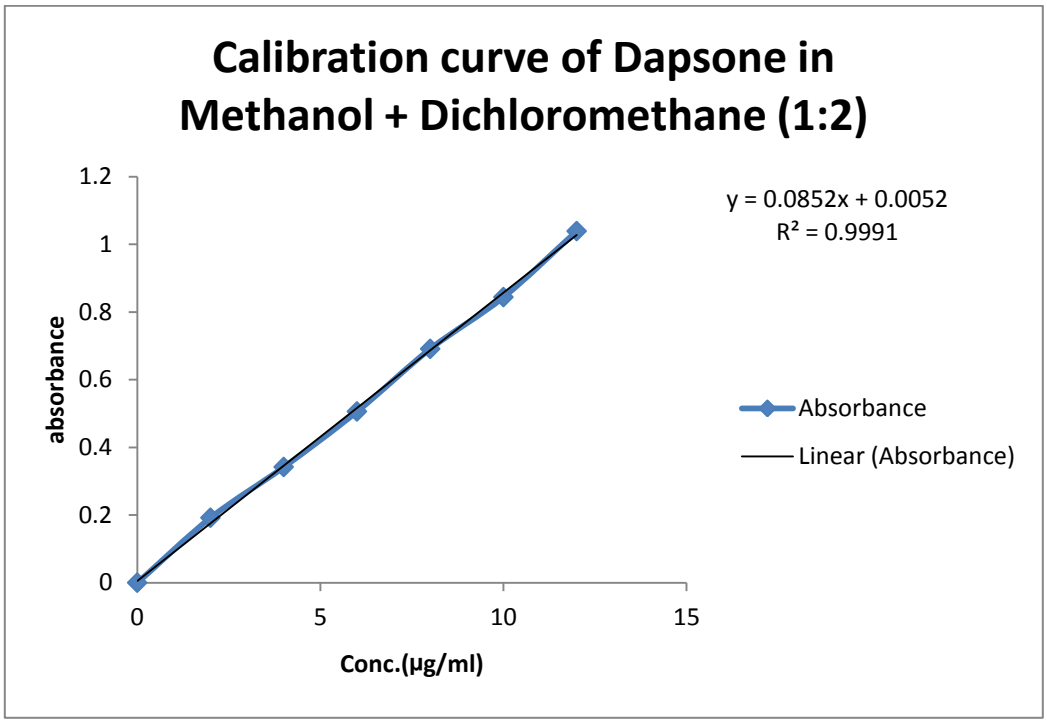

Figure 4.6 Calibration Curve of Dapsone in Methanol + Dichloromethane (1:2)

Regression analysis

Table 4.9 Regression Analysis of the calibration plot of Dapsone in Methanol + Dichloromethane (1:2)

Sr. No.	Regression Parameter	Values
1	Correlation Coefficient	0.9991
2	Slope	0.0852
3	Intercept	0.0052

4.2.5.3 Calibration curve for analysis of Dapsone in phosphate buffer saline (pH 7.4)

- **Preparation of stock solution:**

50 mg Dapsone was weighed into 50 ml volumetric flask and was dissolved in

Methanol and volume was made up to 50 ml.

- **Preparation of dilutions:**

First 1 ml of the stock solutions were pipetted out into a 100 ml volumetric flask and the volume was made up with Phosphate buffer saline pH 7.4 (composition shown in table 4.10).

Then, Suitable aliquots of the first dilution solutions were pipetted out into a 10 ml volumetric flask and the volume was made up with Phosphate buffer solution (pH7.4). The absorption maxima (λ_{max}) were determined by scanning 9 µg/ml solution against the reagent blank on UV-visible spectrophotometer and the absorbance maxima were found at 260 nm. The absorption of all the prepared solutions was then measured at the absorption maxima, 260 nm, against blank. The readings were recorded in triplicate. Mean values (n=3) along with the standard deviation was recorded and the calibration curve is developed.

Table 4.10 Preparation of Phosphate buffer saline (pH 7.4)

Sr. No.	Ingredients	Quantity
1	Potassium dihydrogen orthophosphate, 0.2 M	250 ml
2	Sodium hydroxide, 0.2 M	195.5 ml
3	Distilled water	q.s. to 1000 ml

Table 4.11 Calibration plot of Dapsone in Phosphate buffer saline (pH 7.4)

Sr. No.	Absorbance			Average	Standard Deviation
	(1)	(2)	(3)		
0	0.00	0.00	0.00	0.00	0.00
1	0.11	0.15	0.19	0.15	0.04
2	0.23	0.25	0.27	0.25	0.02
3	0.31	0.35	0.38	0.34	0.035118846

4	0.45	0.43	0.49	0.45	0.030550505
5	0.52	0.55	0.58	0.55	0.03
6	0.63	0.67	0.69	0.66	0.030550505
7	0.74	0.77	0.75	0.75	0.015275252
8	0.88	0.86	0.85	0.86	0.015275252
9	0.98	0.97	0.95	0.96	0.015275252

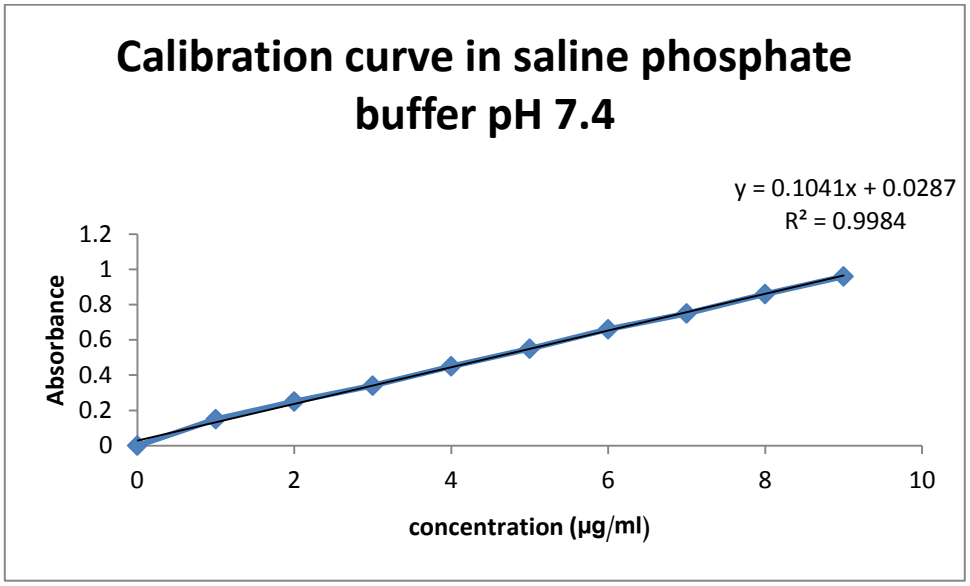

Figure 4.7 Calibration curve of Dapsone in Phosphate buffer saline (pH 7.4)

Regression analysis

Table 4.12 Regression Analysis of the calibration plot of Dapsone in Phosphate buffer saline (pH 7.4)

Sr. No.	Regression Parameter	Values
1	Correlation Coefficient	0.9984
2	Slope	0.1041

3	Intercept	0.0287

4.3 Methods of preparation of solid lipid nanoparticles:

4.3.1 Solvent Evaporation Method:[32]

Drug was weighed accurately and dissolved in fixed amount of dichloromethane. Lipophilic surfactant and lipid in different proportions were added in previous solution (organic phase). High HLB surfactant was added to aqueous phase and the volume was made upto 100 ml with water. Aqueous phase was stirred at 3000 rpm for 20 mins. Then organic phase solution was added to aqueous phase then stirred at 8000 rpm for 3 hrs.

4.3.2 Microemulsification Method:[35]

The lipid and surfactant were molten and mixed by using magnetic stirrer. After that drug was added to this mixture and suitably stirred at 80ºC to ensure that drug is dispersed, then 25 ml water was added at the same temperature. After that it was stirred for suitable hours to give coarse pre- emulsion. This coarse pre- emulsion was probe sonicated for 2 mins. This microemulsion was immediately dispersed in cold water (2 - 3ºC) while stirring.

4.3.3 Evaluation of optimized Solid lipid nanoparticles:

4.3.3.1 Particle size: [46]

The size of optimized batch of Dapsone loaded SLN was measured by Malvern Instruments, Malvern, UK. The sample was diluted 10 times with distilled water and it was analyzed for particle size. The readings were recorded in triplicate.

4.3.3.2 Zeta potential: [46]

The zeta potential can be measured by determination of movement velocity of the particles in electric field. The sample was diluted 10 times with distilled water and it was analyzed by Malvern Instruments for analyzing zeta potential.

4.3.3.3 Entrapment efficiency & Drug loading: [33]

2 ml of Dapsone loaded SLN was centrifuged at 13000 rpm for 30 mins for separation of lipid and aqueous phase. Supernatant was then analyzed for drug content by UV spectroscopy at 260 nm. It expresses amount of free drug entrapped in formulation. Entrapment efficiency and drug loading is calculated by following equation:

% Entrapment efficiency = $W_a - W_s / W_a \times 100$

Where, W_a = amount of drug added in formulation

W_s = amount of drug present in supernatant after centrifugation.

% Drug loading = $(W_t - W_s) / (W_t - W_s + W_L) \times 100$

Where, W_t = total weight of drug used

W_s = weight of drug in the supernatant after centrifugation

W_L= weight of lipid used in preparing SLNs

4.3.3.4 Surface morphology: [47]

Surface morphology of Dapsone loaded SLN was carried out using scanning electron microscopy (JSM- 5610LV; JEOL, Gujarat). The scanning electron microphotographs were taken using a double adhesive tape applied on the aluminium dies and Dapsone loaded SLN were uniformly spread on it.

4.3.3.5 In- vitro drug release study of SLN dispersion: [38]

The optimized batch dapsone loaded SLN dispersion (1 ml) was added to dialysis bag which was soaked previously in medium overnight. The dialysis bag was tied from both the sides and added into 500 ml of conical flask containing 375 ml of phosphate buffer (pH 7.4) as medium. The flask was kept at 37ºC in incubator shaker. At predetermined time intervals, 5 ml aliquots was taken and replaced with the same amount with fresh medium. The amount of dapsone released from the SLN was measured by UV spectrophotometer.

4.3.3.6 Stability study: [49]

To study stability of the formulations, the samples were filled into glass vials and stored in refrigerator (4ºC) or either in controlled room temperature for 15 days. At fixed time intervals, the samples were inspected visually for any cake formation and size measurements were carried out.

Formulations with no cake forming and size increase by less than 10% during 15 days were considered as stable formulations.

4.3.4 Formulation of SLN based hydrogel: [38]

Carbopol 940 is used as gelling agent because it is widely used in pharmaceutical formulations due to its fast dispersibility in water. Carbopol 940 (1g) was dispersed in distilled water (88 g) by stirring at 800 rpm for 60 mins. After that propylene glycol (10 g) was added and neutralization was done by dropwise addition of triethanolamine. Mixing was continued until a transparent gel appeared. The optimized batch of SLN was added into the gel such that the prepared gel will have 5 % (w/v) Dapsone under proper stirring.

4.3.5 Characterization and optimization of SLN based hydrogel of Dapsone

4.3.5.1 pH: [38]

The pH of SLN based gel was determined using digital pH meter. The measurements were taken in triplicates and average values were calculated.

4.3.5.2 Viscosity: [38]

Brookfield viscometer attached with T-bar spindle (no. 94) was used for determination of viscosity. Gel was filled in a beaker of suitable size and spindle was lowered perpendicularly taking care in such a way that spindle does not touch the bottom of beaker. The spindle was rotated at such a speed so as to generate the torque >30%. The viscosity of gel was calculated in triplicates and average values were calculated.

4.3.5.3 Drug content: [38]

A fixed quantity of SLN based gel was weighed accurately and dissolved in 50 ml of phosphate buffer pH 7.4 under bath sonication for 5 mins and drug content was determined using UV spectrophotometer at 260 nm.

4.3.5.4 Spreadability test: [38]

Spreadability was measured on the basis of "Slip" and "Drag" characteristics of gels. An excess gel of about 2 g was placed between two slides. One kg weight was placed on top of both slides for 5 min to expel out air and form a uniform film of gel between two slides and excess gel was scrapped of from edges. The top weight was then subjected to pull of 50 g weight. After applying weight, the time in secs required for separation of two slides was noted. Spreadability was calculated by following equation:

$$S = (M \times L)/T$$

Where, S= spreadability
M= weight tied to upper slide
L= length of glass slide
T= time taken to separate the slide completely from each other.

4.3.5.5 Texture analysis: [38]

Gel strength was determined using a Brookfield Texture Analyzer (USA) in compression mode. Different formulations were transferred into cylindrical holder (figure 4.8) and care was taken to avoid the introduction of air into the samples. A cylindrical analytical probe (38 mm diameter) was forced down into each sample at a defined rate (20 mm/min) and to a defined depth (10 mm). At least three replicate analyses of each sample were performed for each formulation. From the resulting load–time plots, the gel strength (the maximum force required to attain a given deformation i.e. peak load) and adhesive force (the work necessary to overcome the attractive forces between the surface of the sample and the surface of the probe) were derived.

Table 4.13 Various parameters for texture analyzer

Test type	Compression
Trigger point	5 g
Target value	10 mm
Test speed	20 mm/ min
Probe	38 mm

Figure 4.8 Brookfield Texture Analyzer

4.3.5.6 In-Vitro permeation study [38]

The study was carried out using a Franz Diffusion cell. Here, a cellophane membrane previously soaked in phosphate buffer Saline (pH 7.4) was used. The donor compartment was filled with 1 g of SLN based hydrogel. The acceptor compartment was filled with 20 ml of Phosphate Buffer pH 7.4 and the permeation was carried out for 8 hours. At 0.5, 1, 2, 3, 4, 5, 6, 7 & 8 hours, 1 ml aliquots from acceptor compartment were withdrawn and appropriately diluted if required. After each withdrawal, the volume of receptor compartment was compensated by 1 ml of fresh phosphate buffer saline pH 7.4. The temperature of assembly was kept constant at 37º ± 0.05ºC and the volume of receiver compartment was constantly stirred using magnetic stirrer at 200 rpm. The concentration of drug in the withdrawn samples was checked with the help of UV-Visible spectrophotometer.

4.3.5.7 Ex- vivo study: [38]

Franz diffusion cells with a diffusional area of 3.56 cm^2 will be used for permeation studies. The excised rat skin will be set in place with the stratum corneum facing the donor compartment and the dermis facing the receptor compartment. 1 g of the gel of Dapsone would be applied to the skin surface in the donor compartment and the receptor compartment of the cell will be filled with 10 ml of saline phosphate buffer (pH 7.4). During the experiment, the solution in receptor side will be maintained at 37 ± 0.5°C and stirred at 800 rpm. After application of the test formulation on the donor side, 0.5 ml aliquots will be collected from the receptor side at designated time intervals (5, 10, 15, 20, 30, 45, 60, 90, 120 mins). Thereafter, an equivalent volume of receptor fluid will be supplied to the receiver compartment immediately after each sample collection. At the end of 2 hr, the amount of drug remaining on the skin and the drug concentration in the skin will be determined by extraction into a suitable solvent followed by UV analysis.

4.4 Drug solubility studies:

4.4.1.1 Selection of lipid: [44]

Five mg of drug was transferred in a test tube maintained at temperature 5ºC above the melting point of lipid. The solid lipid was added in increments of 2 mg till it was completely

solubilize and a clear pale yellow solution was formed. The amount of molten lipid required to solubilise the drug was noted visually.

Result:

Table 4.14 Screening of lipids

Sr. No.	Lipid	Melting point (ºC)	Solubility (mg)
1	Glyceryl monosterate	58-59	< 2
2	Stearic acid	69.3	
3	Gelucire 39/01	39	
	Gelucire 43/01	43	
4	Compritol ATO 888	70	> 2

Discussion:

From the above results, it was concluded that the highest solubility was found to be with compritol ATO 888 and it was selected for further studies. Highest solubility lipid was selected so that the drug remains intact in the lipid core only.

4.4.1.2 Selection of surfactant: [44]

The excess quantity of drug was dissolved in 1% surfactant solution. Then mixture was stirred for 12 hours using magnetic stirrer. Then drug content in supernatant solution was analyzed spectrophotometrically at 260 nm.

Result:

Table 4.15 Screening of surfactants

Sr. No.	Surfactants	Solubility	HLB

		(mg/ml)	Value
1	Labrasol	695.54	12
2	Labrafil	2.06	9
3	Cremophor EL	207.81	12-14
4	Tween 20	49.63	16.7
5	Tween 80	760.84	15
6	Span 80	1.62	4.3
7	Span 20	3.51	8.6

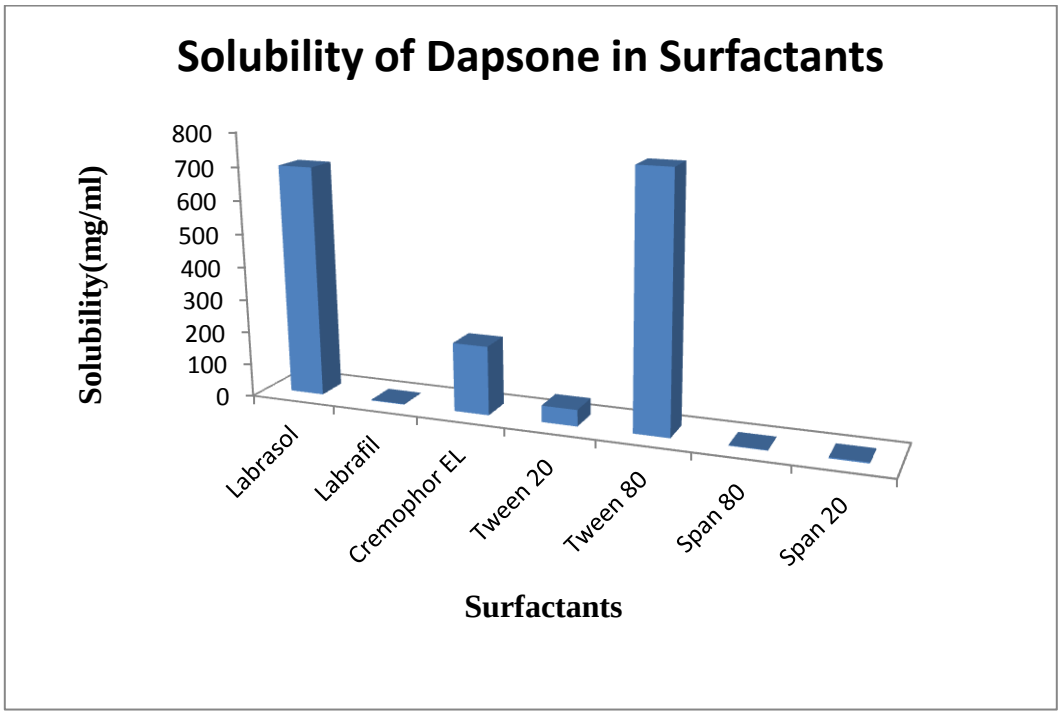

Figure 4.9 Solubility of Dapsone in various surfactants

Discussion:

From the above results, it was concluded that lowest solubility surfactant was selected for further studies. Span 80 having lowest solubility was selected because if the high solubility surfactant is selected the drug would leach out from the lipid core. In order to avoid these circumstances, the lowest solubility surfactant was selected.

4.5 Preliminary Trials:

4.5.1 Preliminary trials for the selection of suitable method for preparation of solid lipid nanoparticles:

Solid lipid nanoparticles were prepared by two methods for identifying better way for manufacturing solid lipid nanoparticles of better quality. The two methods were used are solvent evaporation and microemulsification technique. Six batches were prepared by both methods and evaluated. (Table 4.16 to 4.19)

4.5.1.1 Preparation of Solid lipid nanoparticles by solvent evaporation technique:

Table 4.16 Composition of batches by solvent evaporation method:

Ingredient/ Batches	SE1	SE2	SE3	SE4	SE5	SE6
Dapsone (%)	5	5	5	5	5	5
Compritol ATO 888 (%)	0.5	1	1.5	2	2.5	3
Span 80 (%)	1	2	3	1	2	3
Tween 20 (%)	1	1	1	1	1	1
Aqueous solvent	Water	Water	Water	Water	Water	Water
Organic	DCM	DCM	DCM	DCM	DCM	DCM

solvent						

Table 4.17 Results of SLN batches by Solvent evaporation method

Batches/ Parameters	**SE1**	**SE2**	**SE3**	**SE4**	**SE5**	**SE6**
Appearance	Milky white dispersion	Discoloration	Milky white dispersion	Discoloration	Discoloration	Milky white dispersion
Entrapment efficiency (%)	14.31	-	13.99	-	-	17.41
Drug loading (%)	20.19	-	18.72	-	-	27.57

Discussion:

From the above results, it can be concluded that Batches SE1, SE 3 and SE6 showed entrapment efficiency and drug loading. This may be due to either the drug has been leach out or has not gone in the lipid core. Batch SE2, SE4 and SE5 was not evaluated further due to discoloration of solution.

Table 4.18 Composition of batches by microemulsification method:

Ingredient/ Batches	**ME1**	**ME2**	**ME3**	**ME4**	**ME5**	**ME6**
Dapsone (%)	5	5	5	5	5	5
Compritol ATO 888	50	100	150	50	100	150

(mg)						
Span 80 (%)	1	2	3	1	2	3
Water	25	25	25	25	25	25

Table 4.19 Results of SLN batches by microemulsification method

Batches/ Parameters	**ME1**	**ME2**	**ME3**	**ME4**	**ME5**	**ME6**
Entrapment efficiency (%)	71.55	65.31	68.86	60.35	50.56	55.76
Drug loading (%)	50.1	49.72	49.1	48.69	41.02	39.75

Discussion:

The microemulsion method gave higher % entrapment efficiency when compared with solvent evaporation. Hence, it was selected as method of preparation for solid lipid nanoparticles.

4.5.2 Optimization of various process parameters:

4.5.2.1 Drug to lipid ratio:

Four different ratios were prepared as Table 4.20 keeping Span 80 (1% v/v), time of stirring (2 hrs), speed of stirring (1200 rpm) constant.

Table 4.20 Optimization of Drug: lipid ratio:

Batch No.	**Drug: lipid ratio**
SLN 1	1:1
SLN 2	2:1
SLN 3	3:1
SLN 4	4:1

Table 4.21 Results: Batches SLN 1 to SLN 4

Batch No.	Drug: lipid ratio	% Entrapment efficiency	% Drug loading
SLN 1	1:1	72.63	50.02
SLN 2	2:1	68.52	45.23
SLN 3	3:1	61.43	42.71
SLN 4	4:1	60.14	38.67

Discussion:

From the above results, it can be concluded that Batch SLN 1 was selected as the optimized drug: lipid ratio. Because as the drug: lipid ratio increases, there is decrease in the % drug loading and % entrapment efficiency. This may be due to the larger lipid matrix with increasing lipid concentration.

4.5.2.2 Concentration of surfactant:

Four different ratios were prepared as Table 4.23 keeping drug: lipid ratio (1:1), time of stirring (2 hrs), speed of stirring (1200 rpm) constant.

Table 4.22 Optimization of Concentration of Surfactant:

Batch No.	Concentration of Surfactant (%)
SLN 5	1
SLN 6	2
SLN 7	3
SLN 8	5

Table 4.23 Results: Batches SLN 5 to SLN 8

Batch No.	Concentration of surfactant (%)	% Entrapment efficiency	% Drug loading
SLN 5	1	72.57	49.25
SLN 6	2	70.47	45.72
SLN 7	3	67.41	37.06
SLN 8	5	65.12	35.75

Discussion:

From the above experiment, it can be concluded that Batch 5 was selected as the optimized concentration of surfactant, because as the concentration of surfactant increases, there is decrease in the entrapment efficiency and drug loading. This may be due to the viscosity provided by Span 80 which retards solvent diffusion and even drug leaching is avoided by decreasing concentration of surfactant.

4.5.2.3 Time of stirring:

Four different ratios were prepared as Table 4.24 keeping drug: lipid ratio (1:1), concentration of surfactant (1% v/v) and speed of stirring (1200 rpm) constant.

Table 4.24 Optimization of time of stirring:

Batch No.	Time of stirring (hrs)
SLN 9	2
SLN 10	2.5
SLN 11	3
SLN 12	3.5

Table 4.25 Results: Batches SLN 9 to SLN 12

Batch No.	Time of stirring (hrs)	% Entrapment efficiency	% Drug loading
SLN 9	2	72.35	49.17
SLN 10	2.5	69.89	41.89
SLN 11	3	65.17	36.72
SLN 12	3.5	62.52	35.19

Discussion:

From the above results, it can be concluded 2 hrs was selected as the optimum time of stirring, As the time of stirring increases there is not much difference in the entrapment efficiency and drug loading. For time convenience, less stirring time is selected.

4.5.2.4 Speed of Stirring:

Four different ratios were prepared as Table 4.26 keeping drug: lipid ratio (1:1), concentration of surfactant (1% v/v) and time of stirring (2 hrs) constant.

Table 4.26 Optimization of speed of stirring:

Batch No.	Speed of stirring (rpm)
SLN 13	600
SLN 14	900
SLN 15	1200
SLN 16	1500

Table 4.27 Results: Batches SLN 13 to SLN 16

Batch No.	Speed of stirring (rpm)	% Entrapment efficiency	% Drug loading
SLN 13	600	61.17	45.12
SLN 14	900	69.80	47.89

SLN 15	1200	71.05	48.02
SLN 16	1500	72.65	49.67

Discussion:

From the above results, it was concluded that 1500 rpm was selected as the optimized speed of stirring. Because as the stirring speed increases, there is increase in the entrapment efficiency and drug loading as the particle sizes tend to become smaller which results in better entrapment efficiency and drug loading.

4.5.2.1 Conclusion driven from the optimization of various parameters:

- Drug : lipid ratio = 1:1
- Concentration of surfactant: 1 %
- Time of stirring: 2 hrs
- Speed of stirring: 1500

So, from the above results, the optimized batch was found to be

Table 4.28 Optimized batch from optimizing various process parameters

Ingredients	Quantity
Compritol ATO 888	50 mg
Dapsone	50 mg
Span 80	1 ml
Time	2 hr
Speed	1500

Table 4.29 Results: Evaluation of Optimized batch

Parameters	Result
% Entrapment efficiency	75.81%
% Drug loading	49.6%

Particle size	78.16 nm
Zeta potential	-28.2 mV
% drug release at 8 hr	77.42%

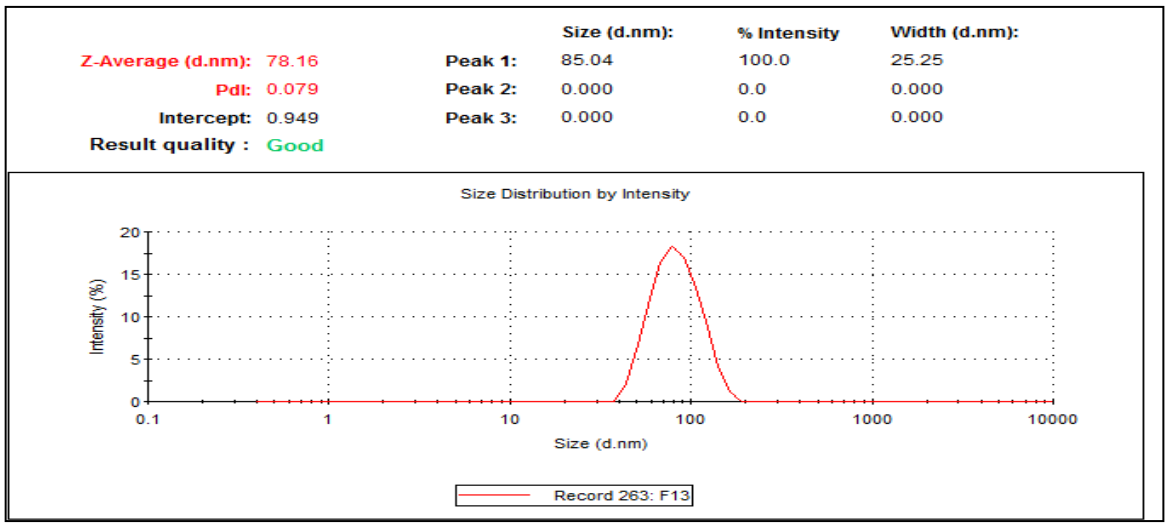

Figure 4.10 Average particle size of optimized batch

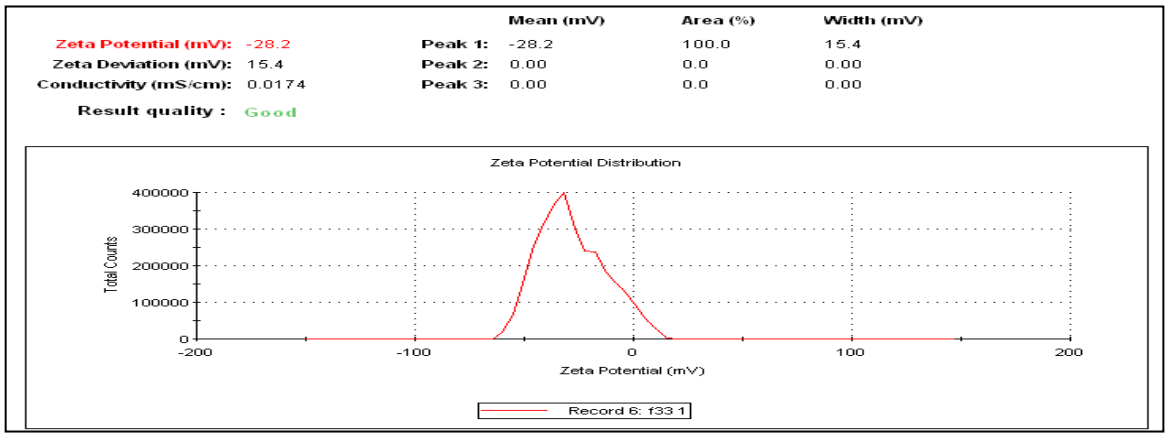

Figure 4.11 Zeta potential of optimized batch

Table 4.30 In vitro drug release of optimized batch:

Time (hrs)	% drug release
0	0
0.5	17.83

1	32.64
2	39.21
3	46.79
4	54.2
5	63.63
6	71.71
7	75.92
8	77.43

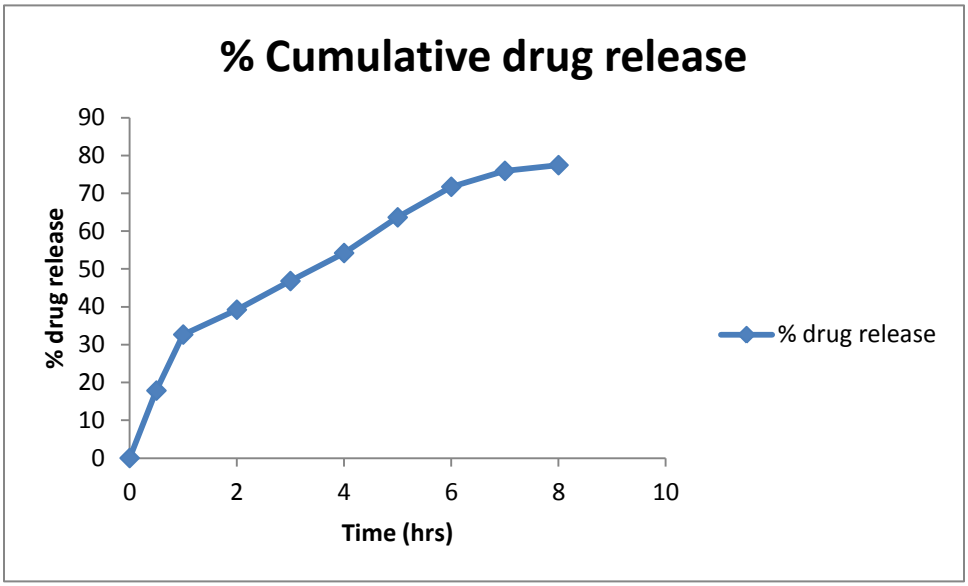

Figure 4.12 % drug release of the optimized batch

4.6 Formulation Optimization of Solid Lipid Nanoparticles by Full Factorial Design

4.6.1. Optimization of Dapsone loaded Solid Lipid Nanoparticles using 3^2 full factorial design:

For the optimization of the preparation of formulations, the concentration of surfactant (X1) and speed of stirring (X2) are chosen as independent variables. These two factors may affect the nanoparticle formulation and three levels of each factor were selected.

Table 4.31 Coded values of 3^2 Full Factorial Design

Independent variable	Coded value	Actual value
Concentration of surfactant (X1)	-1	1
	0	2
	+1	3
Speed of stirring (X2)	-1	900
	0	1200
	+1	1500

Dependent variables	
Y1	% Entrapment efficiency
Y2	% Drug loading
Y3	% Drug release at 8 hours

Table 4.32 Composition of design batches

Batch no.	X1 Concentration of surfactant (%)	X2 Speed of stirring (rpm)	Y1 % Entrapment efficiency	Y2 % Drug loading	Y3 % Drug release at 8 hours
FF1	1	-1	57	48.9	73.1
FF2	-1	0	50.85	32.6	68.2
FF3	+1	+1	64.93	50.44	75.4
FF4	-1	-1	49.5	35.1	65.1
FF5	0	+1	59.4	36.4	72.1

FF6	0	0	55.2	40.7	71.5
FF7	+1	0	60.1	45.3	74.6
FF8	-1	+1	57	31.5	70.4
FF9	0	-1	52.38	38.2	69

4.6.2 Responses of Factorial Design

1. % Entrapment efficiency:

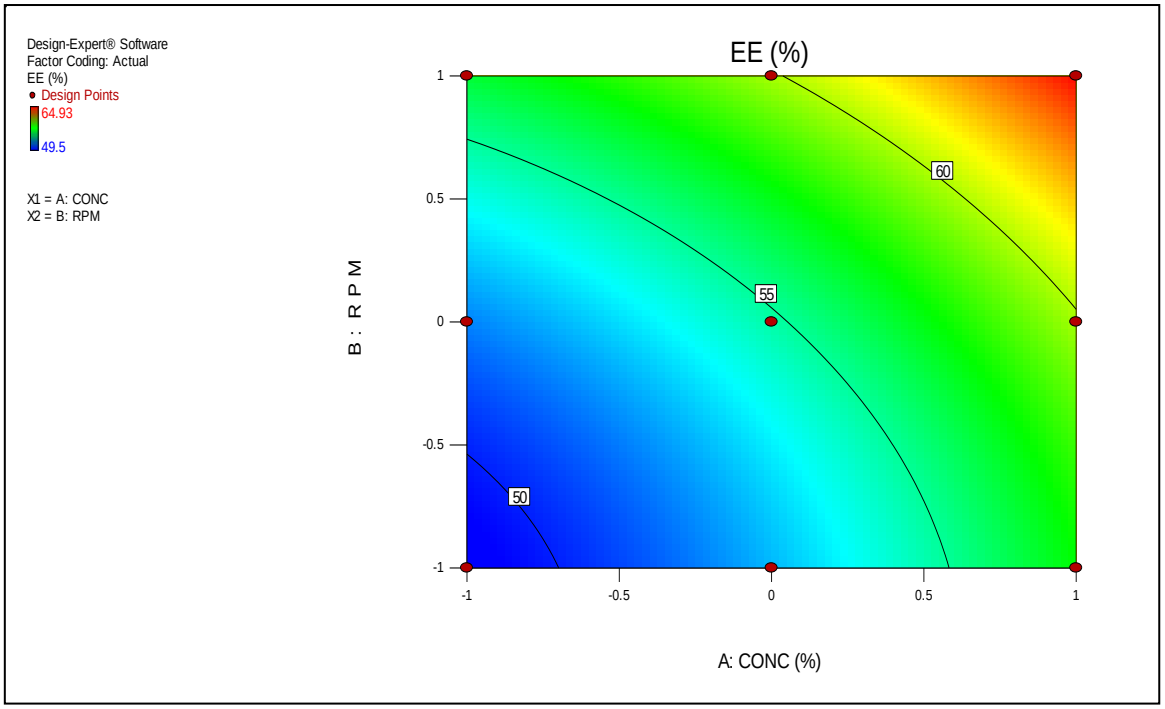

Figure 4.13 Contour plot of % Entrapment efficiency

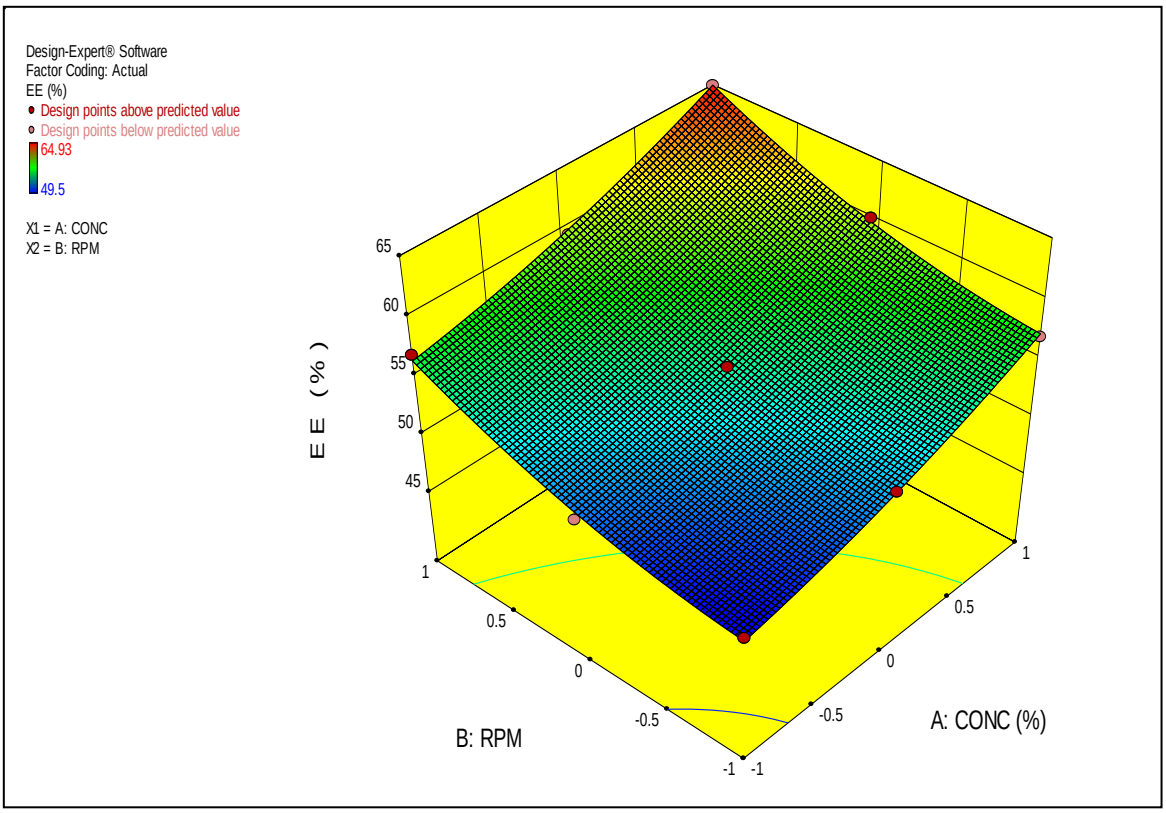

Figure 4.14 Response surface plot of % Entrapment efficiency

Table 4.33 ANOVA table for % Entrapment efficiency using quadratic model

Source	Coefficient Estimate	Sum of Squares	Df	Mean Square	F Value	p-value Prob> F	
Model	Intercept-54.78	190.67	5	38.13	85.30	0.0020	Significant
A-CONC	4.11	101.52	1	101.52	227.07	0.0006	
B- RPM	3.74	84.00	1	84.00	187.89	0.0008	
AB	0.11	0.046	1	0.046	0.10	0.7689	
A^2	0.90	1.63	1	1.63	3.65	0.1520	

B^2	1.32	3.48	1	3.48	7.78	0.0685	
Residual		1.34	3	0.45			
Cor Total		192.01	8				

Table 4.34 Regression analysis for % Entrapment efficiency

Parameter	Result
Std. dev.	0.67
Mean	56.26
R square	0.9930

Full Model equation

Y_{EE}= +54.78 + 4.11*A + 3.74*B +0.11*AB +0.90*A^2 + 1.32*B^2

Reduced Model equation on the basis p value < 0.05

Y_{EE}= +54.78 + 4.11*A + 3.74*B

From the polynomial equation generated, response surface plot and contour plots which are used to study the effect of variable on % Entrapment efficiency, we can conclude that as the concentration of surfactant increases and stirring speed increases, there is increase in the % Entrapment efficiency. Both the factors had similar positive effect. As the polynomial terms (AB, A^2 and B^2) having p value lesser than 0.05, reduced model of the equation was generated. From the above reduced model equation it can be concluded that both concentration of surfactant and stirring speed has same effect.

2.% Drug loading:

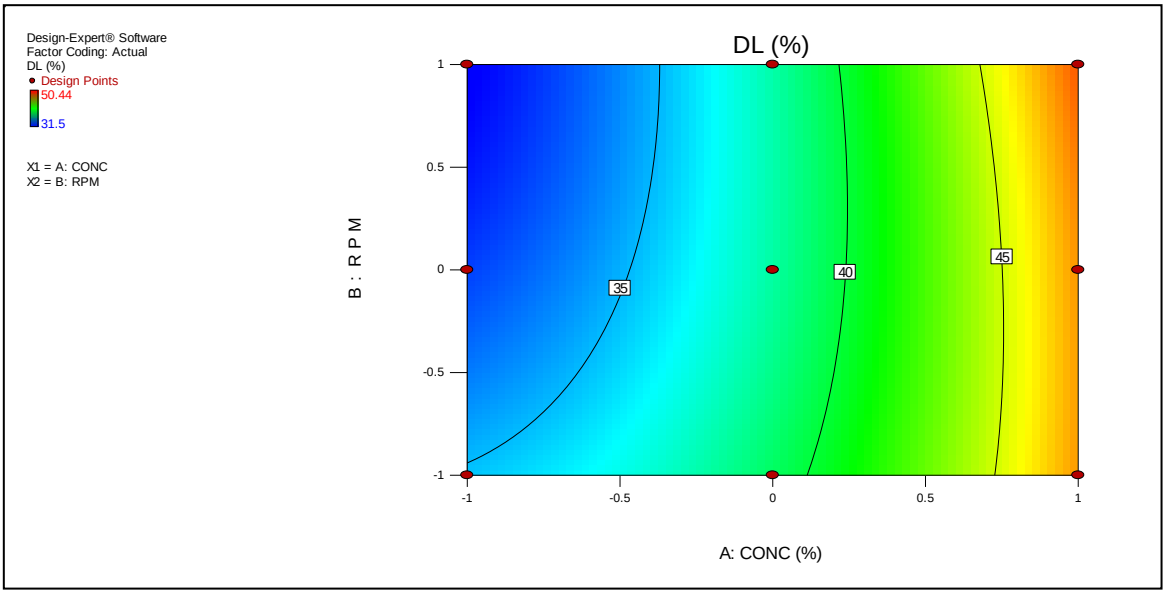

Figure 4.15 Response surface plot for % Drug loading

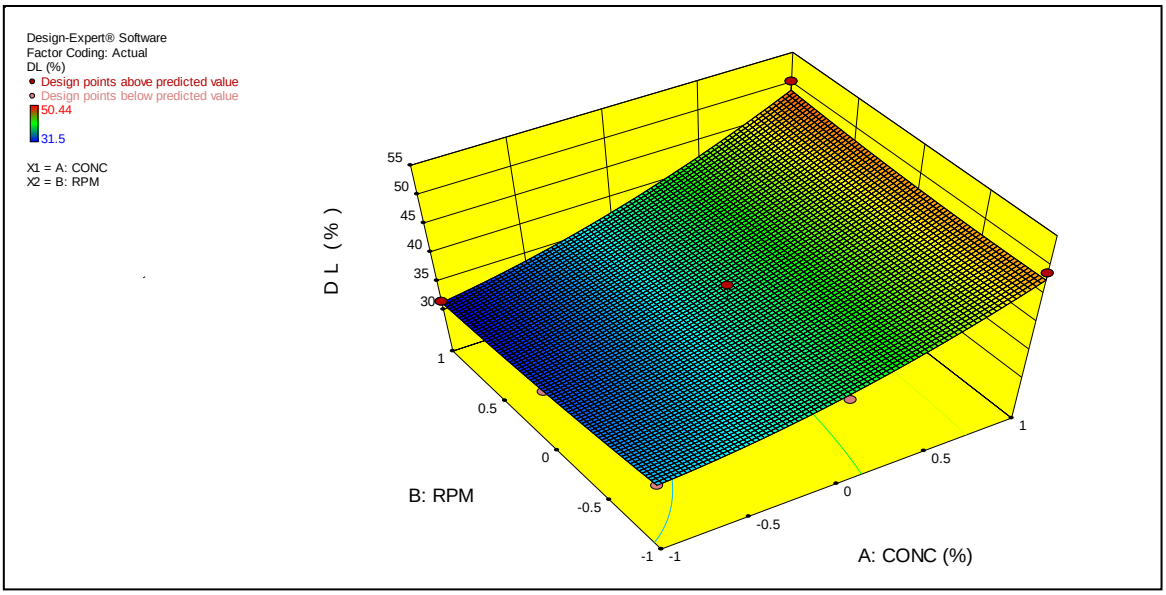

Figure 4.16 Contour plot for % Drug loading

Table 4.35 ANOVA table for % Drug loading using quadratic model

Source	Coefficient Estimate	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	
Model	Intercept-38.06	363.58	5	72.72	10.72	0.0395	Significant
A-CONC	7.57	344.13	1	344.13	50.75	0.0057	
B- RPM	-0.64	2.48	1	2.48	0.37	0.5878	
AB	1.28	6.60	1	6.60	0.97	0.3964	
A^2	2.21	9.74	1	9.74	1.44	0.3168	
B^2	0.56	0.62	1	0.62	0.091	0.7822	
Residual		20.34	3	6.78			
Cor Total		383.92	8				

Table 4.36 Regression analysis for % Drug loading

Parameter	Result
Std. dev.	2.60
Mean	39.90
R square	0.9470

Full Model equation

Y_{DL}= +38.06 + 7.57*A -0.64*B + 1.29*AB + 2.21*A^2 + 0.56*B^2

Reduced Model equation on the basis p value <0.05

Y_{DL}= +38.06 + 7.57*A-0.64*B

From the polynomial equation generated, response surface plot and contour plots which are used to study the effect of variable on % Drug loading, we can conclude that as the concentration of surfactant increases, there is increase in the drug loading. Here the stirring

speed has not much effect. As the polynomial terms (B, AB, A^2 & B^2) having p value lesser than 0.05, reduced model of the equation was generated. From the above reduced model equation it can be concluded that the increase in concentration of surfactant increases % drug loading.

3. % DRUG RELEASEAT 8 HOUR:

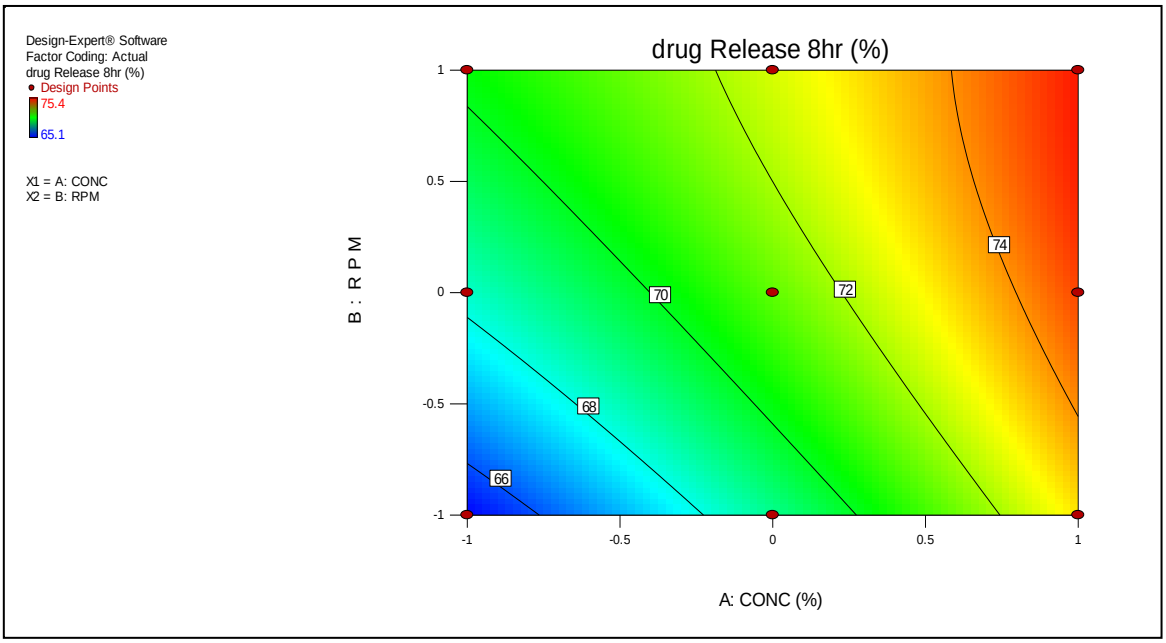

Figure 4.17 Response Surface Plot for % Drug Release at 8 hour

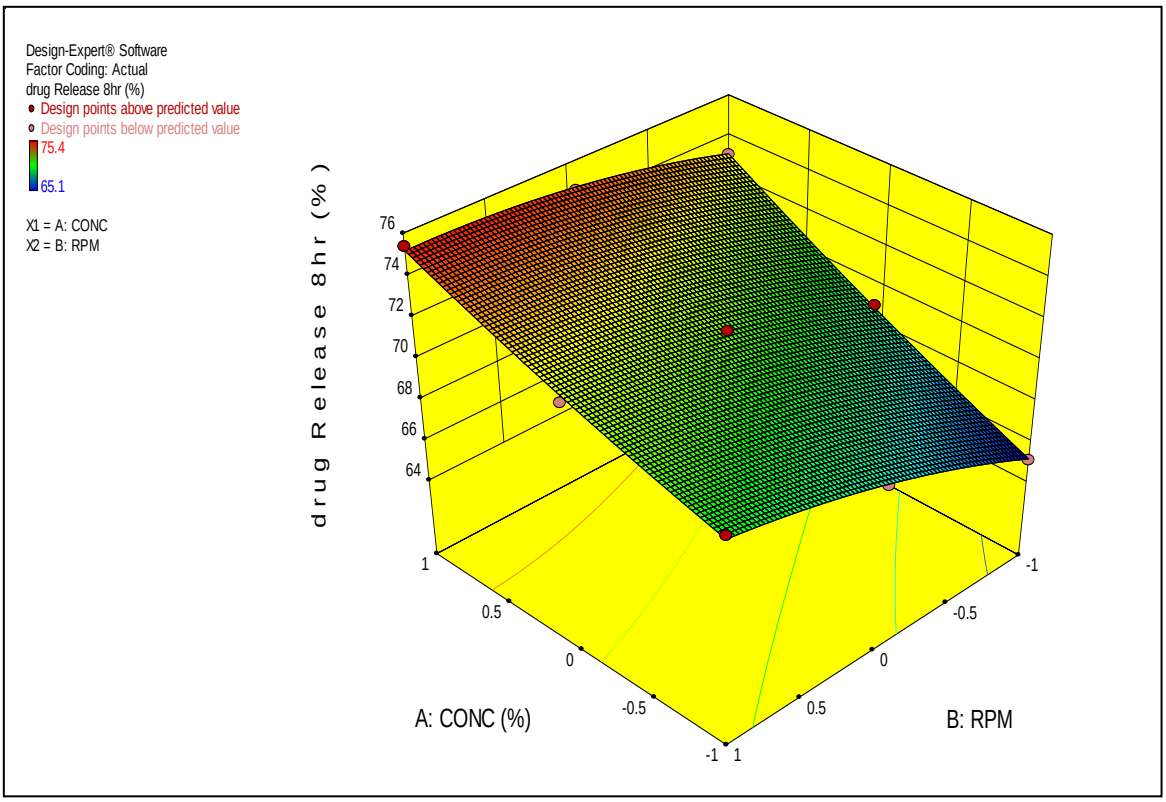

Figure 4.18 Contour Plot for % Drug Release at 8 hour

Table 4.37 ANOVA table for % Drug release at 8 hr using quadratic model

Source	Coefficient Estimate	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	
Model	Intercept-71.26	84.88	5	16.98	169.14	0.0007	Significant
A-CONC	3.23	62.73	1	62.73	624.95	0.0001	
B- RPM	1.78	19.08	1	19.08	190.11	0.0008	
AB	-0.75	2.25	1	2.25	22.42	0.0179	
A^2	0.27	0.14	1	0.14	1.42	0.3195	
B^2	-0.58	0.68	1	0.68	6.78	0.0801	
Residual		0.30	3	0.10			
Cor Total		85.18	8				

Table 4.38 Regression analysis for % Drug release at 8 hr

Parameter	Result
Std. dev.	0.32
Mean	71.04
R square	0.9965

Full Model equation

Y_{DR}= +71.26 + 3.23*A + 1.78*B – 0.75*AB + 0.27*A^2 – 0.58*B^2

Reduced Model equation on the basis p value <0.05

Y_{DR}= +71.26 + 3.23*A + 1.78*B

From the polynomial equation generated, response surface plot and contour plots which are used to study the effect of variable on % Drug release at 8 hr, we can conclude that as the concentration of surfactant increases there is increase in the drug release whereas the stirring speed has less effect as compared to concentration of surfactant which also results in increase in % drug release. As the polynomial terms, (AB, A^2 and B^2) having p value lesser than 0.05, reduced model of the equation was generated. From the above reduced model equation it can be concluded that the concentration of surfactant and stirring speed both has significant effect on drug release.

Table 4.39 In- vitro drug release of 9 batches:

BATCHES/ TIME (HRS)	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.5	13.5	12.3	14.8	15.1	14.8	16.5	16.5	16.0	17.2
1	22.5	21.2	23.4	26.8	25.1	28.4	28.4	31.8	33.7

2	30.6	32.3	33.3	34.2	35.0	36.0	37.0	40.1	42.1
3	38.2	40.1	41.2	42.1	53.7	44.6	49.7	50.2	50.7
4	46.5	49.3	50.5	52.2	62.1	54.5	55.2	58.9	61.1
5	53.5	54.0	61.1	60.3	66.8	63.0	62.1	68.2	67.3
6	62.5	65.1	67.0	66.8	68.9	69.0	70.4	70.4	72.1
7	64.0	67.3	69.9	68.7	70.4	71.0	72.1	73.2	74.7
8	65.1	68.2	70.4	69.0	71.5	72.1	73.1	74.6	75.4

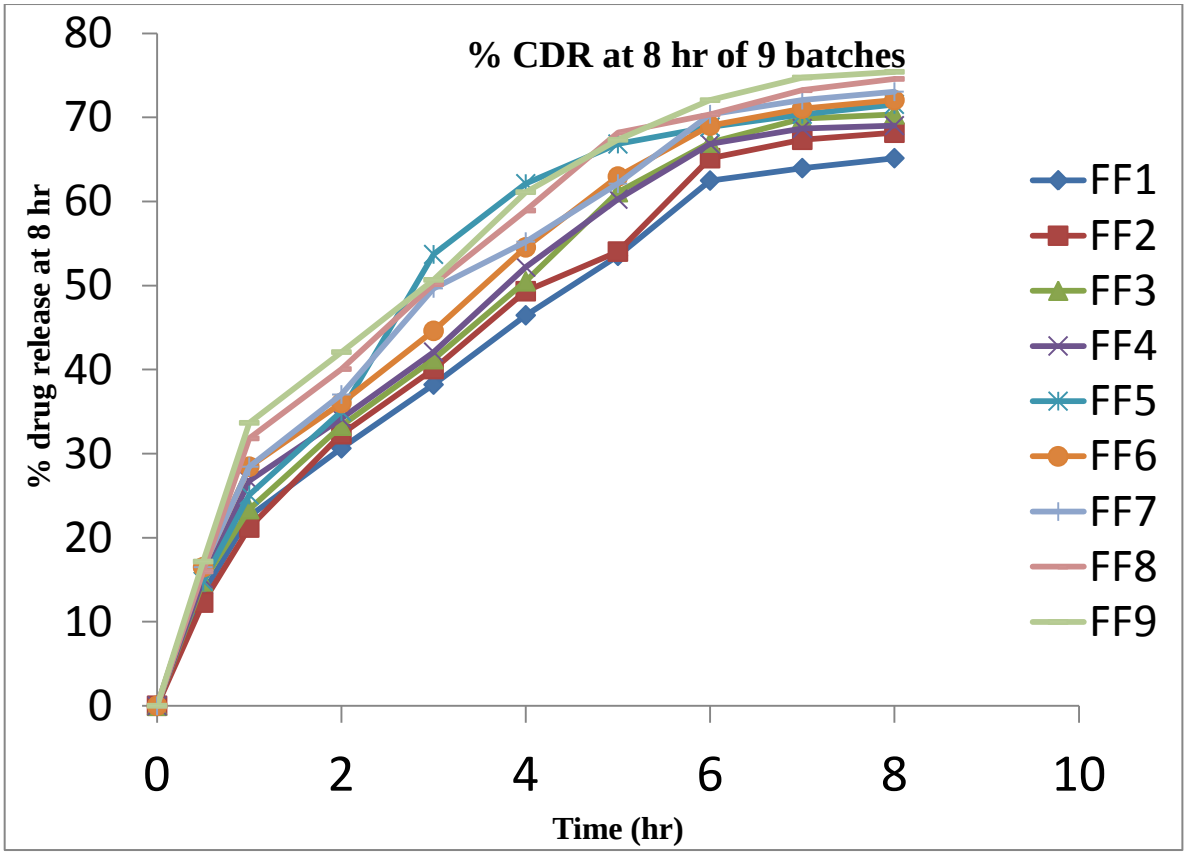

Figure 4.19 Plot of % CDR at 8 hr of 9 batches

Result & Discussion:

From the above plot of % CDR at 8 hours of batches FF1- FF9, it was observed that there is increase in drug release with increase in concentration of surfactant and stirring speed.

Overlay plot of design region:

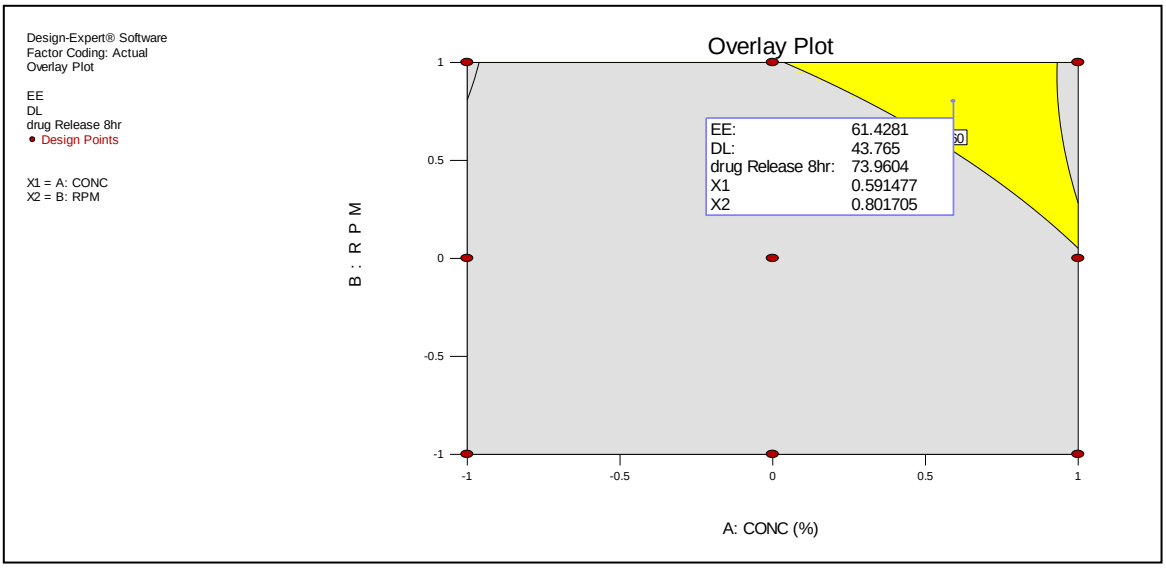

Figure 4.20 Overlay plot of design region

4.6.2.1 Formulation of Check point Batch

Table 4.40 Composition of check point batch

Parameters	Coded value	Actual value
X1- Concentration of surfactant (%)	0.59	2.59
X2- Speed of stirring (rpm)	0.80	1440

Table 4.41 Result of check point batch

Parameters	Predicted value	Observed value
% Entrapment efficiency	61.42	62.59
% Drug loading	43.76	45.76
% Drug release at 8 hr	73.96	74.21

Results & Discussion:

The results observed with the check point batch were found to be similar with the predicted values derived from the linear equation. Hence, the design & statistical model which we have implemented is mathematically valid and one can reach to an optimized point in short period of time with minimum efforts by adopting systematic formulation approach.

4.6.2.2 Selection of Best Batch:

The selection of best batch for solid lipid nanoparticles was based on the high % entrapment efficiency and % drug loading and maximum drug release profile.

Batch FF9 was found to have 64.93% entrapment efficiency, 50.44% drug loading and 75.4 % drug was released at 8 hrs. Hence, Batch FF3 was selected as optimized batch.

Table 4.42 Optimized Formula Obtained from Design

Ingredients	Quantity
Dapsone	50 mg
Compritol	50 mg
Span 80	3 ml
Time	2 hrs
Speed	1500 rpm
Water	q.s. to 100 ml

Scanning electron microscopy (SEM) analysis:

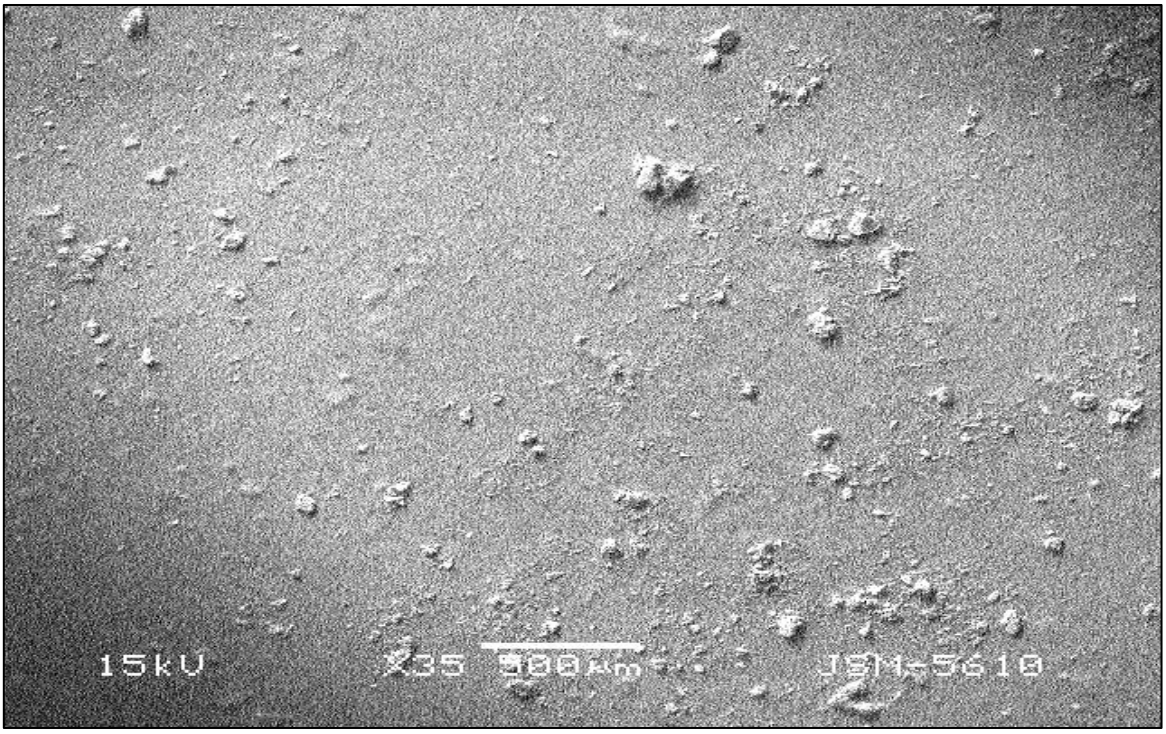

Figure 4.21 SEM image of Optimized solid lipid nanoparticles dispersions [46]

Result and Discussion:

The SEM image of optimized formulation shows that particles are roughly spherical and somewhat uniformity is observed.

4.6.2.3 Stability study:

Table 4.43 Results: Evaluation parameters showing stability study of SLN of optimized batch

Sr. No.	Evaluation parameter	Before	After
1	Appearance	Milky white dispersion	Milky white dispersion
2	% Entrapment Efficiency	71.60	72.45
3	% Drug loading	49.72	49.23

4	Particle size (nm)	90.44	91.26
5	Zeta potential (mV)	-25.5	-25.6

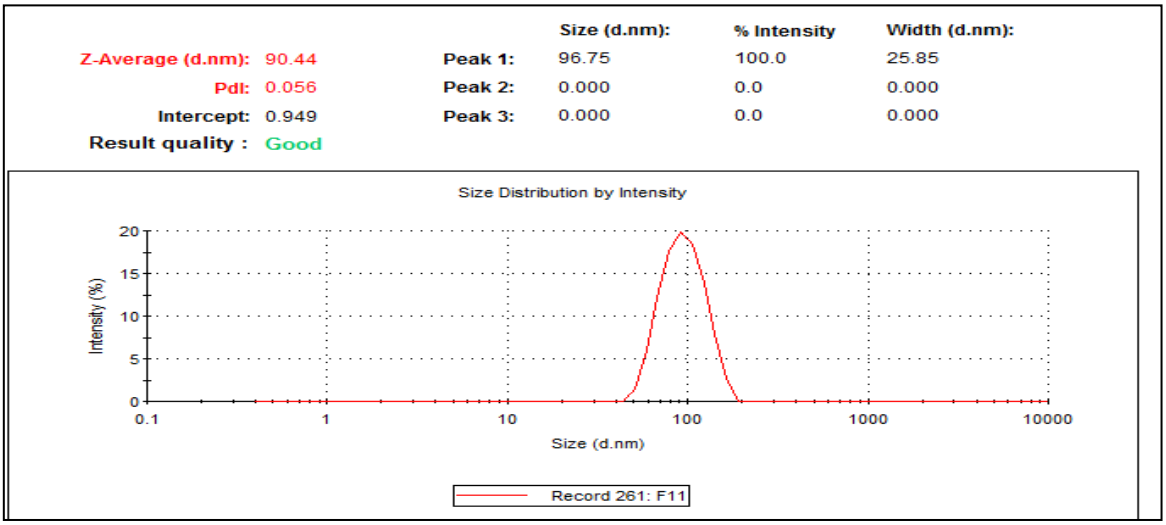

Figure 4.22 Average particle size before 15 days

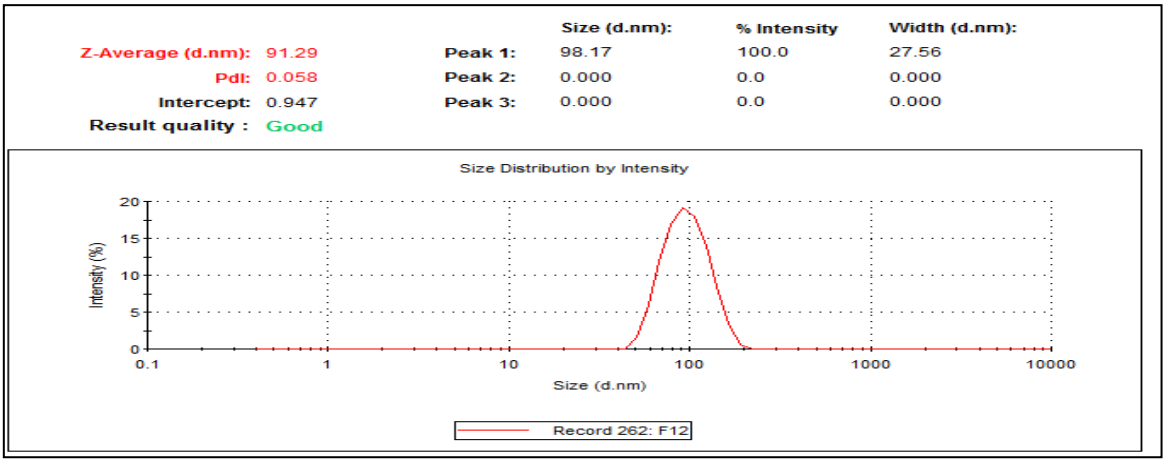

Figure 4.23 Average particle size after 15 days

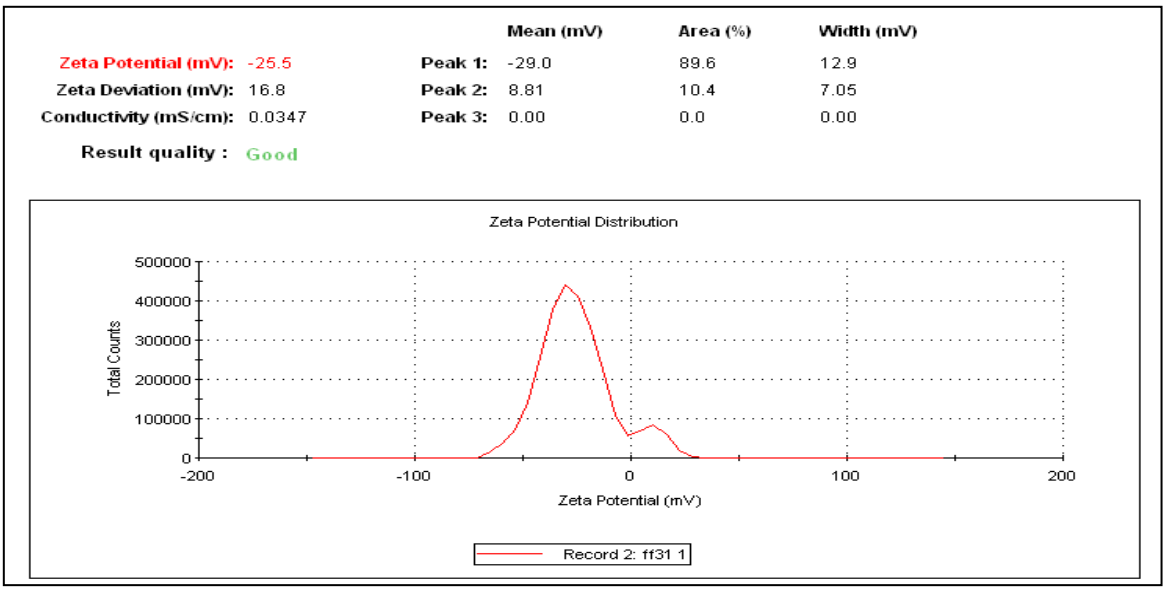

Figure 4.24 Zeta potential before 15 days

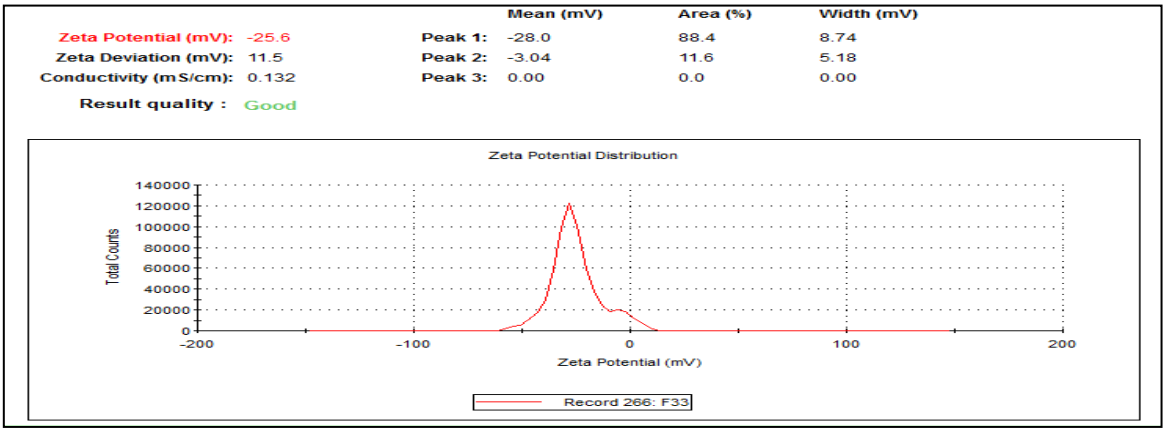

Figure 4.25 Zeta potential after 15 days

Result and Discussion:

There is no significant change in properties like appearance, % entrapment efficiency, % drug loading, particle size and zeta potential at 4ºC for 15 days. Hence, it was concluded that Dapsone loaded solid lipid nanoparticles was stable.

4.7 Development and Characterization of Solid Lipid Nanoparticles Based Gel

4.7.1 Formulation of solid lipid nanoparticles based gel

Table 4.44 Composition of SLN based gel

Sr. No.	Components	G 1 0.5 %	G 2 1%	G 3 1.5%	G 4 2%
1	Drug (%w/v)	5	5	5	5
2	Compritol (mg)	50	50	50	50
3	Span 80 (ml)	3	3	3	3
4	Carbopol 940 (%w/v)	0.5	1	1.5	2
5	Triethanolamine	1	1	1	1
6	Water	q.s. 100 ml	q.s. 100 ml	q.s. 100 ml	q.s. 100 ml

4.7.1.1 Characterization and optimization of SLN based gel of Dapsone

4.7.1.1.1 Physico-chemical characterization of SLN based gel of Dapsone

Table 4.45 Results: Evaluation parameters of SLN based gel of Dapsone

Parameters*/ SLN based gel	G 1 0.5 %	G 2 1 %	G 3 1.5 %	G 4 2 %	Marketed**
pH	7.4	7	7.2	7.1	7
Viscosity	20121 ±	23287 ±	25176 ±	28672 ±	23198 ±

(cPs)	116.49	175.61	217.88	352.17	456.69
Peak load(g)	381.26	688.20	1172.06	1346.78	680.56
Drug content (%)	96.54 ± 0.62	96.58 ± 1.71	96.01 ± 0.55	96.72 ± 0.24	NA
Spreadability (g cm/sec)	25.6 ± 0.9	27.9 ± 0.9	28.2 ± 0.5	28.9 ± 0.2	27.4 ± 0.6

*(n=3, mean ± SD), **(marketed: Benzoyl peroxide 5%, Pernox)

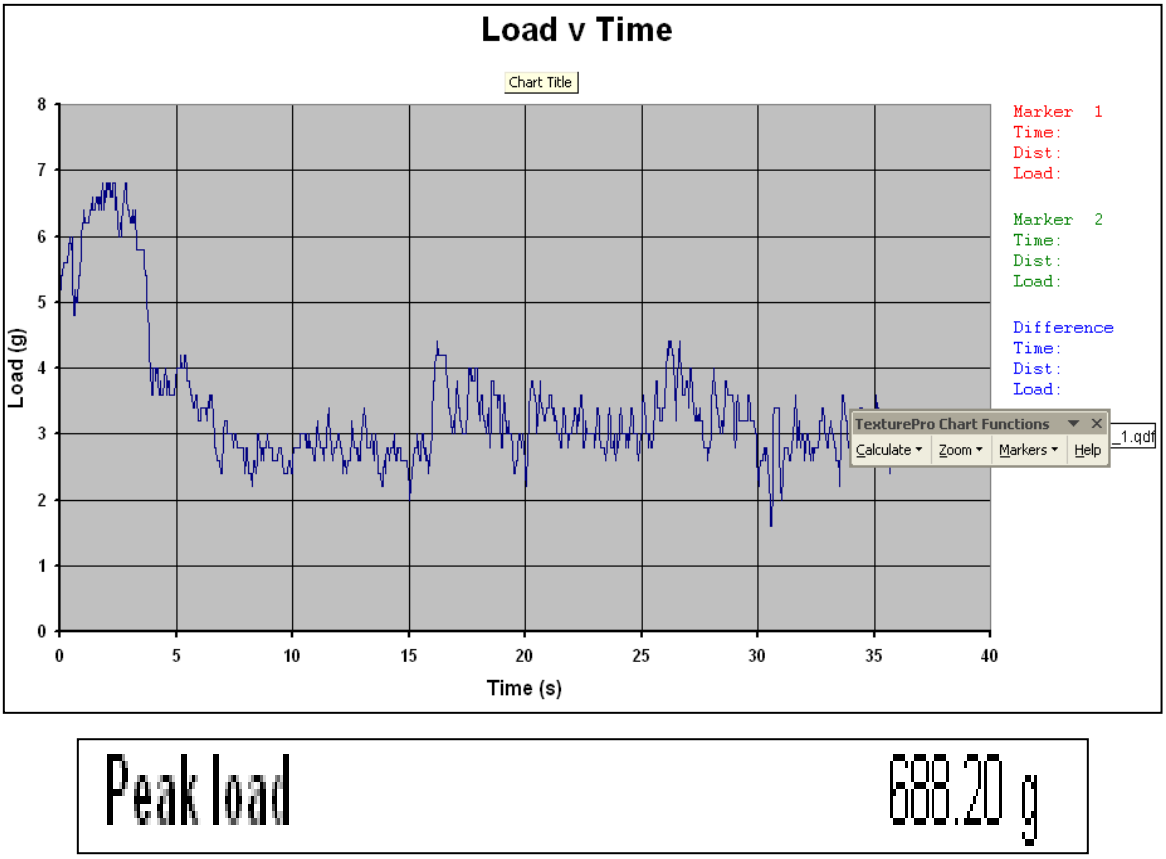

Figure 4.26 Plot of load Vs time

Result and Discussion:

From the above observations, the peak load, pH, viscosity, spreadability of the 1% Carbopol 940 containing SLN based gel was found similar to the marketed formulation. Hence, 1% Carbopol containing SLN based gel was used for further studies.

4.7.1.2 In-Vitro permeation study

Table 4.46 In-vitro permeation study of Marketed gel and SLN based gel

Time (hrs)	Marketed gel	SLN based gel
0	0	0
0.5	10.3	22.04
1	21.9	34.50
2	33.3	43.43
3	40.1	51.17
4	45.4	57.91
5	50.2	65.32
6	53.9	75.92
7	60.3	82.66
8	64.0	85.02

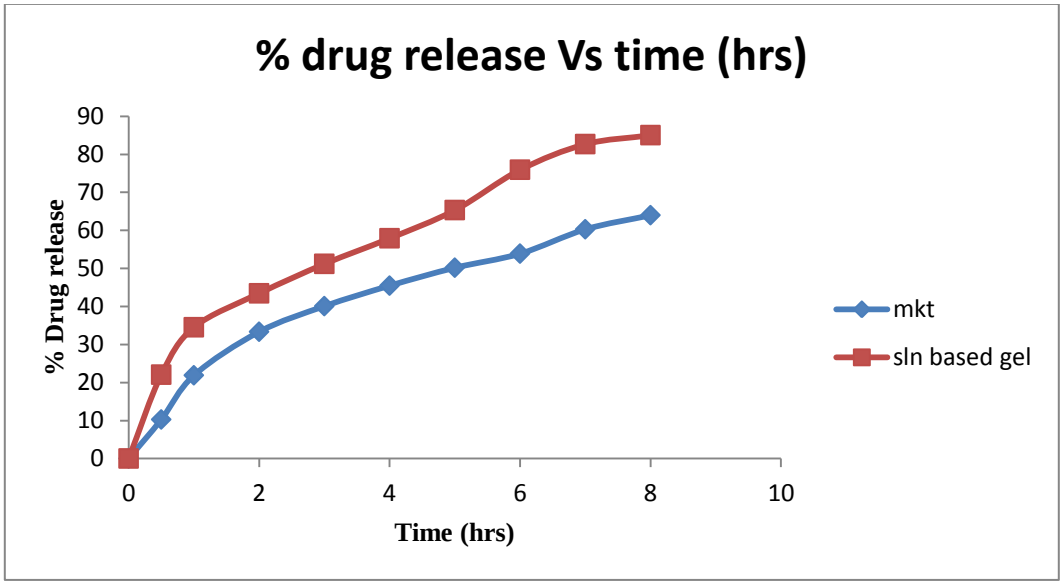

Figure 4.27 In-vitro permeation study of SLN based gel and marketed gel

Result and Discussion:

From the above results, it can be concluded that there is significant increase in drug release at 8 hours of SLN based gel as compared to marketed formulation. So, it can be said that SLN based gel containing 1% Carbopol offers better release than marketed gel and was used for further studies.

4.7.1.3 Ex- vivo studies:

Table 4.47 Ex- vivo permeability study of SLN based gel and marketed gel

Time (mins)	Marketed gel	SLN based gel
0	0	0
5	20.18	21.87
15	21.7	33.65
30	34.66	43.76
45	43.59	50.16
60	57.4	57.4
90	58.24	60.76
120	58.41	70.02

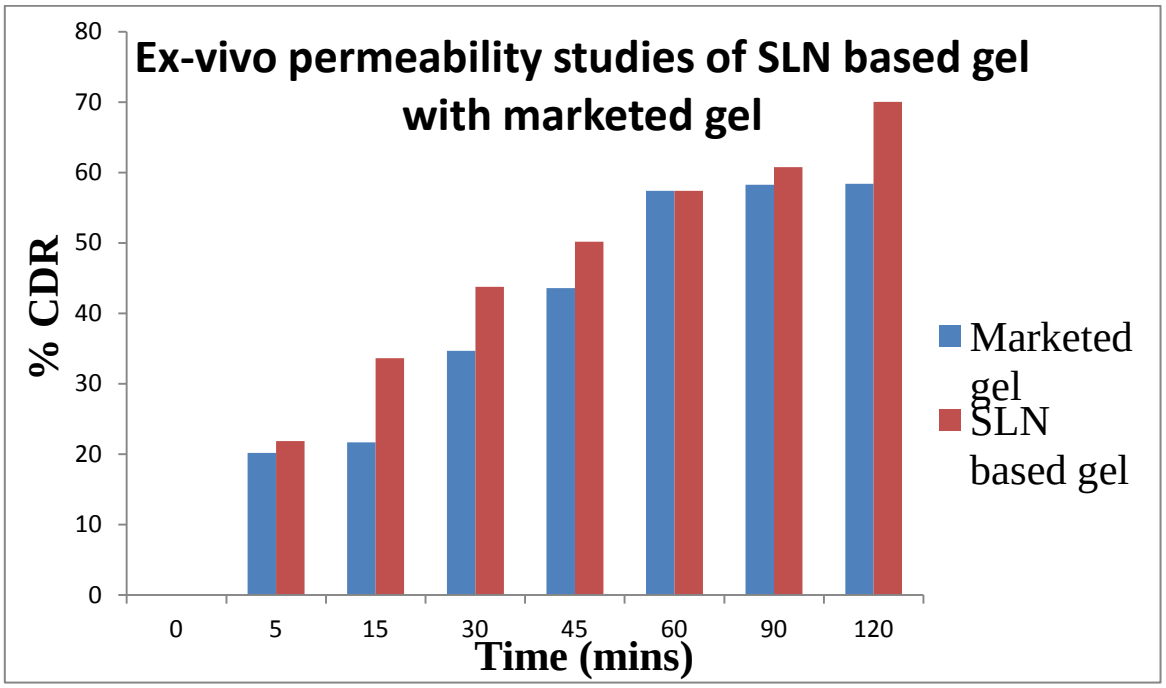

Figure 4.28 Plot of Ex-vivo permeability studies of SLN based gel with marketed gel

Result and Discussion:

From the above results, it can be concluded that the Dapsone loaded SLN based gel showed higher skin permeability deposition than marketed gel.

Chapter – 5

Conclusion

5. Conclusion:

Eczema is a term used for medical conditions in which skin becomes inflamed or irritation occurs. The estimation for eczema been affected upto 2010 was 230 million globally i.e. 3.5% of the population. Dapsone was used to treat eczema for the patients who are insensitive to other anti-acne agents. Dapsone having low water solubility and oral side effects, it is right choice to formulate it with solid lipid nanoparticles. Further for the easy convenience of patients, solid lipid nanoparticles were incorporated into gel for the topical delivery.

Hence, the objective was to develop topical gel containing SLN dispersion loaded with Dapsone to limit side effects of drug, improving its solubility for treatment of eczema.

Lipid and surfactant were selected on the basis of solubility of drug. Here, high solubility of drug in lipid was selected and lowest solubility of drug in surfactant was selected for the formulation. From the study, Compritol ATO 888 was selected as the lipid and Span 80 was selected as the choice of surfactant.

The choice of method for preparation of solid lipid nanoparticles was selected on the basis on maximum % entrapment efficiency and % drug loading. It was prepared by both methods: Solvent evaporation method and microemulsification method. From the results, it was observed that maximum % entrapment efficiency and % drug loading was obtained by microemulsification method. So, it was selected as the proper method for preparation of solid lipid nanoparticles.

After selection of best method for preparation, the various process parameters were optimized like drug: lipid ratio, concentration of surfactant, speed of stirring and time of stirring. From this study, it was observed that drug: lipid ratio was 1:1, concentration of surfactant was 1%, speed of stirring was 1500 rpm and time of stirring was for 2 hours.

The optimized batch was evaluated and particle size was 78.16 nm, zeta potential of -28.2 mV, % entrapment efficiency of 75.81%, drug loading of 49.6% and in vitro drug release at 8 hour was 77.42% was observed.

The 3^2 full factorial design was used for optimization of Dapsone loaded solid lipid nanoparticles. The concentration of surfactant (X1) and speed of stirring(X2) was choosen as independent variable and % entrapment efficiency (Y1), % drug loading (Y2) and % drug release at 8 hour (Y3) were taken as dependent variables. The polynomial equation was obtained and contour plot of various responses were plotted against optimal design space. Optimum formulation was selected on the basis of % entrapment efficiency, % drug loading and % drug release at 8 hour. The optimized formulation batch contained 64.93% entrapment efficiency, 50.44% drug loading and 75.4% drug release at 8 hour was observed.

SEM analysis of optimized batch of SLN was carried out which showed somewhat spherical uniformity of particles. The stability study of SLN dispersion was carried out for 15 days at 4℃ refrigeration and was found similar observations before 15 days and after 15 days.

For optimized batch of solid lipid nanoparticles, solid lipid nanoparticles based gel was made using Carbopol 940 and were evaluated for drug content, pH, spreadability, peak load, viscosity and drug release profile.

The results showed similar pH of 7 near to skin. Viscosity 23287 cPs, peak load 688.20 and spreadability 27.9 g cm/ sec were found of 1% Carbopol containing SLN which were nearly to marketed gel.

In-vitro permeation study showed that 1% Carbopol containg SLN based gel showed 85.02% release at 8 hr as compared to marketed gel. Hence, 1% Carbopol containing solid lipid nanoparticles gel was selected for further studies. Ex-vivo permeation study was carried out on rat abdominal skin of marketed gel and SLN based gel and was found that SLN based gel showed 70.02% release at 8 hour which showed better permeability.

The present study was done with an aim of developing solid lipid nanoparticles for the treatment of eczema and was found to be the suitable vehicle due to its excellent permeability of SLN based gel.

Chapter – 6

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