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REVIEW OF SOLID LIPID NANOPARTICLES BASED NANOGEL FOR DERMAL DELIVERY OF INDOMETHACIN

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Abstract:
Nanogels composed of Nano size particles formed by physically or chemically cross linked polymer networks that swells in a good solvent. The nanogel systems have proven their potential to deliver drugs in controlled, constant and targetable mode. With the promising field of polymer sciences it has now become predestinated to prepare smart nano-system which can establish effectual for treatment, diagnosing as well as clinical trials progress.Nanogels is been proving as a promising drug delivery system and offers variety of characteristics like on site drug delivery system, sustained release formulation, high drug entrapment properties, water solubility, biodegradability, low toxicity etc. Due to these multi functionality properties and features nanogel utilized extensively in many drug deliver fields. Composite with polymers, metals and other active molecules nanogel turned out as excellent drug delivery system.Although, Indomethacin possesses some favorable properties for topical administration like low molecular weight, low daily therapeutic dose yet, the inherent poor aqueous solubility and high melting point make it unsuitable for topical application. It does not exhibit enough lipophilicity for permeation across the skin. A number of topical/transdermal drug delivery systems, which vary in their compositions and structures have been developed to improve the skin permeation of Indomethacin. However, the poor drug loading capacity, poor drug controlled and sustained release capacities have limited their use as topical/transdermal carriers. The level of interest in lipid-based carrier systems have increased substantially for topical administration of drugs because of the use of fats and oils of natural origin and pharmaceutically accepted surfactant as excipients.

Keywords: *Solid Lipid Nanoparticles, Nanogel, Freeze drying.*

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INTRODUCTION:

Topical drug delivery means the application of drug to skin for localized effect. The skin is one of the most widespread and freely available structures of the human body. Skin of an average adult body covers a surface approximately 2 m2 and receives about one-third of the blood circulating through the body (“as discussed by Sharma et al. It acts as a regulator in retaining the body heat, plays a part in regulation of blood pressure, and protects against the penetration of ultraviolet rays. Dermal drug delivery has number of advantages like longer duration of action, dosing flexibility, reduced side effects, uniform plasma levels, high patient compliance, and so forth but it has some disadvantages like possibility of local irritation effect, erythema, itching, and low permeability of drugs in the stratum corneum (“as discussed by Bhowmik et al.Stratum corneum is outermost and top layer of epidermis which is impermeable to water and behaves like tough flexible membrane. It contains dead keratinized cells called corneocytes. For the permeation of drug to this barrier many technologies and systems have been investigated and one of the most promising techniques is the vesicular carrier for drug delivery through the skin.

Novel drug delivery carriers have great potential for dermal delivery. The lipidic and nonlipidic vesicular systems like liposome, transfersome, ethosome, and niosome are used to overcome the problem associated with topical conventional formulation. Drug delivery system using novel vesicular carrier, such as liposome or niosome, has distinct advantages over microspheres, nanoparticles, and other carriers in terms of better entrapment of drugs (payload characteristics), target site specificity, and handling premature drug release (burst effect). In 1985, niosomes were studied as an alternative to liposome because they offer some benefits over liposome such as being more stable, nontoxic, and economic due to low cost of nonionic surfactant as compared to phospholipids which are prone to oxidation. Incorporation of surfactants within niosomes may also enhance the efficacy of the drug, possibly by facilitating its uptake by the target cells. Niosomes are biodegradable, biocompatible, relatively nontoxic, and an alternative of liposome. They can be utilized in the delivery of wide variety of drugs as it has capability to entrap hydrophilic, lipophilic, and amphiphilic drugs. For transdermal route of administration NSAIDs, hormone, antibacterial, and antifungal drugs are most preferably used.

For the successful delivery of any new developed pharmaceutical formulation it is expected to deliver the therapeutic active drug to the target site at minimum effective concentration with negligible discomfort, maximum patient compliance to the therapeutic use and minimum side effects. Among various routes of administration, the topical route is the most favored route for local delivery of therapeutic agent. Due to its advantage of easy of application, low cost of production and convenience, topical route has become more popular over last few years. Current trend of oral and parenteral route offer the challenges related to adverse effects of drug and dosage form along with patient compliance and issue related to stability. However, conventional topical drug delivery systems have limitations such as less retention time and low bioavailability. Hence existing topical drug delivery and innovations in this system aims to improve the efficacy of drug and to achieve an optimal concentration of a certain drug at its site of action for an appropriate duration [1,2].

Topical route of administration have several advantages over other drug delivery systems.
These advantages are enlisted below.

Advantages of topical drug delivery system [3-6]:

1. It avoids first pass metabolism.
2. Expedient and easy to apply.
3. Avoids the disadvantages and risks of intravenous therapy
4. Avoids the problem associated with oral therapy like the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc.
5. Lowers the total drug administration.
6. Avoids wavering in drug levels.
7. Medication can be easily terminated whenever needed.
8. Availability of larger application area than other like buccal or nasal cavity
9. Target the drug more selectively to a specific site.
10. Avoids the gastro-intestinal incompatibility.
11. The drugs with short biological half-life and narrow therapeutic window can be administered.
12. Improving physiological and pharmacological response.
13. Improve patient acceptance.
14. Self-medication is possible.

Topical drug delivery can be defined as application of medication containing formulation to the skin to directly treat the cutaneous or subcutaneous disorders and diseases like acne or fungal infections by providing the drug to the surface of the skin or within the skin. In spite of many advantages of transdermal and dermal drug delivery over other drug delivery system, relatively few topical drug formulations are commercially available in market. The main challenging step in the topical delivery is the crossing of most impermeable epithelia of human body that is stratum corneum. Stratum

corneum becomes a barrier for the exogenetic substances. Hence this fact is to be considered at the time of formulating a new formulation for the topical administration of drug so that maximum penetration of the drug into the skin without irreversible disturbing the skin barrier function can be achieved.

Anatomy and Physiology of Skin and barrier properties [7,8]:

Skin is one of the largest organ, separates the most stable internal environment from the most unstable external environment. Skin compose of epidermis, dermis and subcutis, each plays a fundamental role of maintaining chemical balance and protection of skin from microorganisms, dust and varied climatic conditions. Refer Figure 1 for illustration of Skin.

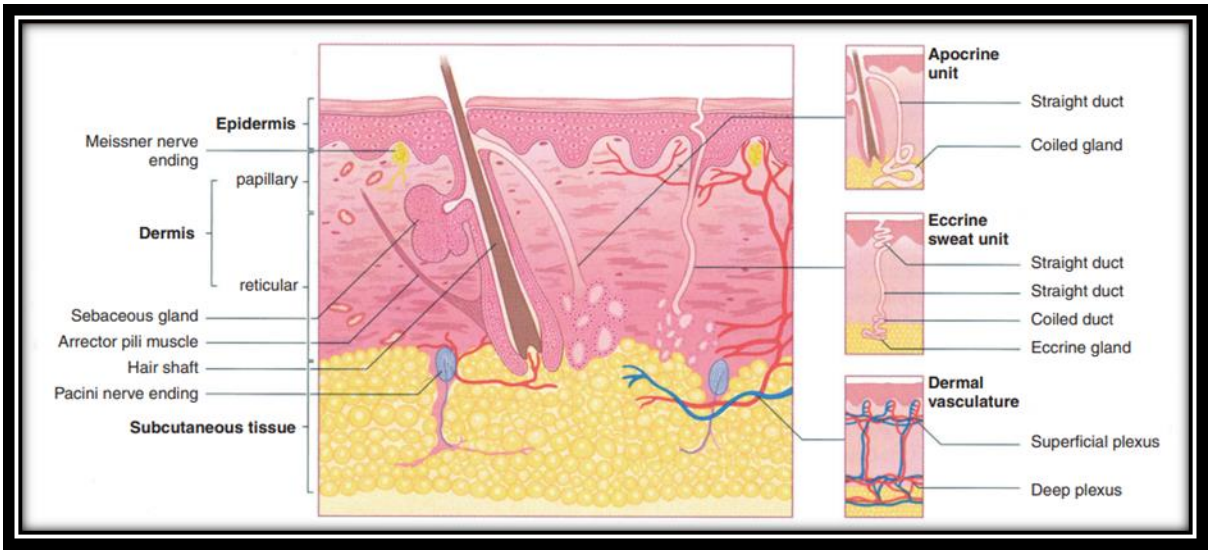

Figure 1: Cross-Section of Human Skin

The skin is the largest organ of the body, accounting for about 15% of the total adult body weight. It performs many vital functions, including protection against external physical, chemical, and biologic assailants, as well as prevention of excess water loss from the body and a role in thermoregulation. The skin is continuous, with the mucous membranes lining the body's surface. The integumentary system is formed by the skin and its derivative structures. The skin is composed of three layers: the epidermis, the dermis, and subcutaneous tissue. The outermost level, the epidermis, consists of a specific constellation of cells known as keratinocytes, which function to synthesize keratin, a long, threadlike protein with a protective role. The middle layer, the dermis, is fundamentally made up of the fibrillar structural protein known as collagen. The dermis lies on the subcutaneous tissue, or panniculus, which contains small lobes of fat cells known as lipocytes. The thickness of these layers varies considerably, depending on the geographic location on the anatomy of the body. The eyelid, for example, has the thinnest layer of the epidermis, measuring less than 0.1 mm, whereas the palms and soles of the feet have the thickest epidermal layer, measuring approximately 1.5 mm. The dermis is thickest on the back, where it is 30–40 times as thick as the overlying epidermis Epidermis forms the outermost layer of skin. The cells of epidermis travel upward and become dead flat cell called stratum corneum. Stratum corneum composed of corrneocytes and intercellular lipids which forms the compact impermeable layer. Dermis forms the elastic layer below the epidermis. Subcutaneous layer consist of sheet of fat rich areolar tissue attaching the dermis to the underlying structure of skin.

Biochemistry of skin: [8,9]:

Epidermis composed of lytic enzymes and proteolytic enzymes generated from the end product of glucose metabolism. The end product of glucose metabolism i.e lactic acid accumulates in the skin which drops down the tissue pH from usual 7.0 to less than 6.0. The fibroblast cells of dermis increases the synthetic and proliferative activity during the wound healing.

Contribution of topical dosage form in pharmaceutical market [10,11,12]:

The pharmaceutical industries are standing up with the building blocks of drug delivery system. Along with different diseases, limitations of drugs and difficulty in formulating dosage form. A novel delivery system are gaining focus nowadays to overcome the limits of properties of drugs and to treat different disease

conditions. Various factors have contributed in formulation of dosage form like the effective delivery of drug to target site, poor efficacies of drugs, minimizing side effects of drugs and patient compliance. Among the various drug delivery system topical/transdermal drug delivery system effectively delivers the drug to the skin. Low dose with continuous release of drug is possible with topical drug delivery systems for e.g. various hormones, nicotine and therapeutic agents can be successfully administered through skin. Hence the topical market has been increased up to 8% and gaining increasing acceptance and popularity among different dosage form. The topical drug delivery market is expected to reach USD 125.88 billion by 2021 from USD 92.40 billion in 2016 at a compound annual growth rate of 6.4% during forecast period. The topical route is also associated with challenges like delivery of large drug molecule, skin barrier properties and disease condition of skin hence the market participants are researching on novel technologies to enhance dermal drug delivery.

Solid lipid nanoparticles [13-15]

Solid lipid nanoparticles (SLN) were developed as a colloidal carrier at the beginning of the 1990s as an alternative system to the existing traditional carriers like emulsions, liposomes, niosomes and polymeric nanoparticles. Nanoparticles made up of solid lipid have more advantageous than any other carrier system. SLN have more entrapment of drug in solid lipid. Solid lipid nanoparticles are composed of lipid in solid form at room temperature along with surfactant (emulsifier) for stabilizing of SLN dispersion. The reasons for the increasing interest in lipid-based system are many – fold and include.

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipoid excipients.
3. An improved ability to address the key issues of technology transfer and manufacture scale-up.

Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid shown on Fig. 2. They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable.

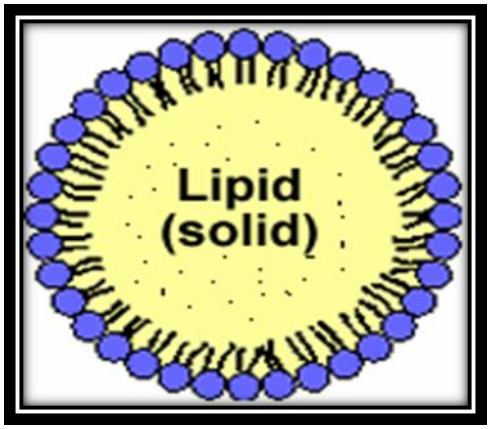

Figure 2: Structure of solid lipid nanoparticle (SLN)

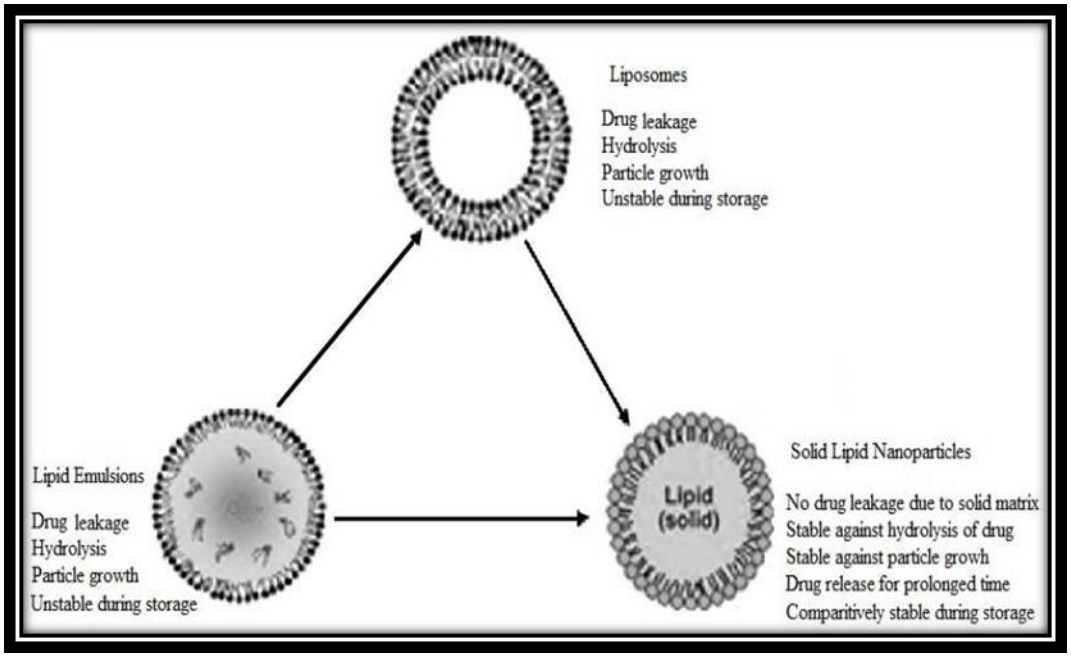

Figure 3: A diagrammatic representation on SLN over emulsions and liposomes

Different types of lipids and surfactants reported in the formulation of solid lipid nanoparticles are given in table 1.

Table 1: Lipids and Surfactants used

Lipids	**Surfactant**
Triacylglycerols	Phospholipids
Tricarpin	Soy lecithin
Trilaurin	Egg lecithin
Tripalmitin	Phosphatidylcholine
Tristearin	Ethylene oxide/propylene oxide copolymer
Acylglycerol	Poloxamer 188
Glycerol Monostearate	Poloxamer 182
Glycerol behenate	Poloxamer 407
Glycerol palmitostearate	Poloxamer 908
Fatty acids	Sorbitan ethylene oxide
Stearic acid	Polysorbate 20
Palmitic acid	Polysorbate 60
Decanoic acid	Polysorbate 80
Behenic acid	Alkylaryl polyether alcohol polymers
Waxes	Tyloxapol
Cetyl palmitate	Bile slts
Cyclic complexes	Sodium cholate
Cyclodextrin	Sodium glycocholate
Para-acyl-calix-arenes	Sodium taurocholate Sodium taurodeoxycholate Alcohols Ethanol Butanol

Solid lipid nanoparticles (SLNs) are considered to be the most effective lipid based colloidal carriers, introduced in early nineties. This is the one of the most popular approaches to improve the oral bioavailability of the poorly water soluble drugs. SLNs are in the submicron size range of 50-1000 nm and are composed of

physiologically tolerated lipid components which are in solid state at room temperature. The schematic representation of different particulate drug carriers such as emulsions and liposomes and their advantages are compared with SLNs in Figure 3. SLNs combine all the advantages of polymeric nanoparticles, fat emulsions and liposomes.

Advantages of SLN:
• Control and / or target drug release.
• Excellent biocompatibility
• Improve stability of pharmaceuticals
• High and enhanced drug content.
• Easy to scale up and sterilize.
• Better control over release kinetics of encapsulated compounds.
• Enhanced bioavailability of entrapped bioactive compounds.
• Chemical protection of labile incorporated compounds.
• Much easier to manufacture than biopolymeric nanoparticles.
• No special solvent required.
• Conventional emulsion manufacturing methods applicable.
• Raw materials essential the same as in emulsions.
• Very high long-term stability.
• Application versatility.
• Can be subjected to commercial sterilization procedures.

Disadvantages of SLN:
• Particle growth.
• Unpredictable gelation tendency.
• Unexpected dynamics of polymeric transitions.

Aims of solid lipid nanoparticles:
• Possibility of controlled drug release
• Increased drug stability.
• High drug pay load
• No bio-toxicity of the carrier.
• Avoidance of organic solvents.
• Incorporation of lipophilic and hydrophilic drugs.

Preparation of solid lipid nanoparticles:
SLNs are prepared from lipid, emulsifier and water/solvent by using different methods and are discussed below.

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 reliable and powerful technique, which is used for the production of SLNs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated.
Two general approaches of HPH are hot homogenization and cold homogenization, work on the same concept of mixing the drug in bulk of lipid melt.

Hot homogenization:
Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. HPH of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles.

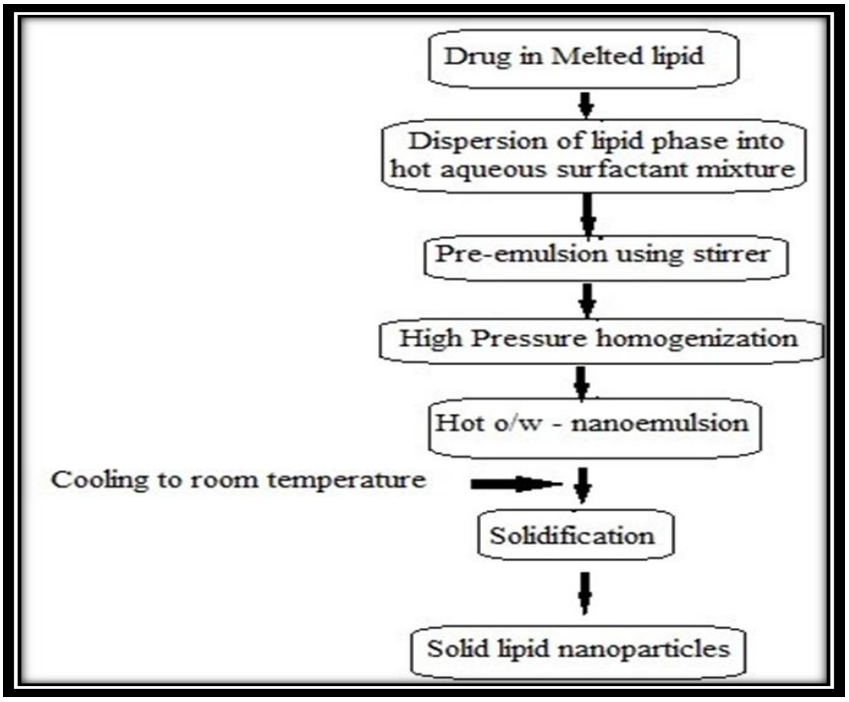

Figure 4: Solid lipid nanoparticles preparation by hot homogenization process

Cold homogenization:

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts. In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.

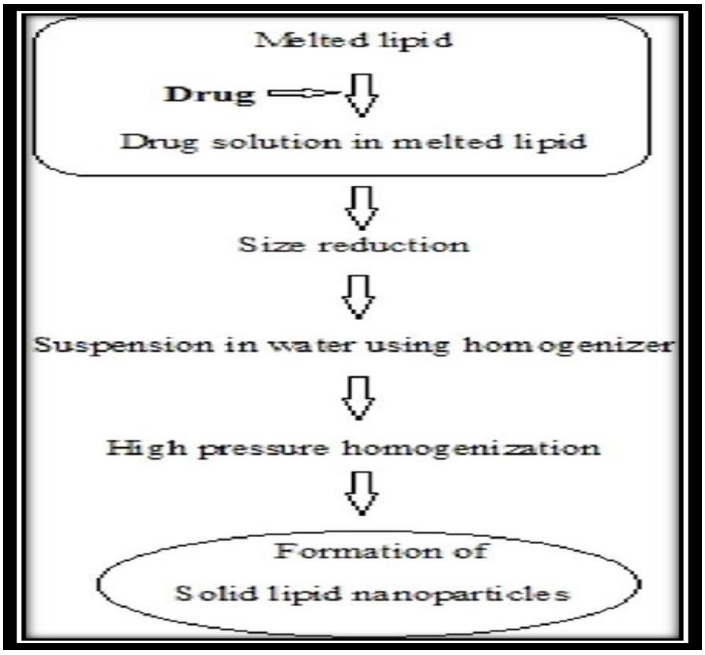

Figure 5: Solid lipid nanoparticles preparation by cold homogenization process

➢ **Advantages**
- Low capital cost.
- Demonstrated at lab scale.

➢ **Disadvantages**
- Energy intensive process.
- Demonstrated at lab scale Biomolecule damage.
- Polydisperse distributions.
- Unproven scalability.

Ultrasonication/high speed homogenization:
SLNs are also prepared by ultrasonication or high speed homogenization techniques. For smaller particle size combination of both ultrasonication and high speed homogenization is required.

➢ **Advantages**
- Reduced shear stress.

➢ **Disadvantages**
- Potential metal contamination.
- Physical instability like particle growth upon storage.

Solvent evaporation:
SLNs can also prepared by solvent evaporation method. The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar).

➢ **Advantages**
- Scalable.
- Mature technology.
- Continuous process.
- Commercially demonstrated.

➢ **Disadvantages**
- Extremely energy intensive process.
- Polydisperse distributions.
- Biomolecule damage.

Solvent emulsification-diffusion method:
The particles with average diameters of 30-100 nm can be obtained by this technique. Voidance of heat during the preparation is the most important advantage of this technique.

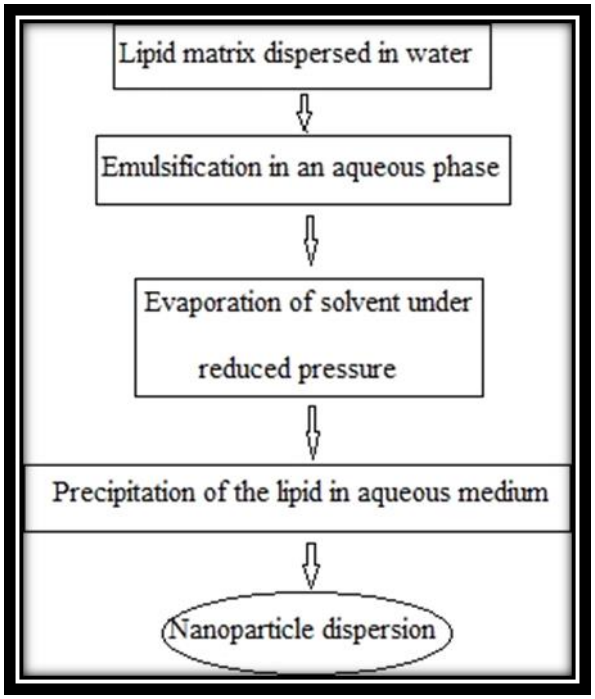

Figure 6: Systematic representation for emulsification-diffusion method

Supercritical fluid method:
This is an alternative method of preparing SLNs by particles from gas saturated solutions (PGSS).

- **Advantages**
- Avoid the use of solvents.
- Particles are obtained as a dry powder, instead of suspensions.
- Mild pressure and temperature conditions.
- Carbon dioxide solution is the good choice as a solvent for this method.

Microemulsion based method:
This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. SLN dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content too much of water needs to be removed. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation. Due to the dilution step; achievable lipid contents are considerably lower compared with the HPH based formulations.

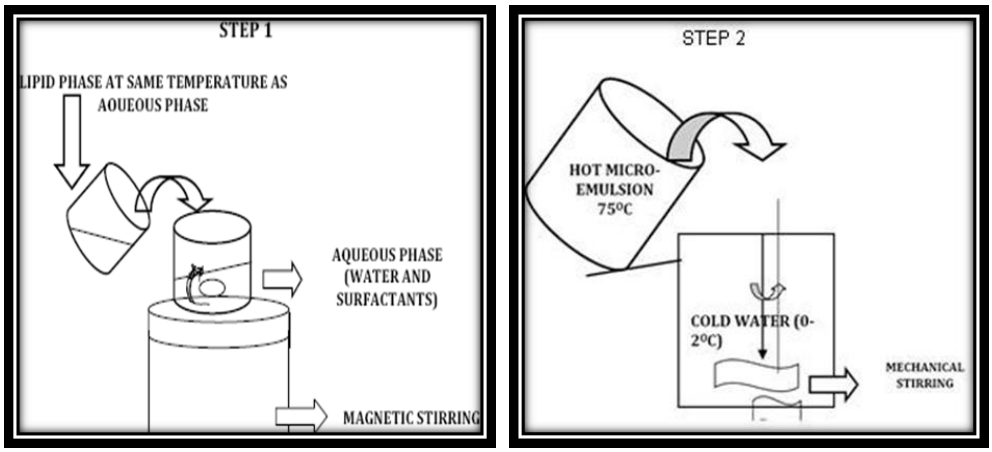

Figure 7: Microemulsion method

- **Advantages**
- Low mechanical energy input.
- Theoretical stability
- **Disadvantages**
- Extremely sensitive to change.
- Labor intensive formulation work.
- Low nanoparticle concentrations.

Spray drying method
It is an alternative technique to the lyophilization process. This recommends the use of lipid with melting point more than 70oC. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture.

Double emulsion method
Here the drug is encapsulated with a stabilizer to prevent the partitioning of drug in to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion.

Precipitation method
The glycerides are dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles.

Film-ultrasound dispersion
The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.

Secondary Production Steps
a. Freeze drying
Lyophilization is a promising way to increase the chemical and physical stability over extended periods of time. Lyophilization had been required to achieve long term stability for a product containing hydrolysable drugs or a suitable product for per-oral administration. Transformation into the solid state would prevent the Oswald ripening and avoid hydrolytic reactions. In case

of freeze drying of the product, all the lipid matrices used, form larger solid lipid nanoparticles with a wider size distribution due to presence of aggregates between the nanoparticles. The conditions of the freeze drying process and the removal of water promote the aggregation among SLNs. An adequate amount of cryoprotectant can protect the aggregation of solid lipid nanoparticles during the freeze drying process.

b. Sterilization

Sterilization of the nanoparticles is desirable for parenteral administration and autoclaving which is applicable to formulations containing heat-resistant drugs. Effects of sterilization on particle size have been investigated and it was found to cause a distinct increase in particle size.

c. Spray drying

Spray drying might be an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a dry product. This method has been used scarcely for SLN formulation, although spray drying is cheaper as compared to lyophilization. The lipids with melting points at temperature >70°C had been recommended for spray drying.

Influence of excipients [22]

a. Particle size

Alteration of the size significantly affects the physical stability, biofate of the lipid particles, and release rate of the loaded drug. Hence the size of the SLNs has to be controlled within reasonable range. Well formulated systems (liposomes, nanospheres and nanoparticles) should display a narrow particle size distribution in the submicron size range (as having size below 1µm), according to the definition of colloidal particles.

b. Influence of the ingredients on product quality

The particle size of lipid nanoparticles is affected by various parameters such as composition of the formulation (such as surfactant/ surfactant mixture, properties of the lipid and the drug incorporated), production methods and conditions (such as time, temperature, pressure, cycle number, equipment, sterilization and lyophilization). Large particle size is obtained at lower processing temperature. The hot homogenization technique gives a smaller particle size, generally below 500 nm, and a narrow particle size distribution as compared to cold homogenization. Mean particle size as well as polydispersity index (PI) values are reported to be reduced at increasing homogenization pressure up to 1500 bar and number of cycles (3-7 cycles).

c. Influence of the lipids

Using the hot homogenization, it has been found that the average particle size of SLN dispersions is increasing with higher melting lipids. However, other critical parameters for nanoparticle formation will be different for the different lipids. The examples include the velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties and the shape of the lipid crystals (and therefore the surface area).
Further, increasing the lipid content over 5-10% resulted in larger particles (including microparticles) and broader particle size distribution in most cases.

d. Influence of the emulsifiers

The concentration of the surfactant/surfactant mixture strongly affects the particle size of the lipid nanoparticles. In general, smaller particle sizes were observed when a higher surfactant/lipid ratio was chosen. The decrease in surfactant concentration resulted in increase of particle size during storage.
Surfactants decrease the surface tension between the interface of the particles causing portioning of the particles and thereby increasing the surface area.

Drug incorporation models of SLN [23]

Factors affecting loading capacity of a drug in lipid are:
1. Solubility of drug in lipid melt.
2. Miscibility of drug melt and lipid melt.
3. Chemical and physical structure of solid matrix lipid.
4. Polymorphic state of lipid material.

Drug incorporation models are as follows

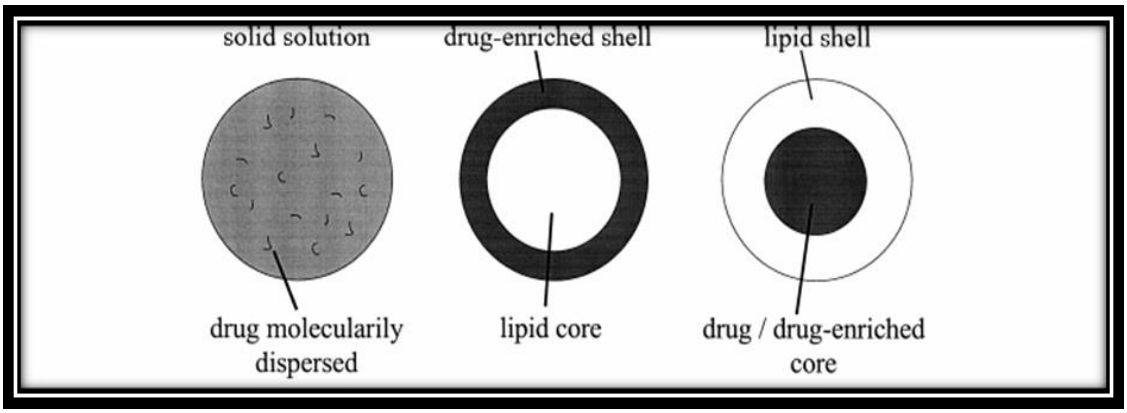

Figure 8: Drug incorporation models

Solid solution model:
1. Drug is molecularly dispersed in lipid matrix when SLN is prepared by cold homogenization.
2. Drug-enriched shell model.
3. A solid lipid core forms upon recrystalization temperature of the lipid is reached.
4. Drug-enriched core model.
5. Cooling the nanoemulsion leads to a super saturation of the drug which is dissolved in the lipid melt leads to recrystalization of the lipid.

Fate of SLN after oral administration [24]
The oral route continues to be a challenge as well as the most attractive way to administer drugs because of its unquestionable commercial potential. Incorporation of drugs into lipid nanoparticles opens the perspective of enhanced and / or less variable bioavailability and prolonged plasma levels. While these systems may provide the greatest flexibility in the modulation of the drug release profile within GIT and provide protection against chemical degradation for labile drug molecules (Peptide drugs).

Drug incorporation and loading capacity [25]
The particle size, loading capacity and the size distribution of SLN's is found to vary with lipid (triglycerides, fatty acids, steroids, waxes etc), emulsifier (anionic, cationic, non - ionic) and the method of preparation etc.
Factors determining the loading capacity of the drug in the lipid are
• Solubility of the melted lipid.
• Miscibility of the drug melt in the lipid melt.
• Chemical and physical structure of solid lipid matrix.
• Polymorphic state of lipid material.
The pre – requisite to obtain a sufficient loading capacity is a sufficiently high solubility of the drug in the lipid melt. Typically the solubility should be higher than required because, it decreases when cooling down the melt and might be even lower in the solid lipid. To enhance the solubility in the lipid melt one can add solubilizers. In addition, the presence of mono and diglycerides in the lipid used matrix material promotes drug solubilization. The chemical nature of the lipid is also important because lipids which form highly crystalline particles with a perfect lattice lead drug expulsion.

Estimation of incorporated drug Entrapment efficiency [26]
This is the prime importance in SLN, since it influences the release characteristics of drug molecule. The amount of drug encapsulated per unit weight of nanoparticles is determined after separation of the entrapped drug from the SLN formulation. This separation can be carried out using the techniques such as ultracentrifugation, centrifugation filtration and or gel permeation chromatography.

Centrifugation filtration
Filters such as ultra-free – mc or ultra-sort – 10 are used along with classical centrifugation techniques. The degree of encapsulation can be assessed indirectly by determining the amount of drug remaining in supernatant after centrifugation filtration/ultra-centrifugation of SLN suspension or alternatively by dissolution of the sediment in an appropriate solvent and subsequent analysis.

Principles of drug release [23]
The general drug principles of drug release from lipid nanoparticles are as follows:
• There is an inverse relationship between drug release and the partition co-efficient of the drug.
• Higher surface area due to smaller particle size in the nanometer size range gives higher drug release.
• Slow drug release can be achieved when drug is homogenously dispersed in the lipid matrix. It depends on the type and the drug entrapment model of SLN.

• Crystallinity behavior of the lipid and high mobility of the drug lead to fast drug release. There is an inverse relationship between crystallization degree and mobility of drug.
Factors contributing to a fast release are the large surface area, a high diffusion co - efficient due to small molecular size, low viscosity in the matrix and a short diffusion distance δ for the drug. The increase in the velocity with decreasing particle size was reported.

Storage stability of SLN [27]
The physical properties of SLN's during prolonged storage can be determined by monitoring changes in zeta potential, particle size, drug content, appearance and viscosity as the function of time. External parameters such as temperature and light appear to be of primary importance for long - term stability. The zeta potential should be in general, remain higher than - 60mV for a dispersion to remain physically stable.
4°C - Most favorable storage temperature.
20°C - Long term storage did not result in drug loaded SLN aggregation or loss of drug.
50°C - A rapid growth of particle size was observed.

In vitro and ex vivo methods for the assessment of drug release from SLN [28]
A large number of drugs including very hydrophilic molecules have been postulated to be incorporated into SLN.
Various methods used to study the in vitro release of the drug are:
• Side by side diffusion cells with artificial or biological membrane
• Dialysis bag diffusion technique
• Reverse dialysis bag technique
• Agitation followed by ultracentrifugation or centrifugal ultra-filtration

In vitro drug release Dialysis tubing
In vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion is placed in pre - washed dialysis tubing which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method.

Reverse dialysis
In this technique a number of small dialysis sacs containing 1 mL of dissolution medium are placed in SLN dispersion. The SLN's are then displaced into the medium.

Ex vivo model for determining permeability across the gut
A study demonstrated the passage of enalaprilat SLN's across rat jejunum. In short the rat jejunum (20 – 30 cm distal from the pyloric sphincter) was excised from the rats after sacrificing the animal used for the study. Another study excised 10 cm long segments of duodenum (1 cm distal to pyloric sphincter); jejunum (15 cm to pyloric sphincter), ileum (20 cm proximal to cecum) and colon (2 cm distal to cecum) were immediately cannulated and ligated on both sides used for their permeability studies

Analytical characterization of SLN
An adequate characterization of the SLN's is necessary for the control of the quality of the product.
Several parameters have to be considered which have direct impact on the stability and release kinetics:
• Particle size and zeta potential.
• Degree of crystallinity and lipid modification.
• Co – existence of additional structures and dynamic phenomena.

a. Measurement of particle size and zeta potential [28]
Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by particle movement. This method covers a size range from a few nanometers to about 3 microns. PCS is a good tool to characterize nanoparticles, but it is not able to detect larger micro particles. Electron Microscopy provides, in contrast to PCS and LD, direct information on the particle shape. The physical stability of optimized SLN dispersed is generally more than 12 months. ZP measurements allow predictions about the storage stability of colloidal dispersion.

b. Dynamic light scattering (DLS) [29]
DLS also known as PCS records the variation in the intensity of the scattered light on the microsecond time scale.

c. Static light scattering (SLS)/fraunhofer diffraction
SLS is an ensemble method in which the light scattered from a solution of particles is collected and fit into fundamental primary variable.

d. Acoustic methods
It measures the attenuation of the scattered sound waves as a means of determining size through the fitting of physically relevant equations.

e. Nuclear magnetic resonance (NMR) [29]
NMR can be used to determine both the size and qualitative nature of nanoparticles.

f. Electron microscopy [30]
Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) are the direct method to measure nanoparticles, physical characterization of nanoparticles with the former method being used for morphological examination. TEM has a smaller size limit of detection.

g. Atomic force microscopy (AFM)
A probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on forces at play between the tip and the surface.

h. Powder X - ray diffraction and differential scanning calorimetry (DSC)
The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature.

Sterilization of SLN [31]
For intravenous and ocular administration SLN must be sterile. The temperature reach during sterilization by autoclaving presumably causes a hot o/w micro emulsion to form in the autoclave, and probably alters the size of the hot nanoparticles. On subsequent slow cooling, the SLN reformed, but some nano-droplets may coalesce, producing larger SLN than the initial ones. SLN are washed before sterilization, amounts of surfactants and co surfactants present the hot systems are smaller, so that the nano-droplets may be not sufficiently stabilized.

Measurement of crystallinity and lipid modifications [23]
Thermodynamic stability, lipid packing density and quantification are a serious challenge due to the increase, while drug incorporation rates ML.
Due to the small size of the particles and the presence of emulsifiers, lipid crystallization modification changes might be highly retarded. Differential scanning calorimetry (DSC) and X- ray scattering are widely used to investigate the status of the lipid. Infrared and Raman spectroscopy are useful tools for investigating structural properties of lipids27. Their potential to characterize SLN dispersions has yet to be explored.

Co – existence of additional structures
The magnetic resonance techniques, nuclear magnetic resonance (NMR) and electron spin resonance (ESR) are powerful tools to investigate dynamic phenomena and the nano-compartments in the colloidal lipid dispersions. Dilution of the original SLN dispersion with water might cause the removal of the surfactant molecules from the particle surface and induce further changes such as crystallization changes of the lipid modification.

Table 2: Additional structure determination

Parameter	Method of analysis
Molecular weight	Gel chromatography
X-ray	photoelectron spectroscopy

SLN in cosmetic and dermatological preparations [32]:
An area of big potential for SLN and with a short time-to market are topical products based on the SLN technology, that means pharmaceutical but also cosmetic formulations. SLN are considered as being the next generation of delivery system after liposomes. Due to the lower risk of systemic side effects topical treatment of skin disease appears favourable, yet the stratum corneum counteracts the penetration of xenobiotics into viable skin. Particulate carrier systems may mean an option to improve dermal penetration. Since epidermal lipids are found in high amounts within the penetration barrier, lipid carriers attaching themselves to the skin surface and allowing lipid exchange between the outermost layers of the stratum corneum and the carrier appear promising. Besides liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been studied intensively. Following the evaporation of water from the lipid nanodispersion applied to the skin surface, lipid particles form an adhesive layer occluding the skin surface. Then hydration of the stratum corneum may increase by which reducing corneocyte packing and widening of the inter-corneocytes gaps can facilitate drug penetration into deeper skin strata. Occlusive effects appear strongly related to particle size. Nanoparticles have turned out 15-fold more occlusive than microparticles, and particles smaller than 400 nm in a dispersion containing at least 35% lipid of high crystallinity has been most potent.

SUMMARY AND CONCLUSION:

The aim of the present study was to develop Solid Lipid Nanoparticles Based Nanogel for Dermal Delivery of Indomethacin. Nanogels composed of nanosize particles

formed by physically or chemically cross linked polymer networks that swells in a good solvent. The nanogel systems have proven their potential to deliver drugs in controlled, constant and targetable mode. With the promising field of polymer sciences it has now become predestinated to prepare smart nano-system which can establish effectual for treatment, diagnosing as well as clinical trials progress.

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Authors have no conflicts of interest to declare.
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REFERENCES:

1. Chintala P. K., Padmapreetha J. Formulation and in-vitro evaluation of gel containing ethosomes entrapped with etodolac. International Journal of Pharmaceutical Science and Research. 2014;5(2):630–635.
2. Inoue N., Nogawa M., Ito S., Tajima K., Kume S., Kyoi T. The enantiomers of etodolac, a racemic anti-inflammatory agent, play different roles in efficacy and gastrointestinal safety. Biological and Pharmaceutical Bulletin. 2011;34(5):655–659. doi: 10.1248/bpb.34.655.
3. Kumar SS., Masilamani K., Srinivas SS., Ravichandiran V. Formulation and Physico-Chemical Evaluation of Ethylcellulose Microspheres Containing Etodolac. International Conference on Biotechnology and Pharmaceutical Sciences; 2011; pp. 372–375.
4. Barakat N. S. In vitro and in vivo characteristics of a thermogelling rectal delivery system of etodolac. APPS Pharmaceutical Science and Technology. 2009;10(3):724–731. doi: 10.1208/s12249-009-9261-y.
5. Tas C., Ozkan Y., Okyar A., Savaser A. In vitro and ex vivo permeation studies of etodolac from hydrophilic gels and effect of terpenes as enhancers. Drug Delivery. 2007;14(7):453–459. doi: 10.1080/10717540701603746.
6. Sharma N., Agarwal G., Rana A. C., Bhat Z. A., Kumar D. A review: transdermal drug delivery system: a tool for novel drug delivery system. International Journal of Drug Development and Research. 2011;3(3):70–84.
7. Bhowmik D., Chiranjib Chandira M., Jayakar B., Sampath K. P. Recent advances in transdermal drug delivery system. International Journal of Pharmaceutical Technology. 2010;2(1):68–77.
8. Balakrishnan P., Shanmugam S., Lee W. S., et al. Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery. International Journal of Pharmaceutics. 2009;377(1-2):1–8. doi: 10.1016/j.ijpharm.2009.04.020.
9. Firthouse P. U. M., Halith S. M., Wahab S. U., Sirajudeen M., Mohideen S. K. Formulation and evaluation of miconazole niosomes. International Journal of PharmTech Research. 2011;3(2):1019–1022.
10. Sathali A. A. H., Sangeetha T. Formulation and evaluation of ocular niosomal in situ gel of levofloxacin hemihydrates. Journal of Pharmacy Research. 2011;4:4331–4337.
11. Sathali A. A. H., Rajalakshmi G. Evaluation of transdermal targeted niosomal drug delivery of terbinafine hydrochloride. International Journal of PharmTech Research. 2010;2(3):2081–2089.
12. Solanki A. B., Parikh J. R., Parikh R. H., Patel M. R. Evaluation of different compositions of niosomes to optimize aceclofenac transdermal delivery. Asian Journal of Pharmaceutical Sciences. 2010;5(3):87–95.
13. Jain A., Deveda P., Vyas N. Development of antifungal emulsion based gel for topical fungal infections. International Journal of Pharmaceutical Research and Development. 2011;2:18–25.
14. Srikanth K., Nappinnai M., Gupta V. R. M., Suribabu J. Niosomes: a prominent tool for transdermal drug delivery. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2010;1(2):308–316.
15. Arora S., Prashar B., Dhamija H., Chandel A., Thakur V. Niosomes: the unique vesicular drug carriers. Journal of Drug Delivery & Therapeutics. 2012;2(1):96–101.
16. Shinde U. A., Kanojiya S. S. Serratiopeptidase niosomal gel with potential in topical delivery. Journal of Pharmaceutics. 2014;2014:9. doi: 10.1155/2014/382959.382959
17. Salih O. S., Samein L. H., Ali W. K. Formulation and in vitro evaluation of rosuvastatin calcium niosomes. International Journal of Pharmacy and Pharmaceutical Sciences. 2013;5(4):525–535.
18. Shilpa D. J., Vijay K. P. Formulation, development and evaluation of niosomal drug delivery system for clindamycin phosphate. Pharma Science Monitor. 2014;5(2):256–274.
19. Hadgraft J. Passive enhancement strategies in topical and transdermal drug delivery. International journal of pharmaceutics. 1999 Jul 5;184(1):1-6.
20. Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. Advanced drug delivery reviews. 2002 Nov 1;54:S77-98.
21. Singh SK, Durrani MJ, Reddy IK, Khan MA. Effect of permeation enhancers on the release of ketoprofen through transdermal drug delivery

systems. Die Pharmazie. 1996 Oct 1;51(10):741-4.
22. Ramesh P. Transdermal delivery of drugs. Indian journal of pharmacology. 1997 May 1;29(3):140.
23. Sinha VR, Kaur MP. Permeation enhancers for transdermal drug delivery. Drug development and industrial pharmacy. 2000 Jan 1;26(11):1131-40.
24. Gerard J. Tortora., Brayan Derrickson., Principles Of Anatomy and Physiology. Mithal BM, Saha RN. A handbook of cosmetics. Vallabh Prakashan, New Delhi. 2000;141.
25. Jain NK. Controlled and novel drug delivery CBS publishers & distributors. Daria Gang, New Delhi. 1997:101-27.
26. http://www.frost.com/prod/servlet/market-insight-print.pag?docid=134287829 [Accessed: Feb. 7, 2022].
27. https://www.boomer.org/c/p4/c07/c07.pdf [Accessed: Feb. 7, 2022].
28. https://www.marketsandmarkets.com/market-Reports/topical-drug-deliverymarket-124871717.html [Accessed: Feb. 7, 2022].
29. Müller RH, Runge SA, Ravelli V, Thünemann AF, Mehnert W, Souto EB. Cyclosporine-loaded solid lipid nanoparticles (SLN®): Drug–lipid physicochemical interactions and characterization of drug incorporation. European journal of pharmaceutics and biopharmaceutics. 2008 Mar 1;68(3):535-44.
30. Lippacher A, Müller RH, Mäder K. Preparation of semisolid drug carriers for topical application based on solid lipid nanoparticles. International journal of pharmaceutics. 2001 Feb 19;214(1-2):9-12.
31. Pandya JB, Parmar RD, Soniwala MM, Chavda JR. Solid lipid nanoparticles: overview on excipients. Asian Journal of Pharmaceutical Technology & Innovation. 2013;1(3):01-9.
32. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian journal of pharmaceutical sciences. 2009 Jul;71(4):349.
33. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery–a review of the state of the art. European journal of pharmaceutics and biopharmaceutics. 2000 Jul 3;50(1):161-77.
34. Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. Journal of Controlled release. 2008 Apr 21;127(2):97-109