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REVIEW ARTICLE

ASPECTS RELATED TO THE SOLID LIPID NANOPARTICLES DELIVERY THROUGH THE TOPICAL ROUTE

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ABSTRACT

The Solid lipid nanoparticles are the submicronic sized particles which have particle size range of 100-1000 nm which can be suitable for skin drug delivery. The Particle size is the major factor influenced at the time of drug delivery, other factor is the physiological acceptable and biodegradable property of the solid lipid nanoparticles. The epidermis i.e. stratum corneum is the rate-limiting factor which requires the appropriate carrier either lipophilic or small particle sized carriers to enhance the penetration of drug. The aspects related while administrating the solid lipid nanoparticles through the skin are the method of preparation, degree of crystallization, adhesiveness and occlusive factor. Small particles can make close contact to the Stratum corneum surface i.e. superficial junctions of the corneocytes clusters and furrows between corneocyte islands may favor accumulation for many hours allowing to the controlled release. Solid lipid nanoparticles and Nanostructured lipid carriers should attach as they are for longer and remain at the application site because of a pronounced adhesive effect. However, it is necessary that the adhesiveness is directly proportional to the decrease in the particle size. Water evaporation results in a transition of the lipid matrix to a more highly ordered structure leading to a drug expulsion. Improved hydration at least temporarily opens the compact structure of the horny layer and the permeability of the barrier increases.

Keywords: Solid lipid nanoparticles, Skin, Mechanism of drug penetration through nanocarriers

Abbreviations: SC- Stratum Corneum, API- Active Pharmaceutical Ingredient, SLN- Solid Lipid Nanoparticles

INTRODUCTION

1.1 TOPICAL DRUG DELIVERY SYSTEM

Dermatologic products applied to skin are diverse in formulation and range in consistency from liquids to powders, but the most popular products are semisolid preparations. Semisolid preparations for dermatological use are generally delivered topically. Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders or general disease with the intent of possessing the pharmacological effect of the drug to the surface of the skin or within the skin. Topical preparations are frequently used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of the skin or mucous. Although some unintended drug absorption may occur, it is sub therapeutics quantities and generally of minor concern. The majority of topical products comprise semisolid formulations that include ointments, creams and gels. But the Drug penetration is Rate-Limiting Factor related to the Stratum Corneum. Where the carriers in which drug should be entrapped to enhance the topical delivery into the Dermis is required. The SC pore size is approximately less than 20 nm in the healthy volunteer So that the small particle sized carriers are required to enhance the drug permeation [1].

a. Advantages of Topical Drug delivery System

- Better patient compliance and avoidance of first pass metabolism.
- Avoid fluctuations in drug levels, inter and intrapatient variations.
- Avoid the Gastro intestinal incompatibility.
- Provide utilization of drugs with short biological half life which have narrow therapeutic window.
- Avoidance of the risk and inconvenience of intravenous therapy
- Achievements of efficacy terminate the medications, when needed.
- A relatively large area of application in comparison with buccal or nasal cavity [1]

b. Disadvantages of Topical Drug Delivery Systems

- Skin irritation or contact dermatitis may occur due to the drug and excipients.
- Poor penetration of hydrophilic drugs through the skin.
- Possibility of allergenic reactions.
- Enzyme in epidermis may denature the drugs.
- Drugs of larger particle size are not easily absorbed through the skin [1]

1.2 ANATOMY AND PHYSIOLOGY OF SKIN

The skin acts as a boundary which separates the external environment from the internal organs. The epidermis acts as a barrier between the varied conditions of the external surroundings and the controlled internal environment of the living tissues and body fluids. The skin provides physical protection of internal organs and acts as a

sensory organ. It controls body temperature and water loss, and functions as a regulatory barrier which controls the movement of substances into and out of the body. The skin has gained increasing favors as a target site for drug delivery as it avoids problems associated with oral drug administration, namely pH and to some extent, enzyme driven drug degradation and hepatic first-pass metabolism. Cutaneous drug administration is not however without its problems. The drug is subjected to the skin's own first-pass metabolic effect. In addition to this, percutaneous absorption is subject to significant variability owing to differences in age, race, sex, site of administration, species, presence or absence of disease and the skin's reservoir capacity for a specific drug.

There are numerous diseases which affect different regions of the skin. Any drug used will be required to reach the site of the disease in order to exert its pharmacological activity. Unless it is for a local effect on the surface only, the drug must either pass through the Stratum Corneum (SC) or go through hair follicles or sweat glands to reach its target site. Once in the skin, a lipid-soluble drug will tend to accumulate in lipophilic regions while more water-soluble drugs will tend to enter the blood capillaries and are removed from the skin [2].

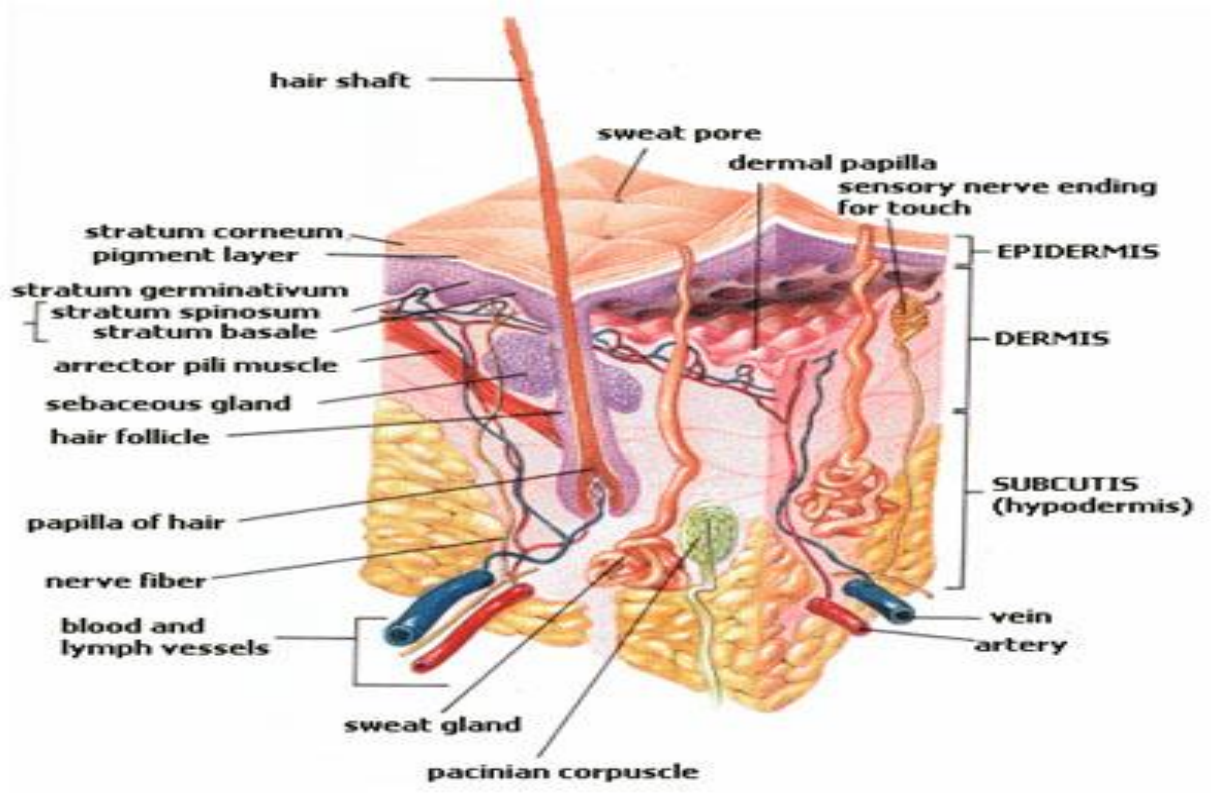

Figure 1.1: Human skin parts [3]

1.2.1 Structure of Skin

1.2.1.1 Epidermis

The important function of the epidermis is the generation of the SC. The epidermis is avascular and is sustained by nutrients it receives by diffusion from the underlying dermal capillaries through the basement membrane. The epidermal layer forms as a result of the death of basal cells via a specialized differentiate process. The epidermis consists of two layers namely the non-viable epidermis (SC) and the viable epidermis [4].

➢ **The Non-Viable Epidermis (SC)**

This is the outermost layer of the epidermis. It is approximately 10-20 micro meter thick and consists of about 15-25 layers of flattened, hexagonal and dead cornified cells surrounded by intercellular lipid. The SC is a very dense layer of tissue (1.4 g/cm^3 in the dry state). Approximately 15 % of the protein content of the SC consists of enzymes and other non-keratin proteins. The barrier function of the SC is enabled by the continuous desquamation of the non-viable epidermis with a total turnover of the SC occurring once every 2-3 weeks. Highly lipophilic compounds may be less absorbed systemically as they may be sequestered in the horny layer. The SC prevents loss of internal body components especially water.

➢ **The Viable Epidermis**

The cells of the SC are generated by the viable epidermis layer of cells. The Viable epidermis consists of several cell layers at varying stages of cell differentiation. These layers are the *stratum granulosum*, the *stratum spinosum* and the *stratum basale* or basal layer. The cells of viable epidermis themselves originate from the basal lamina or basement membrane which is located between the dermis and the viable epidermis.

In order of increasing temperature, there are three phases, orthorhombic, hexagonal and fluid lamellar. The orthorhombic phase is densest. The hydrocarbon chains of crystalline state are not equally distributed in the lattice, resulting in two different distances between lattice

planes (0.37 nm and 0.41 nm). The hexagonal phase is equally distributed for its hydrocarbon chains, the lattice spacing is 0.41 nm. In fluid lamellar phase, the lipids are present in a liquid (molten) state. The interchain distance of liquid state is around 0.46 nm. The mosaic fluid model described by Forslind is the first model postulating the presence of a continuous liquid phase in the SC and of its coexistence with the gel-phase domains (crystalline phases) but there has been no experimental data allowing possible verification of this model. [5]

1.2.1.2 The Dermis

The dermis is the connective tissue layer which supports the overlying epidermis. It consists mainly of fibrous protein collagen which is secreted by the dermal fibroblasts. The dermis also contains elastin fibers which form a mesh of fine threads, interspaced by collagen, around the hair follicles and sweat glands. In addition to the collagen and elastin tissue, various other substances occur in the dermis. These include mucopolysaccharides and soluble trophocollagen. The dermis contains superficial capillaries, sensory nerves, sebaceous glands, sweat glands and hair follicles as in fig. 1.1. [5]

1.2.1.3 The Subcutaneous Layer

The subcutaneous tissue is a fatty layer which develops beneath the dermis. It is also called the hypodermis and it is the innermost layer of the skin. Its most important role is to hold the vessels and nerves that supply into the skin. It connects to the dermis through the aid of collagen and elastin fibers and firmly attaches the skin to the underlying muscle tissue. [5]

1.3 SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles are the nano-carriers which remain solid at room temperature and changes into liquid form while melting at increasing temperature. SLN are composed of 0.1% (w/w) to 30% (w/w) solid lipid dispersed in an aqueous medium and if necessary stabilized with preferably 0.5% (w/w) to 5% (w/w) surfactant. The incorporation of cosmetic and pharmaceutical actives is feasible. The mean particle size of SLN is in the submicron rage, ranging from about 40 to 1000nm. In the second generation of the lipid nanoparticle technology, the particles are produced using blends of solid lipids and liquid lipids (oils). To obtain the blends for the particles matrix, solid lipids are mixed with liquid lipids (oils), preferably in a ratio of 70:30 upto a ratio of 99.9:0.1. The major advantage of SLN is the possibility of production on large industrial scale. However, depending on the drug some potential problems can occur, such as drug leakage during storage and insufficient total drug load. To overcome the limitations of SLN, nanostructured lipid carriers (NLC) have been developed. The later consists of a solid lipid matrix with a high content of liquid lipid. [7]

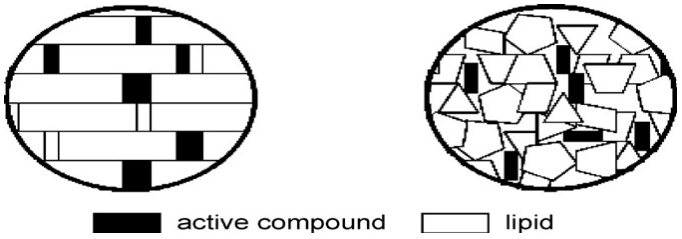

Figure 1.2: Formation of an almost perfect crystalline structure in SLN (left). Formation of a solid particle matrix of NLC (right)

Table 1.1: Lipids and emulsifiers used for preparation of solid lipid nanoparticles [6]

Lipids	Emulsifiers/Coemulsifiers
Triglycerides	Soybean lecithin
Tricaprin	(Lipoid S 75, Lipoid S 100)
Trilaurin	Egg lecithin (Lipoid E 80)
Trimyristin	Phosphatidylcholine
Tripalmitin	(Epikuron 170, Epikuron 200)
Tristearin	Poloxamer 188
Hydrogenated coco-glycerides (Softisan)	Poloxamer 182
Hard fat types	Poloxamine 908
Witepsol W 32	Tyloxapol
Witepsol H 35	Polysorbate 20
Witepsol H 42	Polysorbate 60
Witepsol E 85	Polysorbate 80
Glyceryl monostearate (Imwitor 900)	Sodium cholate
Glyceryl behenate (Compritol 888 ATO)	Sodium glycocholate
Glyceryl palmitostearate (Precirol ATO 5)	Taurocholic acid sodium salt
Cetyl palmitate	Taurodeoxycholic acid sodium salt
Stearic acid	Butanol
Palmitic acid	Butyric acid
Decanoic acid	Dioctyl sodium sulfosuccinate
Behenic acid	Monooctylphosphoric acid sodium

1.4 ADVANTAGES AND DISADVANTAGES OF THE SLN

a. Advantages of SLN

- Possibility of controlled drug release and drug targeting
- Increased drug stability
- High drug Payload
- Incorporation of lipophilic and hydrophilic drugs feasible
- No biotoxicity of the carrier
- Avoidance of organic solvents
- No problems with respect to large scale production and sterilization

b. Disadvantages of SLN

- Lipid crystallization modifications
- Drug Expulsion
- Particles aggregation could be possible [8]

1.5 MECHANISM OF DRUG PENETRATION ACROSS THE SKIN

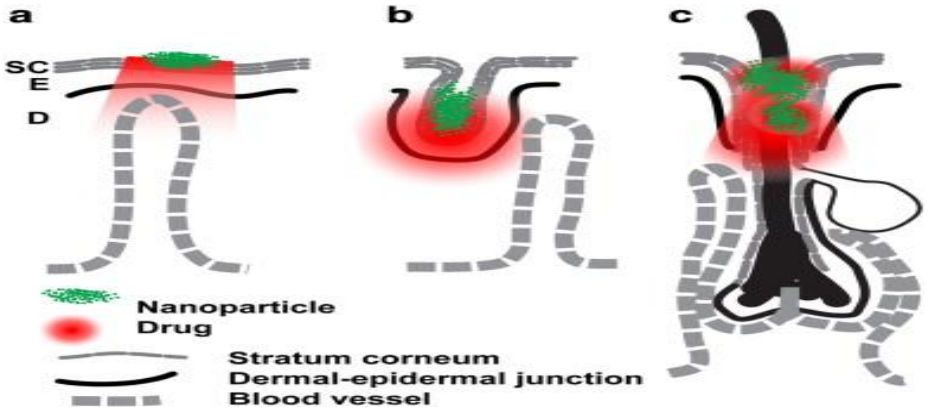

Figure 1.3: Nanoparticle or microparticle drug delivery to the skin [9] where SC indicates the Stratum Corneum, E indicates the Epidermis, and D indicates the Dermis.

1.5.1 This system is divided into three steps

1. Penetration, the entry of a substance into a particular skin layer.

2. Permeation, the penetration through one layer into another.

3. Resorption, the uptake into the vascular system.[5]

1.5.2 Mechanisms of penetration enhancement and epidermal targeting

The nanoparticles and microparticles are formed in this project where the need to describe the drug entry through these carriers to the skin. Improved dermal absorption of the API loaded to lipid carriers may result from the increased contact surface of API and corneocytes, skin occlusion, rapid and steady release, and the surfactant effects. Small particles can make close contact to the SC surface i.e. superficial junctions of the corneocytes clusters and furrows between corneocyte islands may favor accumulation for many hours allowing to the sustained release. SLN and NLC should attach as they are for longer and remain at the application site because of a pronounced adhesive effect. However, it is necessary that the adhesiveness is directly proportional to the decrease in the particle size. The dissolved and finely dispersed drug into the carrier may facilitate the dermal absorption by close contact as well as occlusive effect. SLN are the solid lipids which remains solid at room temperature, so application of a SLN or NLC dispersion or lipid particle loaded cream or gel to the skin surface induces the structural changes of particle structure. Water evaporation results in a transition of the lipid matrix to a more highly ordered structure leading to drug expulsion. Improved hydration at least temporarily opens the compact structure of the horny layer, and the permeability of the barrier increases. The solid matrix of the particles is covered by a softer shell, possibly composed of amphiphilic glycerides with unesterified hydroxyl groups, surfactants and water which facilitate the API enrichment. The close contact made by active compound either attached to the particle surface or dissolved in fluid lipid covering the surface of NLC, to epidermal lipids due to spreading of the API. Penetration by SLN is more significant by Penetration enhancers, because in general potent enhancers are also potent irritants. Examples of penetration enhancers are Ethanol, Span 80, Tween 80 and even sodium cholate. [10] Three pathways of penetration of the SC have been identified and these are transcellular, intercellular and appendageal as discussed in Fig. 1.4

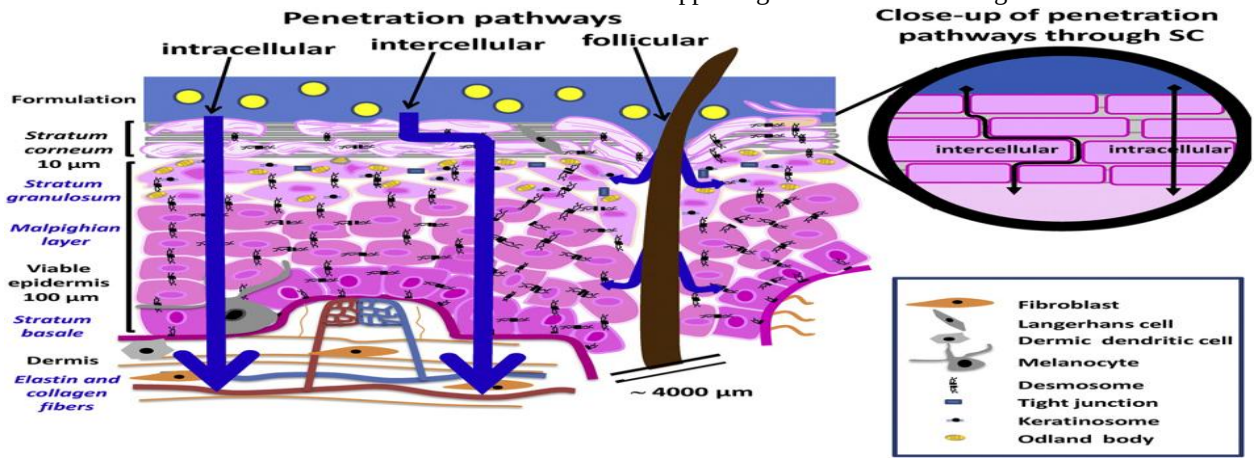

Figure 1.4: Sketch of the three penetration pathways: intracellular, intercellular and follicular. The upper right inset is a close-up of the stratum corneum showing the intracellular pathway and the tortuous intercellular pathway [5]

1.5.3.1 The Intercellular Route [5]

This route of drug absorption appears to predominate for most compounds. It has been suggested that the pharmacological agents applied diffuse through the SC in-between cells following a concentration gradient. That is to say that the drug substances move in the intercellular lipids which exist between keratinocytes in the SC. The rate at which the solute moves through the SC and the skin in this manner is indicated by the diffusion coefficient which considers factors that may hinder the diffusion of the solute such as the tortuosity of the diffusion pathway, the viscosity of the fluids the solute must diffuse through and protein binding of the solute as it moves through the skin.

1.5.3.2 The Appendageal Route

The two main appendages concerned with this type of penetration are the hair follicles and sweat glands. These openings effectively bypass the SC barrier to reach the underlying dermal structures. The role of appendages in transdermal drug penetration has been found to be controversial. Early studies using human skin suggested that a follicular or 'shunt' pathway could possibly be important immediately following topical drug application, however, because of its larger surface area, the intercellular pathway becomes dominant after application. As hair follicle density increases the follicular route of drug penetration may become more significant than it has been shown to be in human studies. In humans, the appendageal route is unlikely on account of the limited surface area available. [5]

1.5.3.3 The Intracellular Route

Although the transcellular route makes maximal use of the available surface area for absorption, it is considered to be an unlikely route of administration because of the numerous repetitive partitioning steps of the solute between the several lipophilic and hydrophilic strata in the skin. *In vivo* experiments and morphology studies show that the transcellular route is implausible and that the intercellular path is more likely. [5]

1.6 THE MAIN FACTORS RELATED WITH SLN ADMINISTRATION TO TOPICAL ROUTE

1.6.1 Method of preparation

It influences the structures of the SLN. The drug enriched shell and drug enriched core are of two types of crystallization structures. As in Fig. 1.5, the former is obtained while repartitioning of the drug while cooling. And the drug enriched core will be found in case the drug precipitates first before the lipid recrystallizes. It is obtained when dissolving a drug in the lipid melt at or close to its saturation solubility. Cooling of the nanoemulsion will lead to a super saturation of drug in the melted lipid and subsequently to the drug crystallization prior to the lipid crystallization.

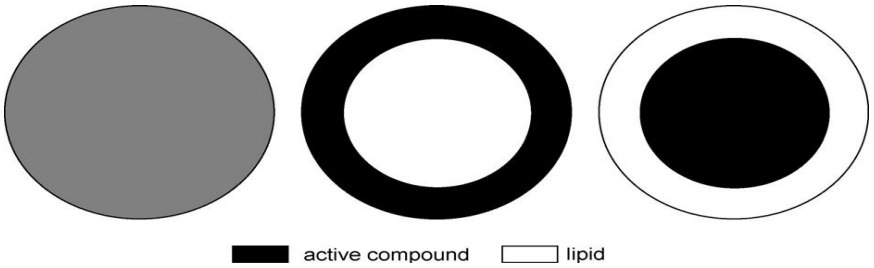

Figure 1.5: Models of incorporated actives in lipid nanoparticles, homogeneous matrix (left), active-free lipid core with active-enriched shell (middle) and active-enriched core With active-free lipid shell (right)

1.6.2 Degree of Crystallization

The polymorphic form is also a parameter to determine the drug incorporation. The SLN are produced from solid lipids only and after preparation at least a part of the particles crystallizes in a higher energy modification (alpha or beta'). During storage, these modifications can transform to the low energy, more ordered beta modification. Due to its high degree of order, the number of imperfections in the crystal lattice is reduced leading to drug expulsion. [7] The main factors to transformations are temperature and water loss in the SLN nanodispersion.

1.6.3 Adhesiveness

It is a general property of the very fine particles that means nanoparticles of different kinds. Such a lipid film formation will be able to restore a damaged protective lipid film on the skin. Such a film can have occlusive effect.

1.6.4 Occlusive effect

The occlusive effect is caused by 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 which by reducing corneocyte packing and widening of the inter-corneocytes gaps can facilitate drug partitioning into deeper skin strata. Occlusive factor generally appear strongly related to the particle size. Nanoparticles have 15-fold more occlusive than microparticles.[10] The occlusive effect of the SLN membrane was evaluated by using Cream base, SLN-containing cream base and gel formulations which were incubated at 24 h. where TEWL (Transepidermal water loss) was determined for each for the moisture content in the SLN was present. As in fig. 1.6, it has shown that, 33 % moisture was present in the skin area as compared to the 23% of formulation having SLN-Free base. [8]

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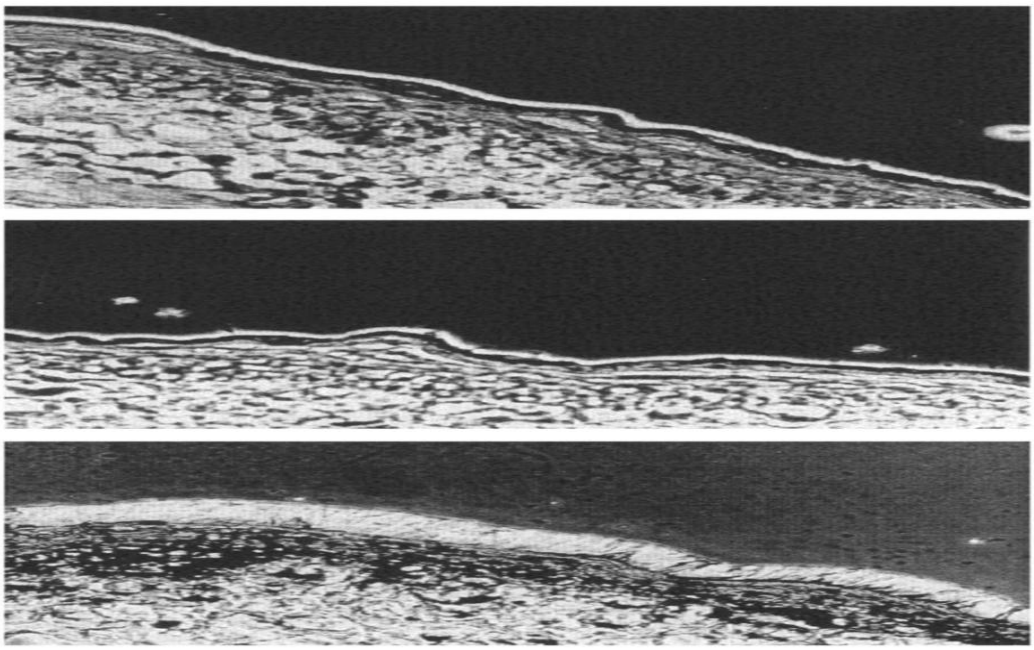

Figure 1.6: Microscopic pictures of untreated porcine skin (upper), skin treated With cream base (middle) and with SLN-containing cream base (lower)

CONCLUSION

The solid lipid nanoparticles are thus promising drug delivery carriers for drug delivery through the topical route. These are small nano-sized particles having lipophilic property. The water-insoluble drug can be penetrated through skin by solubilized in these carriers. The film forming property and close contact of the solid lipid nanoparticles to penetrate the drug through the skin helps in improving controlled release. The chemical degradation can be easily avoided due to its lipophilic property. The main factors affect drug delivery of solid lipid nanoparticles through skin are Method of preparation, degree of crystallization, adhesive effect and occlusive factor. These factors represent optimal delivery of drug in controlled manner through skin.

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