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# LIPID NANO PARTICLES FOR DERMAL DRUG DELIVERY

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## Abstract

Lipid based drug delivery systems have been widely studied and reported over the past decade and offer a useful alternative to other colloidal drug delivery systems. Skin is a popular route of drug delivery for locally and systemically acting drugs and nanoparticles are reported as a potential formulation strategy for dermal delivery. Although the skin acts as a natural physical barrier against penetration of foreign materials, including particulates, opportunities exist for the delivery of therapeutic nanoparticles, especially in diseased and damaged skin and *via* appendageal routes such as the openings of hair follicles. The extent and ability of nanoparticles to penetrate into the underlying viable tissue is still the subject of debate although recent studies have identified the follicular route as the most likely route of entry; this influences the potential applications of these dosage forms as a drug delivery strategy. This paper reviews present state of art of lipid-based nanocarriers focussing on solid lipid nanoparticles, nanostructured lipid carriers and nanoemulsions, their production methods, potential advantages and applications in dermal drug delivery.

*Keywords: Skin, skin penetration, solid lipid nanoparticles, dermal delivery, colloidal carriers, nanostructured lipid carriers, nanoemulsions, dermal applications*

## **1. INTRODUCTION**

Nanoparticulate drug delivery systems have attracted lot of attention as a consequence of their unique size-dependent properties. Among various types of nanoparticles developed for pharmaceutical applications, lipid nanoparticles are considered advantageous due to their versatility and biocompatibility. Recent advances, leading to the production of nanoparticles of uniform size and shape, offer the possibility for development of new therapeutics with potential for drug targeting, controlled and site-specific drug delivery and have resulted in a large number of studies exploring their interaction with the skin. This paper focuses on a range of lipid based nano-systems, i.e., solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions (NEs), their structure and associated features, advantages and their use in dermal drug delivery systems.

### **1.1 Skin as a target site for particle delivery**

Skin is an attractive route of delivery for local and systemic delivery of drugs and is a potential route for nanoparticles to gain entry into the body. The skin, however, affords a natural physical barrier against particle penetration, but there is the potential to deliver nanoparticles for therapeutic applications, especially *via* disruptions in the barrier afforded by hair follicles and to diseased or damaged skin.

#### **1.1.1 Skin structure**

The skin is the largest organ of the body and functions as a protective layer preventing entry of harmful xenobiotics into the body (Fig 1), however, its large surface area and ready accessibility render it an attractive route for drug delivery. The skin structure can be broadly categorized into the non-viable epidermis called stratum corneum (SC), the viable epidermis and dermis. It is the outermost SC layer that affords the barrier properties of the skin and it regulates the flux of chemicals and fluids between the external environment and the body [1,2].

#### **1.1.2 Transport through skin**

Molecules generally penetrate the SC by two separate routes [3], with hydrophilic entities following a transcellular pathway and more lipophilic solutes traversing *via* the intercellular lipids. The diffusion of drug through skin may also occur through appendages in the skin such as the hair shaft and sweat glands. These appendages are breaches in the continuity of the SC barrier, thus presenting follicular or shunt pathways for absorption. The follicular pathway has, until recently, been considered as making a negligible contribution to uptake due to the relatively small percentage of

the skin surface covered in hairs, normally around 0.1% [4]. The follicular route has gained renewed interest being reported as the predominant pathways for nanoparticle entry [5,6], but also as a route for hydrophilic drugs and potentially for larger molecules such as polar steroids that would not normally be expected to cross the skin easily [7].

## **2. LIPID DRUG DELIVERY SYSTEMS**

Lipid based drug delivery systems are an established, proven and commercially exploitable strategy for the formulation of pharmaceuticals intended for oral, topical, parenteral and pulmonary delivery. Lipid nanoparticles display interesting properties at the nanoscale level suitable for therapeutic applications and are attractive for medical purposes due to these important and unique features; these include their large surface to mass ratio, which is much larger than that of other colloidal particles and their ability to bind, adsorb or carry other compounds. Lipid drug delivery systems will perform differently depending on the interplay between the formulation characteristics and route of administration such as dermal, pulmonary and parenteral routes [8–11].

Lipid based nanocarriers possess following advantages [12,13]:

- The ability to improve stability of pharmaceuticals
- The feasibility to carry both lipophilic and hydrophilic drugs
- Manufacturing is relatively easy to scale-up and sterilize
- Most of the lipids used are biodegradable, biocompatible and non-toxic
- The ability to control and target drug release
- They are generally less expensive than polymeric/surfactant based carriers

### **2.1 Solid lipid nanoparticles**

SLNs were developed as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles for controlled drug delivery. [14]. These particles are solid, sub-micron particulate carriers ranging in size from 1 to 1000 nm. They consist of a mixture of physiological and biodegradable or biocompatible lipids, suitable for the incorporation of both lipophilic and hydrophilic drugs within a lipid matrix and are stabilized using surfactants. Generally, lipids used in preparation of SLNs are highly purified triglycerides, complex glyceride mixtures or even waxes [15,16]. There are three main models (Fig 2) for the incorporation of bioactive components into SLNs: (1) homogenous matrix model (2) bioactive-enriched shell model (3) bioactive enriched core model. The type of structure obtained depends upon the components of the formulation such as the HLB of lipids, bioactive compounds, the surfactant used and production methods employed. A homogenous matrix is usually obtained when adopting cold homogenization methods or when extremely lipophilic drugs are incorporated into SLNs using hot homogenization techniques. The drug is then released from such formulations by a dissolution-controlled mechanism. If phase separation occurs during the cooling process from the liquid oil droplets a bioactive enriched shell type may result; such formulations show a burst release of active compound. Conversely, a bioactive-enriched core may be formed when the opposite phenomenon occurs, which means the drug starts precipitating first and therefore, the shell has reduced amounts of encapsulated components. Drug release from these formulations is governed by a membrane-controlled release mechanism following Fick's law of diffusion [17].

### **2.1.1 Production method**

There are several different methods reported in literature for production of SLNs. These methods are high pressure homogenization [16,18,19], microemulsion technique [20], emulsification-solvent evaporation [16], emulsification-solvent diffusion method [21], solvent injection or solvent displacement method [22], phase inversion [23], multiple emulsion technique [24], ultrasonication [25] and membrane contractor technique [26]. High-pressure homogenization techniques have several perceived benefits over other methods, e.g. easy scale up, reduction in requirements for organic solvents and relatively short production times, thus this method is often used in many pharmaceutical applications. Both hot and cold high-pressure homogenization techniques can be used to produce lipid nanoparticles. During hot homogenization methods, the drug loaded lipid phase is melted and mixed with an aqueous emulsifier phase using a high shear process. Usually, homogenization at elevated temperatures results in smaller particle sizes due to reduced viscosity of the inner phase due to the temperatures required. However, elevated temperatures can potentially accelerate degradation of drug and/or the carrier. Cold homogenization has been developed to overcome such problems associated with hot homogenization and to address uneven drug distribution within the aqueous phase during homogenization. In

cold homogenization methods, the drug is combined with the molten lipid and rapidly cooled using dry ice or liquid nitrogen. Once solidified, the drug-/ lipid mixture can then be milled to form microparticles. The resultant microparticles are suspended in a cold surfactant solution which is homogenized at, or below, ambient temperature to produce the nanoparticles [27,28].

## 2.2 Nanostructured lipid carriers

Second generation lipid carriers, namely nanostructured lipid carrier (NLCs), were developed by Radtke and Müller (2001) to overcome some limitations associated with SLNs, such as low encapsulation efficiency and the risk of drug expulsion during storage due to an increasing purity of lipid [29]. Compared to SLNs, NLCs have a reduced water content and a higher drug loading capacity for many active compounds within the particle suspension and the potential expulsion of active compounds during storage is minimised [30,31]. For NLCs, the particles are produced using a blend of solid lipid with liquid lipid but are based on the preparation methods described for SLNs [32]. In NLCs, a major portion of the oil constituents of the O/W emulsion is replaced by a solid lipid leading to a solid particle matrix at body temperature [33,34]. To obtain NLCs, solid lipids are blended with the oily liquid lipids preferably in ratios ranging from 70:30 up to 99.9:0.1 [35].

Depending on production method and the composition of the formulations, NLCs can be further classified as follows, [17,33,36]:

A) Imperfect type NLCs: These NLCs have an imperfectly structured solid matrix. Such imperfections can be increased by using glycerides composed of different fatty acids e.g. differing in the length of C-chain or a mixture of saturated and unsaturated acids. The disordered crystal accommodates more drug molecules, either in a molecular form or as amorphous clusters of drug (fig. 3A).

B) Amorphous type NLCs: The phenomenon of crystallization can lead to expulsion of drug from the formulation. In order to reduce this, NLCs can be prepared by maintaining the polymorphicity of the lipid matrix by mixing solid lipids with specialised lipids such as hydroxyoctacosanylhydroxystearate, isopropyl palmitate or medium chain triglycerides. (fig. 3B).

C) Multiple type NLCs: These are oil-in-lipid-in-water type NLCs. The solubility of lipophilic compounds is higher in liquid lipids (oils) compared to solid lipids. Based on this principle, multiple type NLCs can be developed. In this type of NLC, a larger than normal amount of oil is combined with the solid lipids (fig. 3C). Inclusion of the oil, in excess of

its solubility, leads to phase separation, producing small, oily nano-compartments surrounded by the solid lipid matrix. This reduces drug leakage from the system and facilitates controlled release.

## **2.3 Nanoemulsions**

Nanoemulsions (NEs) are nanoscale droplets of thermodynamically stable dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules [37,38]. They are normally oil-in-water emulsions with mean droplet diameters ranging from 50 – 1000 nm. NEs differ from microemulsions such as due to their smaller droplet size; most NEs are optically transparent in contrast to microemulsions due to the droplet size being smaller than the wavelength of visible light. Microemulsions cause multiple scattering of visible light and hence have a white opaque appearance [39,40].

Nanoemulsions can be differentiated into three types based on the composition of dispersed phase and continuous phase [41]:

- Oil-in-water nanoemulsions where oil droplets are dispersed in the continuous aqueous phase
- Water-in-oil nanoemulsions where water droplets are dispersed in the continuous oil phase
- Bi-continuous nanoemulsions where microdomains of oil and water are interdispersed within the system

Nanoemulsions possess many advantages such as rapid and efficient penetration of the drug, improved solubility of lipophilic drugs and the same emulsion can carry both lipophilic and hydrophilic drugs. They are non-toxic and non-irritant, hence they can be applied easily to skin and mucous membranes and can be incorporated into a variety of formulations such as foams, creams, liquids, sprays [42,43].

### **2.3.1 Production methods**



Nanoemulsions can be most effectively produced using high-pressure equipment. The most common methods used to produce nanoemulsions are high-pressure homogenization and microfluidization. They can also be prepared using ultrasonication and emulsification [44,45].

In high-pressure homogenization methods, mixture of oil, surfactant and aqueous phase is passed through narrow gap (in the range of few microns) under high pressure (100 – 2000 bar). The fluid accelerates over short distances under very high shear stresses and the cavitation forces break apart the particles forming submicron entities. The operating pressure and number of times the coarse pre-emulsion is cycled through the microfluidizer or homogenizer will influence the particle size of the nanoemulsion produced [46,47].

### **3. NANOCARRIERS FOR DERMAL DRUG DELIVERY**

Topical delivery of compounds through the skin has been documented throughout history, but it is only since 1970's with the successful of transdermal patches, that the route has widely explored for systemic delivery of drugs. Investigating the extent and possible mechanism of nanoparticle penetration through skin is key to being able to fully exploit these carriers for therapeutic purposes. Topical application of these nanocarriers, especially lipid nanoparticles, has reported benefits for both local effects in the skin (affording the opportunity to deliver drug to the epidermis and dermis) and systemic activity, achieved by drug permeation into deeper skin layers and transdermally [48]. They can also cause formation of a film on the skin surface, thus enhancing occlusion and affecting skin permeation,

There is still much debate in the literature regarding the mechanism of penetration of nanoparticles through the skin, for example concern about how nanometer-sized particle can penetrate the SC membrane *via* a much smaller intercellular space. There is similar uncertainty regarding the predominant factors governing penetration and the underlying mechanisms involved [49]. Although there are several reports of penetration and accumulation of nanocarriers in the surface layers of the SC, such nanocarriers have shown a mixed ability to improve drug penetration deeper into skin [50]. A more promising approach for nanocarrier dermal drug delivery is follicular targeting. The shunt pathway *via* follicles is a significant route for penetration, especially for nanoparticles which can target hair follicles [51].

In the hair follicles, the follicular infundibulum effectively increases the surface area and presents as a disruption of the epidermal barrier towards the lower parts of the follicle; it additionally functions as a reservoir for drugs and carriers [52]. Follicles are deep invaginations within the skin where the SC is thinner and the vascularization is denser. There are a number of potential sites within the hair follicle for targeting for both therapeutic and cosmetic applications [53]. Additionally, drug delivery can be targeted to sebaceous gland associated with hair follicles for the therapy of acne,

androgenetic alopecia and other sebaceous gland dysfunctions. A further target site is the bulge region, located deep within the follicles and is reported to be a reservoir of keratinocyte stem cells [54]. Hence, follicular drug delivery provides a route to bypass the intact SC and drugs may reach dermis by entering the follicles and then passing through the sebaceous gland or penetrating into the epithelium of the follicular sheath [55]. It is difficult to differentially distinguish the route of entry of drugs and nanoparticles into the skin as most *in vitro* techniques use a diffusion cell model and the total amount of drug either delivered into, or through, the skin is quantified. Such techniques can be adapted to study follicular transport using an adapted stripping method [53]. Following normal tape stripping processes (normally 10-15 successive applications of an adhesive tape), to remove the SC, a cyanoacrylate glue is applied to the stripped surface and covered with a further adhesive tape layer. Once removed, this glue layer can be used to determine follicular deposition. The sectioning of skin for use in diffusion cells may cause a reduction in transport *via* the follicular route due to sectioning of elastic fibres which maintain integrity of the follicles.

In recent years, attention has been directed towards lipid-based colloidal carriers since it is obvious that these lipid carriers are often a preferred drug delivery system for dermal drug delivery [56]. There have been numerous studies and patents exploiting the topical delivery of lipid-based colloid systems, formulated into different structures for various disease treatments, and for either local or systemic delivery [57].

### **3.1 Lipid nanoparticles as a carrier in dermal applications**

A variety of lipophilic and hydrophilic drugs such as antimicrobials, antifungals and challenging compounds like proteins and peptides have been entrapped into lipid nanoparticles. Lipid nanoparticles can then be further incorporated into a cream, hydrogel or ointment to obtain semisolid formulation suitable for application to the skin.

It has been claimed that SLNs systems give improved UV absorbance, which is of great significance in the cosmetic industry. A lipophilic amine (stearylamine) was used in the SLNs formulation to improve encapsulation efficiency of tretinoin using an ion-pairing mechanism [58]. Organic solvents were avoided and the SLNs were stable for extended periods. Skin irritation, assessed using a rhino mouse model, was reduced compared to a marketed tretinoin cream. Tretinoin derivatives, isotretinoin, retinol and vitamin A palmitate have also been incorporated into SLNs for topical application. The isotretinoin loaded SLNs were relatively small, 30 – 50 nm in size, with encapsulation efficiencies of up to 99.7% depending on the concentration of surfactant used in the formulation [59]. Retinol was also incorporated into SLNs with a larger particle size of > 200 nm [60]. The skin retention of retinol in a porcine model was found to be

0.9 µg higher (over 6 h) compared to nanoemulsion control group. Vitamin A palmitate has been formulated into SLNs of 350 nm [61]. The pharmacokinetics of this formulation were determined in human cadaver skin with Keshary Chien cells. Drug release from SLNs was 67.5% after 24 h compared with 54.4% for the gel control. Lipid nanoparticles were investigated as a delivery system for prednicarbate. Santos *et al.* reported an improved extent of prednicarbate uptake using prednicarbate loaded SLNs in human skin *in vitro* [62]. There was improved uptake of the corticosteroid following application of SLNs compared to conventional corticosteroid cream or ointment. A similar strategy can also be applied to topical nanoparticles for antimicrobial delivery. Silver nanoparticles have been incorporated to wound dressings to exploit its antimicrobial activity and several commercial products are available. Safety concerns regarding the application of silver in this way have been recently outlined discussed in detail [63]. The use of other types of antimicrobial nanoparticles is less well studied and may prove a useful alternative to silver. Miconazole-containing SLNs were prepared using a hot homogenisation method and demonstrated a higher skin penetration compared to a control gel formulation in an *ex vivo* study using excised human cadaver skin [64]. Similarly econazole nitrate has been incorporated into SLNs [65]. The particles had a high encapsulation efficiency (97-102%), diameters ranging between  $140 \pm 13$  and  $154 \pm 5$  nm and demonstrated an ability to control drug release as well as increase skin penetration. NLCs containing the lipophilic antifungal agent clotrimazole were shown to have higher encapsulation efficiencies than similar SLNs due to their liquid components, but both seemed suitable for topical delivery remaining stable over extended periods [66]. Dermal absorption of cyproterone acetate, used for topical acne treatment, was incorporated into a range of different nanoparticles including SLNs, NLCs and NEs. Although activity was reduced in cell lines, skin penetration of the drug associated with SLNs was four times higher than a control cream formulation in excised human skin. A dermal targeting effect was shown, with only low levels found in the dermis, thus reducing the potential for systemic absorption and side-effects [67].

Delivery of lipid soluble bioactive compounds can be challenging, especially in aqueous based preparations. Omega-3 fatty acids, the major essential fatty acids, are susceptible to oxidative deterioration and it has been shown that encapsulation of these acids is a strategy that can be used to improve stability [68,69]. There are current challenges facing the development of carotenoids as nutraceutical compounds due to their relatively poor water solubility, high melting points and chemical instability which can be overcome by incorporating them within the oil phase in NEs [70]. It has been shown that NLCs were able to encapsulate such lipophilic drugs and improve their stability and bioavailability [71]. NLCs have major applications in cosmetic applications which require a high crystallinity of the carrier (e.g. UV protection) [72]. COX-2 selective anti-inflammatory drugs such as celecoxib and valedoxib have been incorporated into NLC-based systems. Joshi *et al.* compared an NLCs based gel of celecoxib with a micellar gel of the

same composition and measuring *in vitro* skin penetration using rat skin and the pharmacodynamic efficiency by Aerosil induced rat paw oedema. The *in vitro* permeation of celecoxib from the NLCs gel was less than the permeation from the micellar based gel, which confirms the findings about nanoparticles leading to a drug deposit in the skin resulting in sustained release. The *in vivo* comparison of the percentage edema inhibition produced by NLC and micellar gel showed a significant higher inhibition after application of the NLCs based gel up to 24 h [73]. Indomethacin, a potent non-steroidal anti-inflammatory drug, is widely used topically for the treatment of dermatitis and rheumatic diseases. Ricci *et al.* investigated the *in vitro* penetration of indomethacin from NLCs containing gel through the SC and epidermis, the *in vivo* indomethacin release by tape-stripping test and the *in vivo* anti-inflammatory activity using the UV-B induced erythema model. It was found that the anti-inflammatory effect was prolonged for indomethacin-loaded NLC gel compared to a control gel formulation [74].

Nanoemulsions have been shown to effectively deliver recombinant proteins or inactivated organisms to mucosal surfaces to produce an immune response. The first applications of this, an influenza vaccine and an HIV vaccine, are in clinical trials and further are on going for vaccines including Hepatitis B and anthrax [75–77]. *In vivo* studies have shown that a NEs incorporating clobetazol propionate for psoriasis and atopic dermatitis is safe for human use and was not irritant to the skin [78].

A variety of different animal models has been used to evaluate percutaneous delivery of molecules; these include porcine, mouse, rat and guinea pig models. To evaluate dermal absorption of a molecule, the most relevant membrane is human skin. Skin from various sources, including cosmetic surgery and amputations, has been used for the *in vitro* determination of percutaneous penetration. However, the availability of human skin can be limited and animal skin is therefore frequently used. The most appropriate model for human skin is the pig due to its histological and biochemical properties which have been shown repeatedly to be similar to human skin; thus excised porcine skin is widely accepted as an *in vitro* model suitable for passive diffusion studies [79]. Specifically, porcine ear skin shows most similarities along with a similar follicular structure with hairs and infundibula extending deep into the dermis, as in humans. As live porcine models are not a common laboratory model, rodents such as mice, rats are commonly used in *in vivo* percutaneous permeation studies. The advantages of such models are their small size, uncomplicated handling and relatively low cost [80]. A nanoemulsion formulated with eucalyptus oil, for example, has been studied for its wound healing and skin irritation activity in Wistar rats. Results indicated that the formulation was non-irritant and resulted in a faster wound contraction rate with respect to a control and a neomycin treated rat [81,82]. Thus animal models, other than porcine, can have some roles in the drug development process, e.g. for screening delivery systems and carriers only

selected data have shown a reasonable correlation with human skin. Similarly, tissue cultured human skin and equivalents generally present a lower barrier to drug uptake and so are of limited use in permeation studies [83].

## Conclusions

The exploitation of biocompatible excipients makes the application of lipid nanoparticles an attractive proposition for drug delivery. The importance of skin penetration, particularly *via* skin appendages, and more specifically the hair follicles, has opened new applications for these products with the potential to specific skin penetration pathways using suitable formulations for targeting various sites in skin. The ability to incorporate drugs into lipid nanocarriers offers the opportunity to develop new carriers for drug delivery that could be used for both passive and active drug targeting. However, there is little consistency with regard to the type of drug delivered with nanoparticles and future work needs to be carried out for better understanding of nanoparticle-SC interactions.

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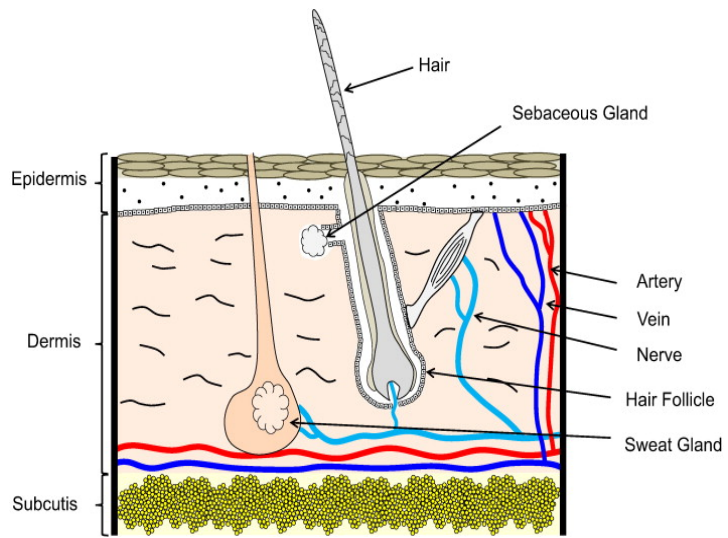


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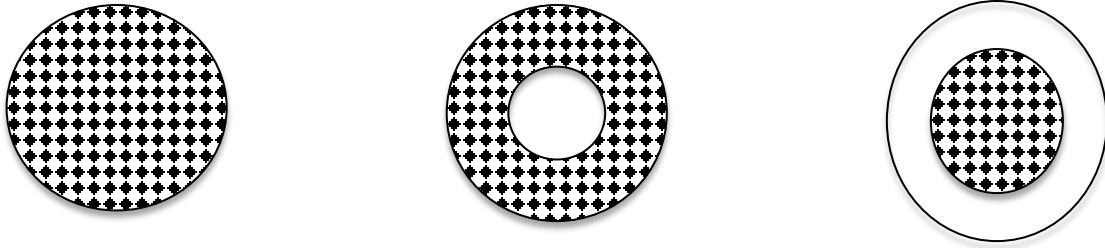
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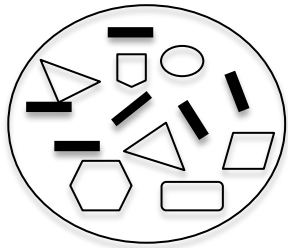
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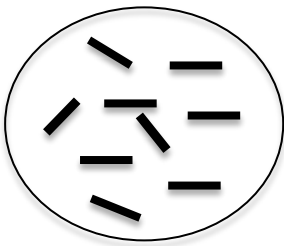
**Fig. (1)** Structure of skin [84]



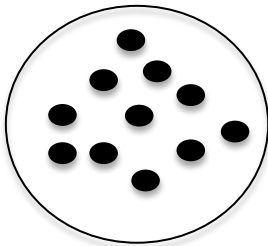
**Fig. (2)** Lipid nanoparticles models, homogenous matrix (left), bioactive enriched shell model (middle), bioactive enriched core model (right).



**Fig. 3(A)** Highly imperfect NLC



**Fig. 3(B)** Amorphous type NLC



**Fig. 3(C)** Multiple type NLC