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Improvement of Drug Penetration through the Skin by Using Nanostructured Lipid Carriers (NLC)

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ABSTRACT

At the beginning of the nineties, solid lipid nanoparticles have been introduced as a novel nanoparticulate delivery system, which is produced from solid lipids. Potential problems associated with SLN such as limited drug loading capacity and drug expulsion during storage. Adjustment of drug release profile and potential problem during storage are avoided or minimised by the new generation, the nanostructured lipid carriers (NLC) SLN are different from nanostructured lipid carriers (NLC) by the composition of solid particles matrix. the SLN and NLC both are alternative carrier system of liposome and emulsion. NLC are made up by mixing solid lipid with spatially incompatible lipids, that lead into special structures of lipid matrix. the NLC is three types (1) the imperfect structures type, (2) the structureless type, (3) the multiple types. They exhibit many features for dermal application of pharmaceutics and cosmetics. The SLN and NLC are having the property of controlled release of the active drug, drug targeting, occlusion, and associated with it penetration enhancements and increase of skin hydration. Due to the production lipid nanoparticles from physiological and/or biodegradable lipids, the carriers system exhibits an excellent tolerability. The lipid nanoparticles are "nanosafe" carrier.

INTRODUCTION

Nanostructured lipid carriers (NLCs), are lipid-based nanoparticles having diameter approximately less than 100 nm, and it's a novel drug delivery system for the delivery of lipophilic active drug with high solubility, stability, powerful skin penetration, and low skin irritation. the NLCs introduced for both pharmaceutical and cosmetic application, and more than 40 products are available on the cosmetic market. The smaller size of NLCs are closely contact with the stratum corneum and increase the amount of the active compound penetrated into the skin. The advantages of NLCs over conventional delivery systems (emulsions, liposome's, polymeric nanoparticles) and include the protection of chemically labile compounds against chemical alteration, and increases of the loading capacity of the active compounds in the particles and lower water content of the particle suspension, and minimizing the expulsion of the active compound during storage.[1,2,3]

Solid lipid nanoparticles (SLN) and nanostructured lipid carrier (NLC) these are the two main types of lipid nanoparticles. in previous two decades focused only SLN and NLC on pharmaceutical non-dermal administration routes, i.e. parental per oral, ocular and pulmonary administration. In the last 8 years, SLN and NLC have been intensively investigated for dermal application because its give many positive features after application to the skin. the small particle size (Due to the lipid matrix) and related adhesive property, the reside time of SLN and NLC on the skin is prolonged. [4,5,6,]The development of SLN overcomes many problems related to 'traditional' nanoparticles carrier technologies which limited the use (e.g. liposome's i.v, injections) or even prevented the market.(e.g. polymeric nanoparticles) the SLN can prepare from regularly accepted excipients, and these excipients are well tolerated, large scale production by high-pressure homogenisation is possible even using existing production lines for i.v. emulsion and the product are low cast. The SLN are possessed some potential limitations.[7]

- Drug expulsion during storage,
- Limitation in drug loading capacity,
- The high water content of aqueous SLN dispersion (70-95%).

Lipid nanoparticles with solid particle matrix derived from O/W emulsion by simply replacing the liquid lipid (oil) by solid lipid. that is being solid at body temperature.

The first generation solid lipid nanoparticle (SLN) was developed at the beginning of the nineties, and the second generation technology is nanostructured lipid carriers (NLC), the particles are produced by using a blend of a solid lipid with a liquid lipid, this blends also at the body temperature.

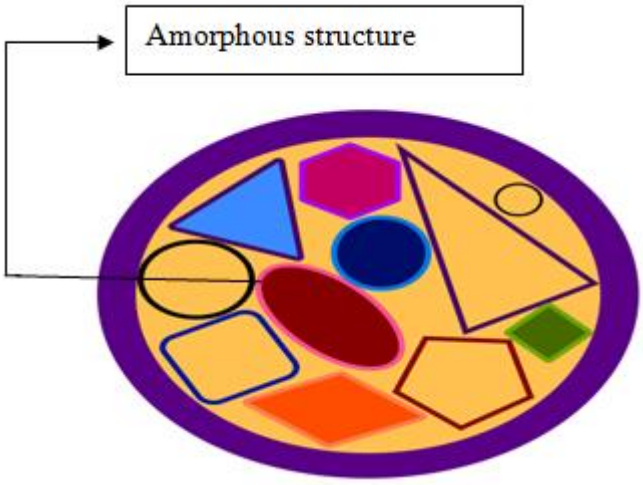


Figure 1:- Nanostructured lipid carriers (NLCs).[6,8]

Superiority of NLCs over the SLN

Lipid nanoparticles and microparticles made from the blends of solids lipids can experience the drug expulsion, especially nanoparticles, that are prepared by highly purified lipids(e.g.testearin). In production time a part of particle crystallizes in higher energy modification (α or β) through the storage, and this modification can be change into lower energy, more organised β modification, this modification is take the higher degree of alignment, and the imperfection marks small crystal lattice , this direct to drug expulsion. The main object of NLC formulation is to produce particles in which the oil is incorporated into the core of a solid lipid; that increases the higher loading capacity and controlled release of the drug. the drug dissolves in the oil and simultaneously encapsulated in the solid lipid. And they having slower polymorphic transition and low crystallinity index, membrane permeability and drug release is also slow, creaming gelling, and particle aggregation during the storage condition.

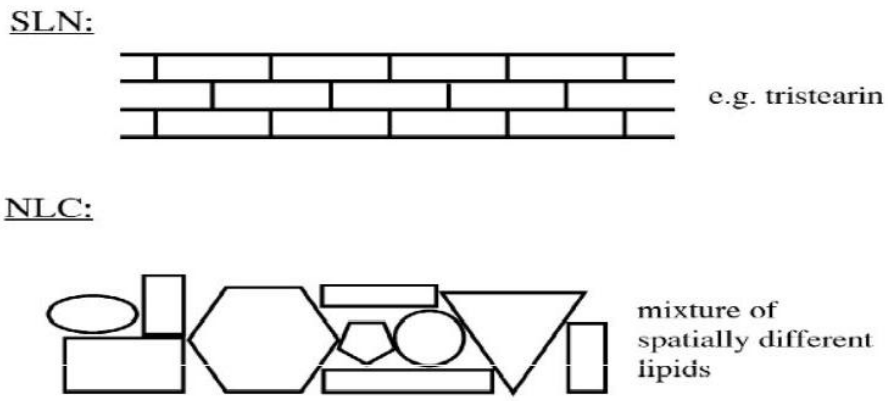


Figure 2:- **Perfect crystal in SLN comparable with a brick wall (upper) and structure with imperfections due to especially very different molecules in NLC type 1** [4,9,]

Type of nanostructured lipid carrier (NLC)

∗ **The multiple type** (O/F/W carrier) the solubility of the drug in the lipophilic phase decreases during the process of cooling after homogenization and the crystallization process during storage. Continuously minimizing the drug solubility overcome the problem drug expulsion from the lipid nanoparticles, especially when the drug concentration in the formulation is very high. When the lipids lack appropriate drug solubility, addition of high lipid to the lipophilic phase show the advantage of solid matrix, which prevented the drug leakage. while the regions (oily nano compartments) show comparatively high solubility for lipophilic drugs.[10]

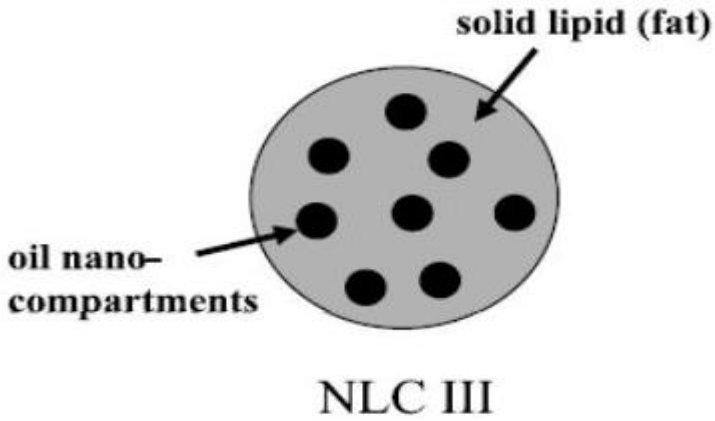


Figure 3:- Structure of multiple type of NLC (oil in solid fat in water, O/F/W). [4,10]

∗ **The imperfect type** (imperfectly structured solid matrix) this type of NLC is made by mixing of different lipids and thus imperfection in the crystal order of lipid nanoparticles are

provided. Therefor, the matrix contains imperfection to accommodate the drugs in amorphous clusters. These are produced by mixing solid lipids with small amounts of (liquid lipid) to improve the drug loading capacity.[11]

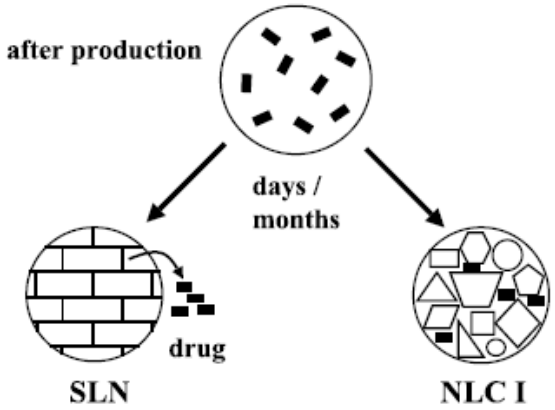


Figure 4:-Crystallisation process during storage to perfect crystal in SLN (left) and unchanged remaining NLC structure with imperfection. [4,10]

* **The amorphous type** (structureless solid amorphous matrix) this type of NLCs produced by mixing special lipids like hydroxy octyl hydroxystearate and isopropyl myristate. during storage, it crystallised in β forms that lead into drug expulsion. this is prevented by the special structure of the lipid matrix like NLC. it is solid in an amorphous, not in crystalline state.

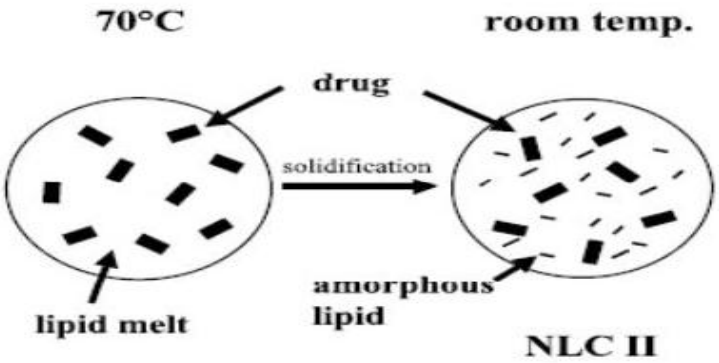


Figure 5:- Structureless type of NLC the lipid solidifies in the solid but amorphous state. [4,10]

Advantage of NLCs

- Better physical stability.
- Ease preparation and scale-up.
- Increase of skin occlusion[9,12,13,14]
- Extended release of the drug.
- High entrapment of lipophilic drugs and hydrophilic drugs.
- Improve benefit/risk ratio.[15,16]
- Increase of skin hydration and elasticity.[17]
- Small sizes of the lipid particles ensure close contact to the stratum corneum thus enhancing drug penetration into the mucosa or skin.
- Controlled particle size
- Increased dispersibility in an aqueous medium.[10]
- An advanced and efficient carrier in particular for substances.
- These carries are highly efficient systems due to their solid lipid matrices, which are also generally recognized as sale or have a regulatory accepted status.[10,18]
- The controlled and sustained release of active drug can be achieved.
- High drug loading capacity.
- Do not generate any toxic metabolites.

Limitation of NLCs

They have certain limitation like;

- Cytotoxic effects related to the nature of matrix and concentration.
- Irritative and sensitising action of some surfactants
- Lack of sufficient preclinical and clinical studies with these nanoparticles in case of bone repair.

Morphology of skin

Skin the skin is the largest organ of the body, with a total area of about 20 square feet. The skin is protecting us from micro sand the elements, and also help in regulating the body temperature, and permits the sensation of touch, heat, cold.

Human skin has selective permeability for drug, lipophilic drug can pass through the skin but the drugs which are hydrophilic in nature cannot pass through the skin. Water soluble drug show either very less or no permeation. To improve the permeation of drug through the skin various mechanisms have been investigated, including the use of chemical or physical enhancers such as iontophoresis or sonophoresis. Permeability enhancer increases the permeability of the skin so that the drug can cross the through the skin easily.

The skin is composed of two primary layers:

- The dermis, which serves as a location for the appendages of skin
- The epidermis, which is provides waterproofing and as a barrier to infection. the epidermis can be further subdivided into following strata or layers:

- ❖ cornified layer (stratum corneum)
- ❖ translucent layer (stratum granulosum)
- ❖ spinous layer (stratum spinosum)
- ❖ germinal layer (stratum basal)
- ❖ stratum lucidum (only in palms and soles)

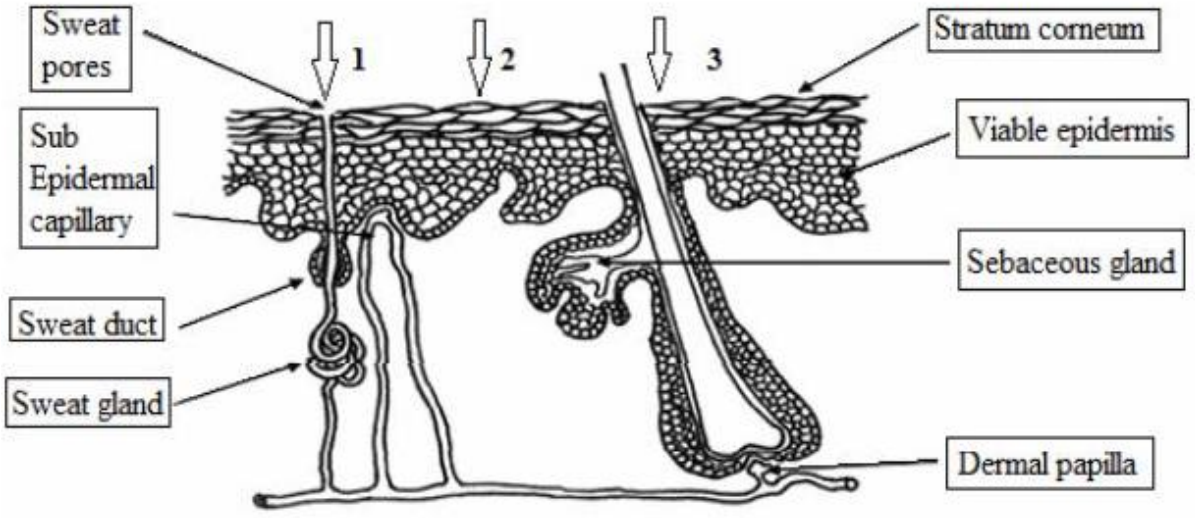


Figure 6:- Simplified representation of skin showing routes of penetration Traditionally it was thought that hydrophilic chemicals diffuse within the aqueous regions near the outer surface of intracellular keratin filaments (intracellular or transcellular route) whilst

lipophilic chemicals diffuse through the lipid matrix between the filaments (intercellular route). [4,19]

Stratum corneum (barrier and reservoir function)

It is composed of 10-30 layer of polyhedral a nucleated corneocytes, with the palms and soles having the most layer. Corneocytes are surrounded by a protein envelope, filled with water-retaining keratin proteins, attached through corneodesmosome and surrounded in the extracellular space by stacked layer of lipid. The stratum corneum layer plays the barrier function of topical/ Transdermal drug delivery. Thus through hair follicles compounds reaching the outermost part of the skin to the blood vessels, such as predominantly penetrate and permits the skin by passing the horny layer, especially using the tortuous intracellular pathway B/W the corneocytes.[20,21] There for skin varies with the physicochemical nature of the compound, and the anatomical region of the application of the drug. drug, as well as other xinobiotics, are well absorbed from the forehead, less so from postauricular spaces, even belly and arm and least from palms and soles. [22,23,24]

To be well-absorbed substance should have a molecular mass below 0.6 kDa, adequacy solubility with oil and water, and having high partition coefficients. [25, 26-29]

The highly lipophilic compound can penetrate via a hair follicle. follicular uptake may be most relevant with rigid API crystalline particles and particulates carrier with a size of 3- 10µm. Other than with horny layer, micrometer size does not exclude penetration into follicular orifices. [21, 30-35]

Besides the stratum corneum acting as a permeation barrier, the horny layer also acts as a reservoir for topically applied substances. For example four days after the application of glucocorticoids under occlusion, vasoconstriction could be re-induced by renewed occlusion of the treatment area. [36]

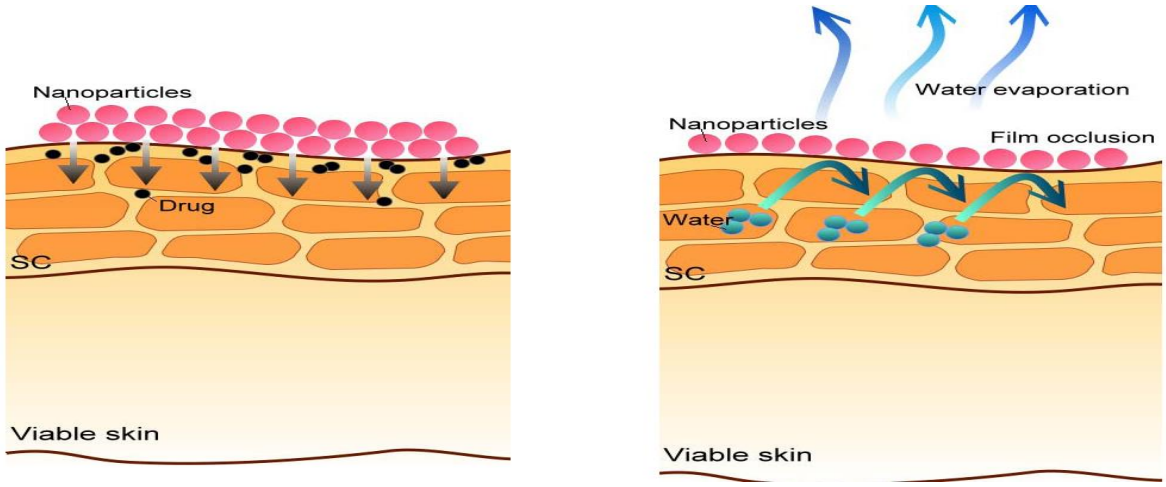
Mechanism of drug penetration (NLCs)

The API is contacted with the skin surface, and penetrate by the three potential pathways, such as sweat ducts, hair follicles and sebaceous gland (collectively called the shunt or appendageal route.) or directly across the stratum corneum.[4]

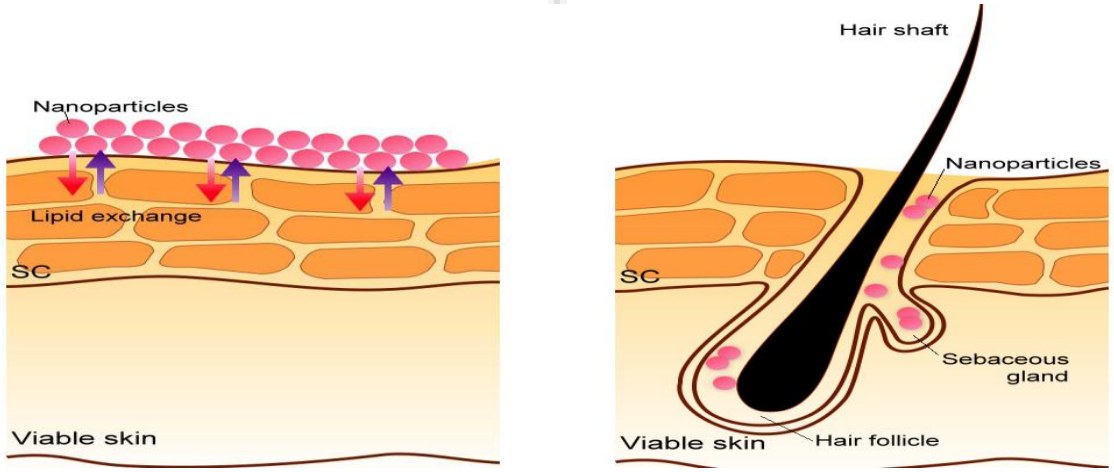
The molecules have adequate solubility in water and oil, with high oil/water partition coefficients. A molecular weight less than 0.6 kDa may penetrate the skin. Therefore, topical administration is limited to hydrophobic and low-molecular weight drugs. Because most drugs are hydrophilic, have low oil/water partition coefficients, high molecular weights, and ionic characters. They do not easily cross the stratum corneum.

The bioavailability of drugs permeating the skin can be increased by using lipid nanoparticle because of the small particulate size having close contact to stratum corneum. Nanosized particles can make close contact with superficial junctions of SC and furrows between corneocytes islands, allowing superficial spreading of the API. Following the evaporation of water from the nanosystems after applying the surface of skin, particles form an adhesive layer occluding the skin. Hydration of stratum corneum thus enhances to reduce corneocyte packing and width inter corneocytes gaps, and also influences partitioning of the drug into stratum corneum. Above the 100 nm particle size of lipid nanoparticle are not considered to permeate the stratum corneum because of their dimensions and rigidity. Since epidermal lipids are rich in stratum corneum, lipid nanoparticles attaching with skin surface would allow lipid exchange between stratum corneum and the nanocarriers. Lipid nanoparticles have the potential to deliver drugs via the follicles. Furthermore, each follicle is associated with sebaceous glands, which secrete the sebum, creating an environment enriched in lipids. This environment is beneficial for trapping of lipid nanoparticles. Sebum is a mixture of triglycerides, squalene, and waxes. Some glyceride lipids present in NLCs may accelerate the entrance into the follicles/sebaceous glands.[10,37,38,39.40.41,42]

The possible mechanisms involved in skin permeation enhancement by NLCs are depicted in Fig.**7.**



1. Close contact to skin surface. **2. Skin hydration by particle occlusion.**



3. Lipid exchange b/w SC & NLCs **4. Entrain into follicles & sebaceous gland**

Figure 7:- Possible mechanisms for skin permeation enhancement of drugs or active ingredients from nanostructured lipid carriers (NLCs).[43]

Almost greater than 80% of people suffer from acne vulgaris during their lives. This is the most common disorder of the human skin. Cyproterone acetate reduces the sebum secretion rate and the acne lesion count. Nanoparticles may carry the drug into the follicles for the success of anti-acne therapy. Incorporation of cyproterone and acitretin into NLCs results in a 2~3-fold increase in drug absorption via excised human skin. Acitretin is loaded in NLCs used as in healing psoriasis. The NLCs are incorporated in Carbopol 934 hydrogel base to detect *in vitro* skin deposition. Significantly higher deposition is found in human cadaver skin from NLC's gel

(81%) as compared to plain gel (47%). A clinical study in humans demonstrates significant improvement in therapeutic response and reduction of local adverse effect with acitretin loaded NLCs. [43,44,45,46]

Aceclofenac is a potent analgesic, antipyretic and anti-inflammatory agent has been approved for the treatment of various kinds of pain, rheumatoid and osteoarthritis arthritis. An arthritic condition required a controlled release drug delivery system for a long period, so that can achieve the goals of the treatment like reduction of the pain, inflammation, and slowing the disease progression and prevention of adverse reaction. The requirement for designing of a topical drug delivery system of Aceclofenac, which could not only increase the presence of the drug locally and for a prolonged period. it also reduces the risk of systemic toxicity. NLC exhibited controlled release behaviour for various active ingredients such as ascorbyl palmitate, clotrimazole, and other antifungal agents. As an alternative route for aceclofenac, transdermal administration eliminates these systemic side effects, which also offer many advantages, such as patient compliance and possibility of continuous and controlled drug absorption. [4,47,48]

Method of improvement of drug penetration

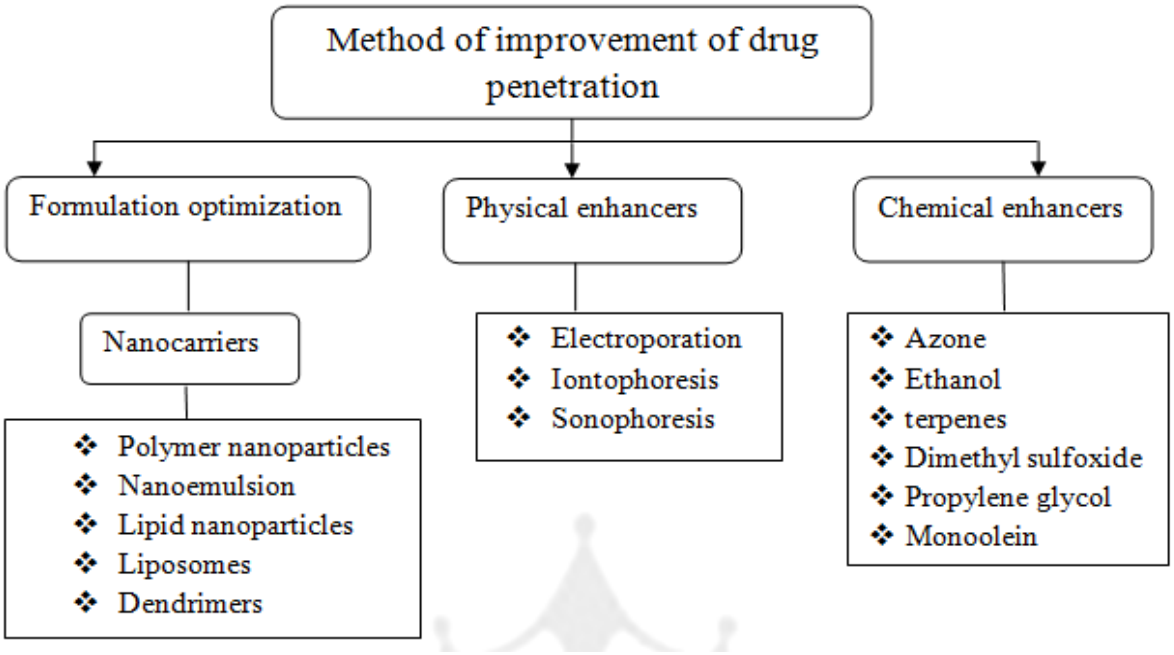


Figure 8:- Method of improvement of drug penetration through the skin and example of each method.[49]

Topical benefit of NLCs

The increase of skin hydration and elasticity The reduction of transepidermal water loss (TEWL) caused by occlusion, that enhance skin hydration after dermal application of NLC, SLN or formulations containing them. An *in vivo* study showed that the SLN containing o/w cream enhances the skin hydration significantly more than the conventional o/w cream. The skin hydration effect after repetitive application of an o/w cream containing SLN and a conventional o/w cream was investigated for 28 days.[50] A significant higher increase in skin hydration was found by Muller *et al*. for an NLC containing cream compared to conventional cream.[4,51]

The increase of skin occlusion The lipid film formation on the top of the skin and the subsequent occlusion effect was reported for lipid nanoparticles. Using very small lipid particles, that produced highly crystalline and low melting point lipids, the more occlusion will be reached. Particles size smaller than 400 nm containing at approximate 35% lipid of high crystallinity have been most effective. Souto *et al*. found a higher occlusive factor for SLN in comparison to NLC of the same lipid content. Comparing NLC with different oil content showed that an increase in oil content leads to a decrease of the occlusive factor.[50,52,53,54,55]

Enhancement of skin permeation and drug targeting The stratum corneum in healthy skin has typically a water content of 20% and provides relatively an effective barrier against percutaneous absorption of exogenous substances. Skin hydration after applying SLN or NLC leading to a reduction of corneocytes packing and an increase in the size of the corneocytes pore. This will facilitate the percutaneous absorption and drug penetration to the deeper skin layers. [16]

An increase of skin penetration was reported for coenzyme Q 10 (Q10)-loaded SLN compared to Q10 in isopropanol and liquid paraffin. The cumulus amount of Q10 were determined to perform a tape stripping test. After five strips the cumulative amount of Q10 was 1%, 28% and 53% of the applied amount from the liquid paraffin, the isopropanol, and the NLC formulation, respectively. Jenning *et al.* showed that enhanced penetration of retinol with epidermal targeting of this active could be achieved by applying retinol-loaded NLC. [56,57]

Improve benefit/risk ratio Skin atrophy and systemic side effect occurred after applying conventional Prednicarbate cream could be avoided when this drug was formulated as lipid

nanoparticles. Predinicarbate uptake was enhanced and it was accumulated in the epidermis with a low concentration in the dermis. [58,59]

In another study Joshi *et al*. compared a valdecoxib loaded NLC Carbopol gel with a valdecoxib market product. The NLC containing gel showed no skin irritation while the market gel showed slight irritation after 48 hrs. Moreover, the NLC based gel showed prolonged activity up to 24 hrs while the activity of the market gel was shorter. This indicates a better skin tolerability and a longer activity of the NLC formulation compared to the marketed formulation.[60]

Tretinoin loaded-SLN formulation was studied by Shah *et al.*, concerning skin irritation. One of the major disadvantages associated with the topical application of tretinoin is the local skin irritation such as peeling, erythema, burning and as well as increased sensitivity to sunlight. In the *in vitro* permeation studies through rat skin, they found that SLN based tretinoin gel has a permeation profile comparable to that of the market tretinoin cream. But on the other hand, Draize patch test showed that SLN based tretinoin gel resulted in remarkably less erythremia episodes compared to the currently marketed tretinoin cream and hence, a better benefit/risk ratio is expected for the formulations containing tretinoin-loaded SLN. Conclusively, applying SLN or NLC can enhance skin penetration of incorporated actives, promote the epidermal targeting and minimize the systemic side effects and improve the benefit/risk ratio.[61]

Enhancement of chemical stability of chemically labile compound Enhancement of chemical stability after incorporation into lipid nanocarriers was proven for many cosmetic actives, e.g. coenzyme Q 10, ascorbyl palmitate, and retinol (vitamin A).[56,62,63]

CONCLUSION

SLN and NLC are well-tolerated carrier system for the dermal application. Many features of SLN and NLC that are advantageous for dermal application of cosmetics and pharmaceutical products have been reported, e.g. occlusive properties, increase in skin hydration, modified release, increasing in skin penetration associated with a targeting effect and avoiding the systemic uptake. the lipid carriers have bright future, because of their intrinsic property to improve the bioavailability of lipophilic drugs with low aqueous solubility.

It could be shown various advantages for many drugs that's are topical formulation containing lipid nanoparticles can enhancing the penetration into the skin increasing treatment efficiency, target the epidermis, reduce the systemic side effect, furthermore an increased activity, as well as prolonged activity, was reported while the benefit/risk ratio increases for many drug. Due to the superior performance of lipid nanoparticles containing topical formulation compared to the market formulation. the market introduction of pharmaceutical topical formulation is expected in the near futures.

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