Nano Lipid Carrier System in Cosmetic Dermal Preparation: A Review

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Abstract

Since the beginning of the 1990s the nano-lipid carriers (NLCs) have been attracting a growing interest from the pharmaceutical technology research groups worldwide. NLCs appeared as consumer products first on the cosmetic market. The article gives an overview of the cosmetic benefits including enhancement of chemical stability of actives, film formation, controlled occlusion, skin hydration, skin bioavailability, and physical stability of the lipid nanoparticles. Solid-lipid nanoparticle as topical formulations. List of the cosmetic products currently available in the market, and bioequivalence protocol, excipients, improvement of the benefit/risk ratio of the topical therapy is shown. Lipid based drug delivery systems are nowadays popular as they are expected to be the promising carriers because of their potential to increase solubility and improve bioavailability of poorly water soluble and/or lipophilic drugs.

Key words: Cosmetics, Dermal, Nano lipid

Introduction

Pharmaceutical breakthrough new technologies have leads to find numerous new mighty therapeutic compounds. To assure progress in drug therapy, the development of new drugs merely is not sufficient. Poor water solubility and insufficient bioavailability of the new drug substances are very extensive issues encountered. Thus, there is an expanding need to develop a pharmaceutical carrier scheme that overcomes these matters, such a carrier should have an adequate pharmaceutical loading capability, free from cytotoxicity and the possibility of possessing pharmaceutical targeting and controlled release characteristics. The system should provide chemical steadiness to incorporate pharmaceuticals. Lipid nanoparticle different categories

A wide range of nano-lipid carrier (NLC) can be used for topical application of drug. To illustrate, several problems have been reported with the conventional topical preparations, e.g., low uptake due to the barrier function of the stratum corneum and unwanted absorption to the systemic circulation.

The literature review provides several systems that can deliver an active pharmaceutical ingredients across the skin presenting advantages in systemic treatment with minimal side effects, the absence of first-pass metabolism, and in topical treatment allowing targetingspecificskinappendages[2]. Among the carriers, solid-lipid nanoparticle (SLN) and NLC have emerged as novel systems composed of physiological lipid materials suitable for topical, dermal, and transdermal administrations. Many features, these carrier systems exhibit suggest for dermal application including cosmetics and pharmaceuticals.

NLCs are the new generation of lipid nanoparticles, attracting major attention as novel colloidal drug carriers for topical use. NLC has been developed to overwhelm the drawbacks affiliated with SLN.[3] SLN is produced by replacing the oil of an o/w emulsion by a solid lipid or a blend of solid lipid, i.e., the lipid particle matrix being solid at both room and body temperature. While NLC consists of a mixture of specially blended solid lipid (long chain) with liquid lipid (short chain), preferably in a ratio of 70:30 up to a ratio of 99.9:0.1. The resulting matrix of the lipid particle shows a melting point depression compared to the original solid lipid, however, the matrix remains solid at body temperature. However, some limitation of the SLN system regarding drug expulsion during storage.

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NOVEL GENERATION OF FLUIDIDNANOCARRIER
Solid lipid nanoparticles (SLN) were developed as an alternative to the existing traditional carriers, such as emulsions, liposomes, and polymeric nanoparticles. Solid lipid nanoparticles (SLN) are prepared either with physiological lipids or lipid molecules with an history of safe use in human medicine, which attract increasing attention as colloidal drug carriers. Under optimized conditions they can be produced to incorporate lipophilic or hydrophilic drugs and seem to fulfill the requirements for an optimum particulate carrier system. Advantages of SLN are the use of physiological lipids, the avoidance of organic solvents, a potential wide application spectrum (dermal, per os, intravenous) and the high pressure homogenization as an established production method. Additionally, improved bioavailability, protection of sensitive drug molecules from the outer environment (water, light) and even controlled release characteristics were claimed by incorporation of poorly water soluble drugs in the solid lipid matrix.

Nanostructured lipid carriers (NLC)
A new generation of nanostructured lipid carriers (NLCs) consisting of a lipid matrix with a special nanostructure has been developed. This nanostructure improves drug loading and firmly incorporates the drug dispersions with solid contents from 30–80%. Carrier system. However, the pressure homogenization and the process can be modified to yield lipid particle NLC system minimizes or avoids some potential problems associated with SLN. The review by Mehnert and Mader14 highlights these aspects:
1. Pay-load for a number of drugs too low
2. Drug expulsion during storage
3. High water content of SLN dispersion.

Lipid drug conjugates (LDC) nanoparticle
A major problem of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. Only highly potent low doses of hydrophilic drugs may be suitably incorporated in the solid lipid matrix. In order to overcome this limitation, so called LDC nanoparticles with drug loading capacities of up to 33% have been developed. An insoluble drug-lipid conjugate bulk is first prepared either by salt formation (e.g. with a fatty acid) or by covalent linking (e.g. to ester or ethers). The obtained LDC is then processed with an aqueous surfactant solution (such as Tween) to a nanoparticle formulation

n using high pressure homogenization (HPH). Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections.

Drug incorporation model of NLC
SLN modified by incorporation of liquid lipid into the solid lipid has been proposed to NLC to overcome the some limitation of old generation SLN. There are three types:

Type I (highly imperfect matrix) In Type I NLC, low liquid lipid (oil) concentration is used compared to solid lipid. Solid lipid and oil are blended to o/w emulsion that when cooled from molten state to room temperature, forms solid particle, due to crystallization process, leads to highly disordered, imperfect lipoid matrix offering space for drug molecules and amorphous structure of drug.

Type II multiple types In Type II NLC, there is a high oil concentration. During crystallization process, phase separation of the two lipids occurs. At certain temperature, they have miscibility gap leading to precipitation of tiny oily nano-compartment. When lipids lack drug solubilities, the addition of higher amount of liquid lipid to the lipophilic phase display the advantages of the solid matrix which prevented drug leakages while liquid lipid shows high solubility for lipophilic drug.

Type III amorphous type
In this type of NLC, by controlled mixture of lipids, particles were created which were solid, not crystalline but in an amorphous state. This amorphous state needs to be preserved.

INTENTION OF TOPICAL PREPARATION
To formulate an effective and efficient topical preparation, i.e., directly concerned with the site of action and the desired effect of the preparation, this preparation may be used for:

Transdermal water loss (TEWL)
Bioactives penetration into the stratum corneum can be enhanced by occlusion caused by the product, which enhances hydration of the stratum corneum due to the inhibition of water evaporation. Application of NLCs on the skin helped to reduce water loss from the skin when compared to the untreated control. This could be due to the small size of particles in NLCs having larger surface area, which give greater adhesive properties. They form a uniform compact layer on the skin surface, thus preventing water evaporation from the skin.

Increase of skin occlusion
The occlusion effect was reported for lipid nanoparticles. By using very small lipid particles,
which are produced from highly crystalline and low melting point lipids, the highest occlusion will be reached. Particles smaller than 400 nm containing at least 35% lipid of high crystallinity have been most effective. Comparing NLC with different oil contents showed that an increase in oil content leads to a decrease of the occlusive factor.(8, 9)

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 leads to a reduction of corneocytes packing and an increase in the size of the corneocytes gaps. This will facilitate the percutaneous absorption and drug penetration to the deeper skin layers.(10)

Enhancement of ultraviolet (UV) blocking activity
Some side effects of organic UV blockers were reported due to the penetration of these compounds into the skin causing skin irritation and allergic reaction. This penetration can be reduced by incorporating these compounds in lipid nanoparticles; furthermore, a significant increase in sun protection factor (SPF) up to about 50 was reported after the encapsulation of titanium dioxide into NLC. Encapsulation of inorganic sunscreens into NLC is, therefore, a promising approach to obtain well tolerable sunscreens with high SPF.(11)

IMPROVE BENEFITS/SKIN RATIO
Skin atrophy and systemic side effect occurred after applying conventional prednicarbacre cream could be avoided when this drug was formulated as SLN. Prednicarbacre uptake was enhanced and it was accumulated in the epidermis with a low concentration in the dermis.

Methods of preparation for SLN and NLC(12,13)
1. Homogenization method
   • Hot homogenization
   • Cold homogenization.
2. Solvent evaporation method
3. Solvent emulsification-diffusion method
4. Microemulsion-based method
5. Supercritical fluid method
6. Spray drying method
7. Double emulsion method
8. Precipitation technique
9. Film-ultrasound dispersion
10. High-speed homogenization followed by ultrasonication

TECHNIQUES FOR SLN PRODUCTION
General ingredients and the emulsifiers The matrixes of SLN are the natural or the synthetic lipids which can be degraded, including triglyceride (tri-stearic acid, tri-palmitic acid, tri-lauric acid etc. long-chain fatty acid), steroid (e.g. cholesterol) waxes (e.g., microcrystal paraffin wax, whale ester wax). The choice of the emulsifiers depends on the administration of the drug, to the parenteral system, there are limits to choose the emulsifiers(16) including the phospholipids [e. g., soybean phospholipids(95), lecithin(epikuron L75, LS loo), yolk phospholipids (L E80 ) lecithin(epikuron –oo)], nonionic wetting agent (e. g., poloxamer 188, 182, 407, 9081, choleolate (e. g., sodium cholate) lecithin(epikuron –oo)], nonionic wetting agent (e. g., poloxamer 188, 182, 407, 9081, choleolate (e. g., sodium cholate, sodium glycocholate, sodium taurocholate, deoxy-sodium taurocholate 1 short-chain spirits (e. g., butanol, butanonic acid 1). Amphotericity materials (e.g., ionic and nonionic type) can stabilize the dispersion of SLN, on the surface of SLN, hydrophobic parts stretch to the core, hydrophilic parts stretch to the disperse medium, so drug with low water-solubility can be entrapped in the SLN to form the colloidal drug system.(51, 52, 53, 54)

High pressure homogenization
HPH is a suitable method for the preparation of SLN, NLC and LDC and can be performed at elevated temperature (hot HPH technique) or at or below room temperature (cold HPH technique)

Film ultrasound dispersion
The term lipid and the drug were put into suitable organic solutions, decompression, rotation and evaporation theorganic 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. Wang et al use the soybean phospholipids as carrier and the film-ultrasound dispersion method to prepare the Olea nune solid lipid nanoparticles (OA-SLN)

SLNpreparedbysolventemulsification/evaporation
For the production of nanoparticle dispersions by precipitation in o/w emulsions24 the lipophilic material is dissolved in water-immiscible organic solvent (cy clohexane) that is emulsified in an aqueous phase. Upon evaporation of solvent nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The mean diameter of the obtained particles was 25 nm with cholesterol acetate as model drug and lecithin/sodium glycocholate blend as emulsifier. The reproducibility of the result was confirmed by Siekmann and Westesen, who produced the cholost er acetate nanoparticles of mean size 29 nm25.

Modulation of drug release
The common principles of drug release from lipid nanoparticles can be explained below: drug release is inversely proportional to the partition coefficient of the drug. Surface area increases due to smaller particle size in nanometer range which results in higher drug release. Slow release of the drug could be accomplished when the drug is equally dispersed in the lipid matrix.

Drug release from lipid particles occurs by diffusion and simultaneously by lipid particle degradation in the body. In some cases, it might be desirable to have a controlled fast release going beyond diffusion and degradation. Ideally, this release should be triggered by an impulse when the particles are administered. NLCs accommodate the drug because of their highly unordered lipid structures. By applying the trigger impulse to the matrix to convert into a more ordered structure, such a desired burst drug release can be initiated. NLCs of certain structures can be triggered this way for example, when applying the particles to the skin incorporated in cream. Increase in temperature and water evaporation leads to an increase in drug release rate [Figure 1] (14,15) and some of the polymers used in topical are show in Table 4

![Diagram of NLC dispersion](image)

**Figure 2:** Aggregation process in low concentrated dispersions (upper) and pearl-like network in nano-lipid carriers dispersions with stabilizing effect

**Characterization of NLC dispersion**
- Particle size
- Zeta potential
- Scanning electron microscope
- Determined % drug entrapment efficiency
  - \( \% \text{ EE} = \frac{W_a - W_s}{W_a} \times 100 \)
  Where, \( EE \) is entrapment efficiency, \( W_a \) stands for the mass of drug added to the formulation and \( W_s \) is the analyzed weight of the supernatant.
- Differential scanning calorimetry.

**Characterization of topical[42-44]**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion</td>
<td>Franz diffusion cell</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Brookfield viscometer</td>
</tr>
<tr>
<td>Refractive index</td>
<td>Abbe’s refractometer</td>
</tr>
<tr>
<td>Spreadibility</td>
<td>Glass plate method</td>
</tr>
<tr>
<td>pH</td>
<td>Digital pH meter</td>
</tr>
</tbody>
</table>

**REGULATORY CONSIDERATION OF TOPICAL**

**Bioavailability and bioequivalence issues**
The issues of bioavailability and bioequivalence were given considerable, since the target organ for topical products is skin, it seems logical that determining drug concentrations in the skin layers should provide an assessment of topical bioavailability. More work in this area is needed to establish procedures for assessing bioavailability of topical dermatological products. Using the skin stripping technique, only stratum corneum is readily accessible and the deeper tissues. At present, there are no accepted non-clinical models or approaches to predict or determine the bioavailability
and bioequivalence of dermatological drugs. Consequently, bioequivalence assessment of test and reference product is based on studies with clinical end points or pharmacodynamics measurements.

Quality control issues
At present, no recognized quality control procedure is available for assessing batch-to-batch uniformity of dermatological products in terms of drug release. A simple procedure to determine the drug release rate from the cream formulations using commercially available diffusion cell and the synthetic membrane has been suggested as a means of accomplishing this, but it is clear that this approach needs to be carefully validated before it can be recommended and widely implemented. Since drug must first be released from the formulation and then permeate through the stratum corneum for therapeutic effect, it may be appropriate to use drug release properties employing synthetic membrane techniques as a quality control test to ensure batch-to-batch uniformity. The quality control test should be able to detect formulation or process factors which may affect the bioavailability and bioequivalence of the drug product.[45]

STUDIES OF TOPICAL BIOEQUIVALENCE

In vitro release testing (IVRT)[48,49]
IVRT utilizes widely accepted Franz diffusion cells to estimate rate of drug release from drug products. It involves the application of a drug product onto a membrane (synthetic membrane, excised animal skin, or excised human skin) that separates the donor and receiver chambers. The receiver chamber simulates sink conditions in vivo. The rate of delivery obtained from these studies is assumed to be similar to the in vivo situation. The method has been widely employed in discovery research for screening formulations and understanding mechanism of cutaneous drug transport.

Tape stripping (TS)
TS provides information on drug uptake, apparent steady-state levels, and drug elimination from the stratum corneum based on a stratum corneum concentration time curve (FDA’s Draft Guidance, 1998). This method is also known as the dermatopharmacokinetic approach similar to blood, plasma, and urine analysis for drug concentrations as a function of time.

Microdialysis (MD)
MD is a continuous sampling technique in which the molecule of interest is collected from the target tissue; thus providing insight into the time course of drug action or biochemical monitoring of the tissue. The technique can be imagined as an artificial capillary, in which a hollow semipermeable probe is carefully inserted into the site of interest: Brain, muscle, eye, and skin. Therefore, it provides valuable information of unbound drug concentration or biomarkers at the site closer to the pharmacological action compared to the conventional plasma/blood drug concentration versus time.[50]

TEWL
TEWL measurements (the rate at which water vapor is lost from the body through the skin) are of great importance in evaluating barrier functionality. Often normal rates of TEWL are compromised due to injury, infection and/or severe damage as in the case of burns. Damage to the stratum corneum and superficial skin layers not only results in physical vulnerability but also results in an excess rate of water loss. TEWL is also affected by variations in sweat gland activity, temperature, and metabolism. Therefore, TEWL becomes a significant factor in dehydration associated with several major disease states. Some Cosmetic products containing lipid nanoparticles are currently available in the market are shown in table1

Table1: Cosmetic products containing lipid nanoparticles are currently available in the market [38, 39]

<table>
<thead>
<tr>
<th>Product name</th>
<th>Active ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nano-lipid restore CLR</td>
<td>Black currant seed oil containing 3 and 6 unsaturated fatty acids</td>
</tr>
<tr>
<td>Nano-lipid basic CLR</td>
<td>Caprylic/CT</td>
</tr>
<tr>
<td>NLC deep effect eye serum</td>
<td>Coenzyme Q10, highly active oligo saccharides</td>
</tr>
<tr>
<td>Extra moist softener</td>
<td>Coenzyme Q10, 3 und 6 unsaturated fatty acids</td>
</tr>
<tr>
<td>Olivenöl anti-falten</td>
<td>O. europaea oil, panthenol, acacia senegal, tocopherylacetate</td>
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Conclusion
Lipid based nanocarriers have the greater importance in the developing field of nanotechnology with several advantages apart from various carriers. Lipid based carriers are a promising nanoscaler delivery system for the pharmaceutical industry due to the fact that: • Large scale production possible, no organic solvents needed High concentrations of functional compounds can be achieved Lyophilization possible Spray drying for lipids with T > 70°C to yield powders. The concept of surface modification is further increasing the importance of SLN and NLC among traditional
colloidal drug carrier system. SLN and NLC delivery are promising candidates that will enable efficient and targeted delivery of novel drug compound. Lipid carriers have bright future, because of their intrinsic property to improve the bioavailability of lipophilic drugs with low aqueous solubility. SLN and NLC offer an economical and patient-friendly device for administration of drugs by topical routes.

References

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