

Nano Structured lipid carriers :A Novel Topical drug delivery system

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Abstract: Topical drug application has been introduced since long time to achieve several purposes on different levels (skin surface, epidermis, dermis and hypodermis). However, several problems have been reported with the conventional topical preparations e.g. low uptake due to the barrier function of the stratum corneum and absorption to the systemic circulation. The scientific literature today provides several systems that can deliver active pharmaceutical ingredients (APIs) across the skin. These include reservoir matrices, matrix diffusion-controlled devices, multiple polymer devices and multilayer matrix assemblies. Among these, topical application of the Solid lipid nanoparticles(SLN) nanostructured lipid carriers (NLC) have emerged as novel systems composed of physiological lipid materials suitable for topical, dermal and transdermal administration. This review focus on, the potential of NLC in Topical delivery system. Topical drug application has been introduced since long time to achieve several purposes on different levels (skin surface, epidermis, dermis and hypodermis). However, several problems have been reported with the conventional topical preparations e.g. low uptake due to the barrier function of the stratum corneum and absorption to the systemic circulation. A lot of research groups paid attention to the topical application of the Solid lipid nanoparticles(SLN) and Nano Structured lipid carriers(NLC). This review presents a broad treatment of Nano Structured lipid carriers(NLC) discussing their advantages, benefit/risk ratios and their possible remedies. Different production methods which are suitable for large scale production and applications of Nano Structured lipid carriers (NLC) are described. Appropriate analytical techniques for characterization of Nano Structured lipid carriers (NLC) like Image analysis , differential scanning calorimetry, Zeta Potential, HPLC are highlighted. Modulation of drug release, factors affecting drug release and application areas are also explained with the drugs incorporated in Nano Structured lipid carriers (NLC). If appropriately investigated, Nano Structured lipid carriers (NLC) may open new vistas in therapy of complex diseases.

Keywords: Nano structured lipid carriers (NLC), Topical drug delivery system, Solid lipid nanoparticles (SLN), Homogenization, SEM, HPLC, DSC, Drug release.

INTRODUCTION

Topical drug application has been introduced since long time to achieve several purposes on different levels (skin surface, epidermis, dermis and hypodermis). However, several problems have been reported with the conventional topical preparations e.g. low uptake due to the barrier function of the stratum corneum and absorption to the systemic circulation.

The scientific literature today provides several systems that can deliver active pharmaceutical ingredients (APIs) across the skin. These include reservoir matrices, matrix diffusion-controlled devices, multiple polymer devices and multilayer matrix assemblies. Among these, topical application of the Solid lipid nanoparticles(SLN) and Nano Structured lipid carriers(NLC) have emerged as novel systems

composed of physiological lipid materials suitable for topical, dermal and transdermal administration. Many features, which these carrier systems exhibit for dermal application of cosmetics and pharmaceuticals, have been pointed out. SLN and NLC are composed of physiological and biodegradable lipids that show low toxicity. The small size ensures a close contact to the stratum corneum and can increase the amount of drug penetrated into the skin. Due to the occlusive properties of lipid nanoparticles, an increased skin hydration effect is observed. Furthermore, lipid nanoparticles are able to enhance the chemical stability of compounds sensitive to light, oxidation and hydrolysis.¹

Increase of skin occlusion:

The lipid film formation on the top of the skin and the subsequent 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. 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.^{2,3,4,5}

Increase of skin hydration and elasticity:

The reduction of transepidermal water loss (TEWL) caused by occlusion leads to an increase in skin hydration after dermal application of SLN, NLC or formulations containing them. An *in vivo* study showed that the SLN-containing o/w cream increased the skin hydration significantly more than the conventional o/w cream. In study shows that 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. A significant higher increase in skin hydration was found by Müller *et al.* for an NLC-containing cream compared to conventional cream.⁶

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.^{7,8,9}

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 SLN. Prednicarbate uptake was enhanced and it was accumulated in the epidermis with a low concentration in the dermis.

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.

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 erythema, peeling and burning 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 erythemic 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 therefore, the benefit/risk ratio is improved.^{8,10,11,12}

Enhancement of 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. It was found that incorporating benzophenone in SLN not only improves the UV blocking activity evaluated using *in vitro* photoprotection assay but also reduces the absorption of the benzophenone into the skin in comparison to a conventional nanoemulsion. Improving the UV blocking activity allows the reduction of the concentration of the UV blocker while maintaining the protective level of the conventional formulation. These findings were confirmed by Song and Lui comparing UV absorption properties of 3,4,5-trimethoxybenzochitin-loaded SLN and SLN free system. Furthermore, a significant increase in 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.^{13,14}

Enhancement of chemical stability of chemically labile compounds:

Enhancement of chemical stability after incorporation into lipid nanocarriers was proven for many cosmetic actives e.g. coenzyme Q 10, ascorbyl palmitate, tocopherol (vitamin E) and retinol (vitamin A).^{8,15,16,17}

Preparation Methods of Nano Structured lipid carriers:

Many methods are used for the preparation of lipid nanoparticles (NLC). These methods are high pressure homogenization, microemulsion technique, emulsification-solvent diffusion emulsification-solvent evaporation solvent injection (or solvent displacement), multiple emulsion technique, phase inversion, ultrasonication and membrane contractor technique.

However, high pressure homogenization is the most used method due to the many advantages it has compared to the other methods, e.g. the avoidance of organic solvents, the short production time and the possibility of production on large scale. High pressure homogenizers are widely used in many industries including food industry (e.g. milk) and pharmaceutical industry e.g. emulsions for parenteral nutrition. Therefore, no regulatory problems exist for the production of pharmaceutical and cosmetic preparations using this production technique.

Lipid nanoparticles can be produced by either the hot or cold high pressure homogenization technique.

METHODS OF PREPARATION

Lipid screening:

Prior to the production of an NLC formulation a lipid screening should be performed to determine the most suitable lipid for the active ingredient to be incorporated in the NLC. This is performed by dissolving increasing amounts of the active ingredient in various melted solid lipids and determining the maximum amount of the active that could be dissolved in each lipid. After dissolution, the lipid/active mixtures are cooled down to room temperature for solidification. The solid mixtures are visually observed for the presence or absence of crystalline active (when this ingredient is a solid substance at room temperature). If the active ingredient is oil, the miscibility of the two materials (melted lipid and oil) is observed. After cooling down the mixture to room temperature the lipid will solidify again and the incorporation of the oil in the solid lipid matrix is investigated. This can be performed by smearing a

piece of the solid mixture on a filter paper and observing if there are any oil spots on the filter paper. Calorimetric analysis can be performed on the solid solutions obtained using differential scanning calorimeter (DSC). These analyses will detect any presence of crystalline active (i.e. undissolved active) and also can show if there is an unincorporated part of active ingredient in the lipid matrix (i.e. oil).¹⁸

Production of the nanoparticles with high pressure homogenization:

Homogenization is a fluid mechanical process that involves the subdivision of droplets or particles into micro- or nanosize to create a stable emulsion or dispersion. Homogenization is a very common processing step in the food and dairy industries. It improves product stability, shelf life, digestion and taste. Homogenization can also significantly reduce the amount of additives (e.g. stabilizer) needed in a product. In the cosmetic industry homogenization is essential for the quality and stability of the products and their texture (skin feeling). The bioavailability of the pharmaceutical products can be enhanced by homogenization, also the tolerance of some drugs can be improved. Moreover, high pressure homogenization has some advantages over other size-reducing processes (e.g. ball milling). It is considered to be a superior process from an economical and product quality prospects. The contamination of the products caused by the personnel or coming from the machine (machine parts wearing) is reduced. Also the exposure to thermal stress and microbiological contamination is clearly less due to the shorter production times. There are two types of high pressure homogenizers available on the market, the jet-stream homogenizers and the piston-gap homogenizers.¹⁹

Preparation of nanoemulsions:

Nanoemulsions are o/w emulsions which consist of a lipid phase (oil), a surfactant and an aqueous phase (water). These nanoemulsions can be prepared at Room temperature, but to maintain the same production conditions for all preparations (as for NLC) they were prepared at higher temperatures (80-90°C). The lipid (oil) phase and the aqueous surfactant solution were heated up to about 80°C, and the active substance (if any) was dissolved in the hot oil phase which is subsequently dispersed by a high speed stirrer at 8000 rpm for 20-30 sec in the hot aqueous surfactant solution. The obtained pre-emulsion is homogenized in a high pressure homogenizer applying a pressure of 800 bar and two homogenization cycles yielding a hot o/w nanoemulsion. The obtained product was filled in silanized glass vials, which were immediately sealed. A thermostated water bath adjusted to 15°C has been

used as cooling system to control the rate of cooling of the obtained product.

Preparation of aqueous NLC dispersions:

Lipid nanoparticles with solid particle matrix are derived from o/w emulsions by replacing the liquid lipid (oil) by a solid lipid at room temperature. The first generation of solid lipid nanoparticles (SLN) was developed at the beginning of the nineties. They were produced from a solid lipid only. In the second generation technology the nanostructured lipid carriers (NLC) are produced by using a blend of solid and liquid lipids, this blend is solid at room temperature.

The production process is identical for both particles SLN and NLC. The solid lipid or lipid blend is melted at 5-10°C above the melting point of the solid lipid, the active substance is dissolved in the melted lipid phase, which is subsequently dispersed by a high speed stirrer at 8000 rpm for 20-30 sec in the aqueous surfactant solution previously heated up to the same temperature. The obtained pre-emulsion is homogenized in a high pressure homogenizer applying a pressure of 800 bar and two homogenization cycles (unless otherwise mentioned) yielding a hot o/w nanoemulsion. The obtained product was filled immediately in silanized glass vials and the vials were sealed properly. The obtained samples were cooled down to room temperature in a thermostated water bath adjusted to 15°C. After cooling down the emulsion droplets crystallize forming lipid nanoparticles with solid particle matrix, depending on the lipids used either SLN or NLC are obtained.^{20,21,22}

CHARACTERIZATION OF PARTICLES:^{23,24,25,26,27}

Several techniques were employed in this work to determine the particle size of the preparations. These techniques were direct measurements (microscopy) and indirect measurements (laser diffractometry and photon correlation spectroscopy).

Imaging analysis:

The major advantage that microscopic techniques have over most of the other methods used for size analysis is that the particle size itself is measured, rather than some property which is dependent on particle size. In other words, microscopic technique is a direct measurement and do not depend on any other factors that might influence the measurements (e.g. temperature, refractive index, etc.). In this work both light and electron microscopy have been used.

Light microscopy:

The size of a particle which can be detected by microscopy is limited by the diffraction of the light used to form the image. The resolution of a microscope is calculated approximately as the wavelength of the light divided by the numerical aperture of the microscope objective. All substances, which are transparent when they are examined by microscope that has crossed polarizing filters, are either isotropic or anisotropic. Amorphous substances, such as supercooled melts and non-crystalline solid organic compounds, or substances with cubic crystal lattices, are isotropic materials, having one refractive index. On the other hand, anisotropic materials have more than one refractive index and appear bright with brilliant colors (birefringence) against a black polarized background. The interference colors depend upon the thickness of the crystal and the differences are either uniaxial, having two refractive indices or biaxial, having three principal refractive indices. Most materials are biaxial corresponding to either, an orthorhombic, a monoclinic or a triclinic crystal system. Light microscopy is an important procedure to know if the relatively larger particles detected by laser diffractometry (LD) technique are really particles or agglomerates of nanosized particles.

TABLE 1: DRUG INCORPORATED IN LIPID NANOPARTICLES²⁸

Acyclovir	Albumin	Amphotericin B	Clobetasol proprionate
Calcitonin	Etomidate	Ascorbyl palmitate	Clotrimazole
Calixarenes	Etoposide	Azidothymidine palmitate	Clozapine
Camptothecin	Ferrulic acid	Betamethasone valerate	Cortisone
Cholesteryl butyrate	5-Fluorouracil	Bupivacaine	Cyclosporin A
Nitrendipine	Gadolinium (III) complexes	Insect repellents	Dexamethasone
Oxazepam	Gonadorelin	Insulin	Diazepam
Oxytetracycline	Hydrocortisone	Ketoconazole	Doxorubicin
Paclitaxel	Idarubicin	Magnetite	Prednisolone
Podophyllotoxin	Indometacin	Mifepristone	Retinoids
Prednicarbate	Thymopentin	Triptolide	Vitamin K

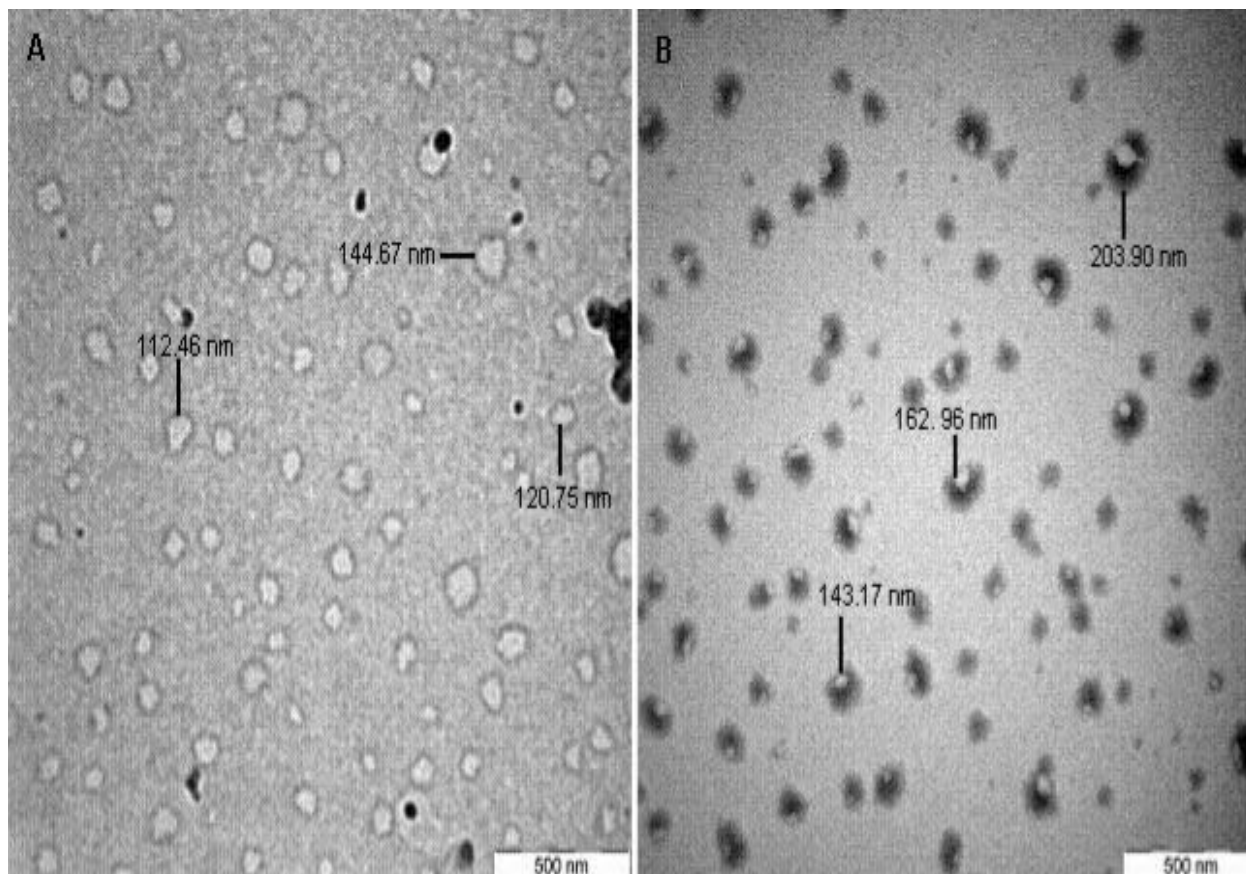


Figure 1:Microscopic image of NLC

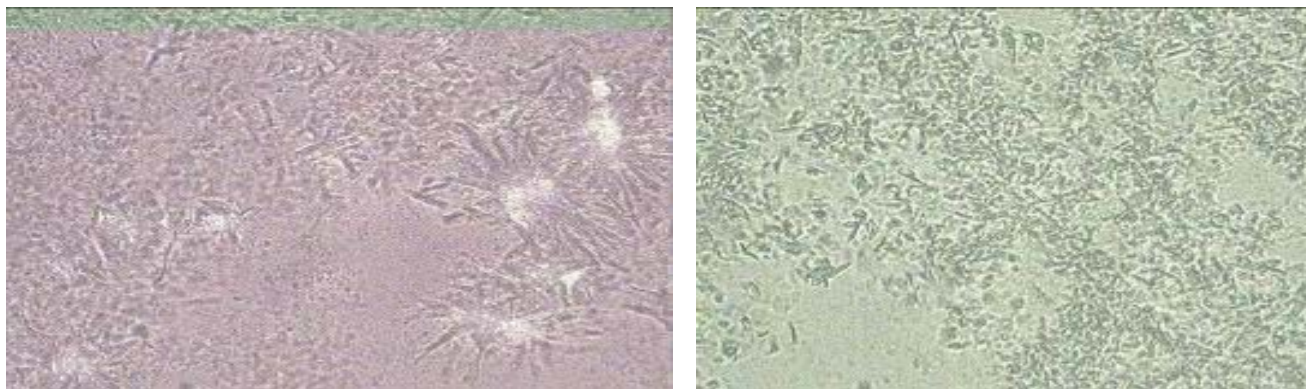


Figure 2: Light Microscopy picture of NLC

Scanning electron microscopy (SEM):

This technique can be used to investigate the shape of the particles prepared and to assess the particle size of these particles. Aqueous NLC dispersions can be applied and spread on a sample holder (thin carbon film). The samples will be placed inside of the vacuum column of the microscope and the air was pumped out of the chamber. An electron gun placed at the top of the column emits a beam of high energy primary

electrons. The beam of the electrons passes through the lenses which concentrates the electrons to a fine spot and scan across the specimen row by row. As the focused electron beam hits a spot on the sample, secondary electrons are emitted by the specimen through ionization. A detector counts these secondary electrons. The electrons are collected by a laterally placed collector and these signals are sent to an amplifier.

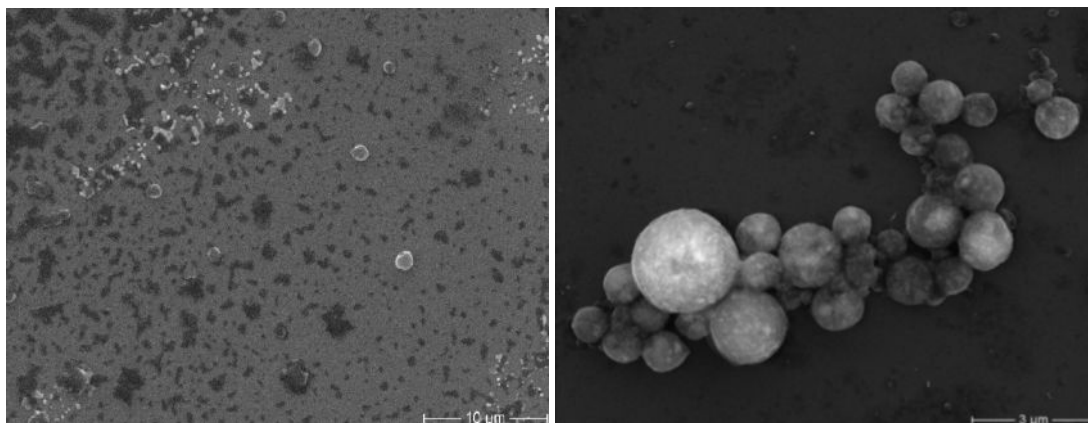


Figure 3: Electron microscopy picture of NLC

Energy dispersive X-ray spectroscopy (EDX):

EDX is an analytical technique used predominantly for the elemental analysis or chemical characterization of a sample. Being a type of spectroscopy, it relies on the investigation of a sample through interactions between the electromagnetic radiation and the matter, analyzing X-rays emitted by the matter in this particular case. Its characterization capability is mainly due to the fundamental principle that each element of the periodic table has a unique atomic structure. This allows the x-rays, which are characteristic of the atomic structure of the element, to be uniquely distinguished from each other. EDX systems are most commonly found on scanning electron microscopes.

Zeta potential (ZP):

Zeta potential is the electric potential of a particle in a suspension. It is a parameter which is very useful for the assessment of the physical stability of colloidal dispersions. In suspensions the surfaces of particles develop a charge due to ionization of surface groups or adsorption of ions. This charge depends on both the surface chemistry of the particles and the media around these particles. The surface charge generates a potential around the particle, which is at the highest near the surface and decays with distance into the medium. The zeta potential can be measured by determining the velocity of the particles in an electrical field (electrophoresis measurement).

Thermal analysis:

As the International Confederation of Thermal Analysis and Calorimetry (ICTAC) defines the thermal analysis, it is “a group of techniques in which a physical property of a substance is measured as a function of temperature whilst the substance is subjected to a controlled temperature program”.

Differential scanning calorimetry (DSC) analysis:

DSC is usually used to get information about both the physical and the energetic properties of a compound or formulation. DSC measures the heat loss or gain as a result of physical or chemical changes within a sample as a function of the temperature. There are 2 types of DSC instruments, the power compensate DSC and the heat-flux DSC .

The power compensate DSC consists of 2 separate ovens while the heat-flux DSC consists of one oven that heat up both the reference and the sample pans . Heat is transferred through the disc (where the sample and the reference pans are placed) and through the sample pan to the contained sample and reference. The differential heat flow is monitored, as well as the sample temperature. Software linearization of the cell calibration is used to maintain calorimetric sensitivity. The cell has a volume of 2 ml and can be used with various inert atmospheres, as well as oxidizing and reducing atmospheres. Different sample pans (hermetic, open or sealed) allow sample volumes of 0.04 ml to 0.1 ml, which can be up to 100 mg depending on sample density.

Examples of endothermic (heat-absorbing) processes are fusion (melting), boiling, sublimation, vaporization, desolvation and solid-solid transitions. An important exothermic, (energy is liberated) process is crystallization. Qualitative measurements of these processes have many applications, such as materials identification, study of purity, polymorphism, solvation, degradation quantitative and qualitative analysis, aging, glass transition temperature and compatibility of substances.

DSC analysis has been used to determine the state and the degree of crystallinity of lipid dispersions, semi-solid systems, polymers and liposomes. It allows the study of the melting and crystallization behavior of crystalline material like lipid nanoparticles. DSC analysis is useful to understand solid dispersions like solid solutions, simple eutectic mixtures or, as in the

case of NLC, drug and lipid interactions and the mixtures of solid lipids and liquid lipids (oils). In general, a melting point depression is observed when transforming the bulk lipid to a particulate form in the nanometer range.

High performance liquid chromatography (HPLC) analysis:

HPLC technique is a suitable and accurate way to determine the content of a substance and/or its chemical stability .

MODULATION OF DRUG RELEASE^{1,2,3}

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 in 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 a cream. Increase in temperature and water evaporation leads to an increase in drug release rate. Based on these cyclosporine-lipid particles are under development to treat psoriasis. The cream itself is saturated with cyclosporine, as well as a cyclosporine-loaded NLC contained in the cream. After application to the skin, accelerated release from the lipid particles should lead to a supersaturated system (similar to microemulsions, but without high surfactant concentration) leading to an improved penetration of cyclosporine into the skin.[1,6]

Factors affecting the Drug release:

The release study must be performed to compare the capacity of different samples to retain the drug incorporated for a longer time and release it slowly from the lipid matrix of the nanoparticles. Many factors that could affect the release profile of the drug from the NLC system. The effect of the particle size, the lipid matrix, the surfactant, the drug concentration in the lipid matrix and the drug type can be studied.

Particle size:

The particle size of a colloidal system (e.g. NLC) is a crucial factor for the release of the material(s) incorporated inside the particles.

Lipid matrix:

Different lipid matrices lead to different release profiles. The lipids have different crystals order and crystallization modification, different melting points

and different hydrophilic lipophilic balance (HLB) values, e.g. Apifil HLB = 9.4, Compritol 888 HLB = 2. This makes the affinity of the drug to be entrapped within the lipid matrix different from one lipid to another.

Surfactant:

Surfactants as they are used to stabilize the particles in the dispersion media (or emulsify the oil in water) may affect the structure of the lipid nanoparticles. This happens because of the interaction between the emulsifying agent molecules and the lipid molecules. Depending on the HLB of the surfactant and the molecular weight of the surfactant molecules, the affinity of the surfactant to the lipid differs. Having the surfactant molecules embedded in the lipid matrix might dramatically affect the crystallization of the lipid, and leave spaces in the lipid lattice. These spaces will give rise to higher loading capacity of drug, incorporation in imperfections inside the particle matrix and eventually a slower release profile. Moreover, the ability of the surfactant to stabilize the oil droplets (in the lipid melted state during homogenization) and form smaller NLCs gives the surfactant also a role through the size of the formed lipid particles. The physicochemical properties of the NLCs are essentially influenced by the type of surfactant used.

Drug loading:

Drug loading might affect the release profile. It depends on the affinity of the drug to mix with the lipid and be enclosed in the matrix.

Drug type:

The drug type affects the release profile because with the different compositions of drugs there are different affinities to the lipid matrix. Nanostructured lipid carriers have unique characteristics that can enhance the performance of a variety of incorporated drug forms.

Advantages of Nanostructured lipid carriers :

Control and/or target drug release, Improve stability of pharmaceuticals, High and enhanced drug content (compared to other carriers), Feasibilities of carrying both lipophilic and hydrophilic drugs, Most lipids being biodegradable, NLC have excellent biocompatibility, Water based technology (avoid organic solvents). Easy to scale-up and sterilize, More affordable (less expensive than polymeric/surfactant based carriers), Easier to validate and gain regulatory approval.

APPLICATION AREAS

All the lipids and surfactants used in traditional pharmaceutical creams can be employed, thus leaving little regulatory hurdles. Data are available showing delivery advantages of lipid particles compared to normal creams and ointments. Because of the high consistency of NLC dispersions, they can be used as topical dosage forms without further processing.

Medha Joshi and Vandana Patravale (2008) formulated Nanostructured lipid carriers (NLC) based topical gel of celecoxib for the treatment of inflammation and allied conditions. NLC prepared by the microemulsion template technique were characterized by photon correlation spectroscopy for size and scanning electron micrograph (SEM) studies. Drug encapsulation efficiency was determined using Nanosep® centrifugal device. The nanoparticulate dispersion was suitably gelled and assessed for *in vitro* release and *in vitro* skin permeation using rat skin. Efficacy of the NLC gel was established using a pharmacodynamic study, i.e., aerosil-induced rat paw edema model. The skin permeation and rat paw edema pharmacodynamic studies were carried out in comparison with a micellar gel which had the same composition as that of the NLC gel except for the solid lipid and oil. The NLC based gel described in this study showed faster onset and elicited prolonged activity until 24 h.²⁹

Donatella Paolino et al (2012) ; studied NLC of lutein is an alternative to a 20% suspension of lutein in safflower oil (FloraGLO® Lutein) represents a good raw material for the production of creams and other semisolid formulations. However, the high viscosity of FloraGLO® and poor chemical stability of lutein in the suspension represents a practical limitation to its use. NLC were prepared with different percentages of FloraGLO® as the liquid phase of NLC. The physical stability of NLC was assessed by storage at room conditions and by Turbiscan accelerated analysis. All the produced nanocarriers were perfectly tolerated after application on the skin. In an *in vivo* model of UV-induced skin erythema, the lutein-loaded NLC were able to improve the photo-protective effects of the antioxidant compared to the commercial suspension, when the NLC formulations were applied before inducing the erythema. This study also proved for the first time the possibility of converting a liquid formulation into a solid, modified release nanocarrier with more manageable formulative features.

NLCs can generally be applied where solid nanoparticles possess advantages for the delivery of drugs. Major application areas in pharmaceuticals are topical drug delivery, oral and parenteral

administration. They also have applications in cosmetics, food and agricultural products.³⁰

E. González-Mira et al (2011) The potential use of nanostructured lipid carriers (NLC) composed of a fatty acid [stearic acid (SA)] or a triglyceride (glyceryl behenate) as solid lipids, and a mixture of medium chain triglycerides and castor oil as liquid lipids, for skin administration of flurbiprofen (FB), has been explored. Two different optimized NLC formulations (FB-SANLC based on SA vs. FB-C888NLC based on glyceryl behenate), with respect to the morphometrical properties (particle size and polydispersity index) and the entrapment efficiency, were used in this study. The *ex vivo* permeation profiles of FB-C888NLC, FB-SANLC and conventional FB solution were evaluated using human skin. An improved FB permeation was observed when the drug was delivered by skin application of FB-C888NLC, attributed to the particle size and matrix crystallinity. The differential scanning calorimetry and X-ray diffraction studies suggested major polymorphic transitions in the lipid matrix of FB-C888NLC. A good correlation between polymorphic transitions and increased drug permeation was observed. However, both NLC dispersions showed a penetration-enhancing ratio (ER) higher than conventional FB solution. The *in vitro* and *in vivo* irritancy and local tolerability were assessed by running, respectively, the SKINTEX™ and Draize test. Both FB-C888NLC and FB-SANLC were classified as nonirritant.³¹

Lipid nanoparticles based market products:

The positive features of lipid nanoparticles led to the market introduction of many cosmetic products.

CONCLUSION

The lipid nanoparticles – SLN and NLC – are carrier systems with good perspectives to be marketed very successfully. The reason for this is that they were developed considering industrial needs e.g. scale up, qualification and validation, simple technology, low cost, tolerability etc. Because of the high consistency of NLC dispersions, they can be used as topical dosage forms without further processing. This Review concentrates on the development of nanostructured lipid carriers (NLC) for topical applications. It also shows the advantages of using the NLC in dermal and personal care formulations and studies the factors that affect these advantages. The smart NLC as the new generation offer much more flexibility in drug loading, modulation of release and improved performance in producing final dosage forms such as creams, tablets, capsules and injectables.

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