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Nanostructured Lipid Carriers in Stability Improvement for Cosmetic Nanoparticles

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ABSTRACT

Nanostructured lipid carriers were developed as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles. The paper reviews advantages- also methods having potential to produce NLC are Hot homogenization method, Cold homogenization method, Solvent Emulsification-evaporation method. Main focus of review was to show how these NLC help to improve the stability of various cosmetic nanoparticles. The stabilities (chemical, photo, and storage) of cosmetic nanoparticles like Vitamin C, Phenyl ethyl Resorcinol, Lycopene, Lutein, CoQ10, α-tocopherol was improved when these drugs are converted into second generation NLC (Nanostructured lipid carriers). So, concluded that lipid nanoparticles have a beneficial role for the improvement of stability cosmetic nanoparticles.

INTRODUCTION

The term ‘‘Nanotechnology’’ was first used in a 1986 book, ‘‘Engines of Creation’’by K. Eric Drexler. Nanotechnology is nothing but “the understanding and control of substances in the range of nanoscale”. The dimensions usually vary between 1 and 100 nm.[1] Nanomaterial is defined as material which appears in one or more dimensions within range up to 100nm or less. The word “nanos” from nanotechnology is the Greek word with meaning dwarf. Nano- delivery systems are precious prospects for nanotechnology in pharmaceutics, cosmetics as well as food industries.[2] Currently nanotechnology has widely used in the field of cosmetic so, consider as “hottest technology”. Nowadays nanoparticles are incorporated in cosmetic and topical field because of their benefits such as increased efficiency, transparency, unique texture and protection of active ingredient so, leads to higher consumer compliance.

Nanoparticles are used in two categories:

i) Labile nanoparticles which get disintegrated into its molecular components when applied to skin (e.g. liposomes, micro-emulsion, nano-emulsion)

ii) Insoluble particles (e.g. Titanium dioxide, fullerenes and quantum dots.)

Titanium dioxide and zinc oxide are white and opaque but when these larger particles convert into nano form they appear as transparent and so, they can be used in moisturizers & foundations. Other one like fullerene used as anti-ageing cream & also as moisturizers it penetrates into the skin very effectively. Other one like aluminium oxide provides a ‘soft effect’**.** [3]

The nano-delivery system is generally divided in to two groups polymer based, lipid based. In case of polymer based nano-delivery, it possesses some limitation such as the number of products based on former are very rare in the market due to the toxicity of polymer, sometimes lack of suitable large scale production. So, due to these reasons currently greater focus is to use lipid-based nano-delivery systems like nano-emulsion, micro-emulsion, liposomes, SLN, NLC etc. Among all of these, NLC has greater approach to use in the cosmetic & topical preparation. [4, 5, 6]

The skin structure [7, 8, 9]

The skin has four distinct layers of tissue.

Non-viable Epidermis (Stratum Corneum): Stratum corneum probably outer most layer of skin, serve as actual physical barrier to most substances that come in contact with the skin. Cells are sloughed from the surface continually and replaced by new ones have formed and matured below in the viable epidermis.

Viable Epidermis: This layer of skin resides between stratum corneum and the dermis. It has a thickness ranging from 50 to 100µm. The structure of the cells in the viable epidermis is similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%.

Dermis (Corium): Just beneath the viable epidermis is the dermis. It is a structural fabric found histologically in normal tissue. The dermis ranges from 2000 to 3000µm thick, consists of a matrix of loose connective tissue composed of fibrous protein (collagen, elastin, and reticulum) embed in an amorphous ground substance.

Subcutaneous Connective Tissues (Hypodermis): The hypodermis is not actually considered a true part of the structure of the skin. It is composed of loose textured, white, fibrous connective tissue in which fat and elastic fibers of hair follicles, often the secretary portion of sweat glands, and cutaneous nerves.

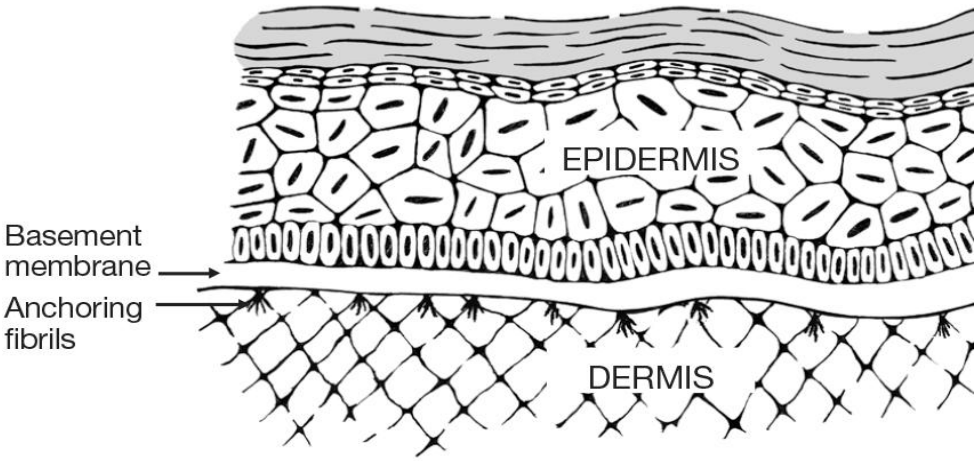

Fig: 1 Structure of skin

The Skin Delivery Systems

In recent years, the use of nano-delivery systems to deliver the active ingredient to the skin has reached the largest height. The reason behind use of nano-carriers is because of its benefits like,

- Increase delivery of active ingredient to the target layer of skin.
- Improved stabilization of active ingredient.
- Reduction in any skin irritation.
- Improved ease of application and removal.[10,11]

Vesicular Systems (Liposome):

Liposomes:

Liposomes, the so called man-made cells can act as delivery vehicles for drugs or nutritional supplements. Their cell wall mainly consists of natural substances, lecithin, which is a mixture of phospholipids, predominantly phosphatidylcholine (PC). Liposome can vary in size, from 15nm up to several µm and can have either a single layer or multilayer structure. The first liposomal marketed cosmetic product was the anti-ageing cream 'Capture' launched by Dior in 1986. One of the reasons for the widespread use of liposomes in the cosmetic industry is their ease of preparation and the ability to enhance the absorption of active ingredients by skin. But they are unstable due to their susceptibility to oxidation and the breakdown of liposomal structure. [1, 10]

Emulsion (Nano-emulsion):

These are defined as "ultrafine emulsion" forms small droplets in the sub-micron range. Dimensions range between 50 to 500nm. This range is smaller than micro-emulsion droplet size which range between 1 to 100µm.[12] Nowadays special attention is for its application in personal care products as potential vehicle for the controlled delivery of cosmetics and the optimized dispersion of active ingredient in the particular skin layer. But these systems are unstable in acidic condition and sometimes controlled drug release from nano-emulsion is very improper due to their small size and also due to liquid state of carrier.[13,14]

Particulate systems

Solid Lipid Nanoparticles

These are introduced at the beginning of the 1990s and designed to combine the advantages of polymer particles, liposomes and emulsions to avoid their disadvantages. The SLN are produced

from one solid lipid or a blend of solid lipid. The SLN are used as NDDS for pharmaceutical drugs in various application routes. They mainly used as carrier system in the cosmetic field for the delivery of active ingredient.[1] But they have also some drawbacks like,

- Low drug loading capacity along with it, sometimes drug expulsion can occur after the polymorphic transitions.
- The crystals formed by these are perfect so drug molecule has very less space in this case for accommodation.
- For the production amount of water required is larger. [15]

Nanostructured Lipid Carrier

Nanostructured lipid carriers are a modified Lipid nanoparticle in which lipidic phase contains the both solid lipid (fat) and liquid lipid (oil) at room temperature. [1] NLC can be produced at large scale because such delivery systems have a great impact on the development of new pharmaceutical dosage forms and in cosmetic product. [16, 17] NLC have been shown to exhibit a controlled release behavior for various active ingredients such as ascorbyl palmitate, clotrimazole, ketoconazole, sunscreens and other antifungal agents. Along with these, it provides very useful information regarding the effect of drugs or excipients on the barrier function of skin. These types of second generation are with all the benefits over all other colloidal carrier systems were mentioned in following table: [18]

Table 1: NLC advantages over other delivery system

Liposomes	Nanoemulsions	Microemulsions
✓ High cost ✓ Low drug payload ✓ Drug leakage ✓ Fast release	✓ Ostwald ripening ✓ Flocculation ✓ Membrane permeability ✓ Drug release ✓ Creaming ✓ Particle aggregation	✓ High concentration of surfactant. ✓ They are prone to disintegration upon the changes of environmental conditions.

Structure

The NLC mainly have three types of structure developed according to the formulation composition and the production parameters.

Imperfect Type:

Distances between fatty acid chains of glycerides and general imperfections in crystal are for the purpose of good drug accommodation. These imperfections accommodate drug in molecular form and it increases, the drug payload. [5, 1]

Amorphous Type:

The crystalline process itself causes expulsion of the drug and forms NLC in amorphous form. It can be produced by using the special lipids like isopropyl myristate. [5, 19]

Multiple Type:

In this solid matrix of the of the lipid nanoparticles contain tiny liquid nanoparticles of the oil. These nanoparticles compartments are surrounded by solid lipid matrix thus allowing controlled release. [1, 20]

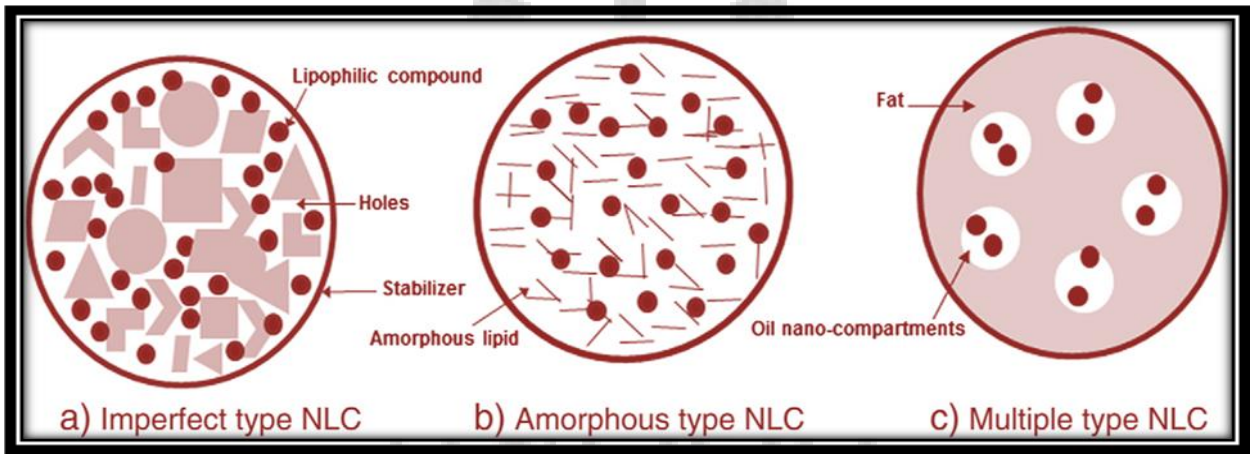

Fig: 2 Structure of NLC

Method for the Production:

Many different methods have been described in the literature for production of lipid nanoparticles, especially SLN. Hot and Cold Homogenization method, microemulsion technique, [16] Solvent Emulsification-evaporation method, Emulsification solvent diffusion method,[21] Solvent injection method or Solvent displacement method,[22] Phase inversion technique,[23] multiple emulsion method,[24] Membrane contractor technique.[25] Among these techniques Hot and Cold Homogenization method, Solvent Emulsification-evaporation methods have potential to produce NLC, are discussed as follows:

Name of methods	Procedure
Hot Homogenization Method	In this approach, the drug is initially dissolved in melted lipid mixture. Then the lipid melt is dispersed in aqueous emulsifier solution at the same temperature by high speed stirring or shearing. The obtained hot emulsion may further be homogenized at the same temperature by instrument homogenizer, high intensity ultrasonic probe / jet / bath or microfludizer, to produce a hot nanoemulsion. Subsequently, NLC are produced by cooling the hot nanoemulsion in cold water, room temperature.[26]
Cold Homogenization Method	In this method, after dissolving the drug in melting lipid mixture, the bulk lipid is rapidly cooled. Subsequently the bulk lipid mixture is milled to form lipid microparticles e.g. ball mill make caution that during milling process the temperature does not exceed the temperature of lipid with lowest melting point. The microparticles are then dispersed in a cold emulsifier solution and further homogenized to produce fine lipid nanoparticles.[1]
Solvent Emulsification Evaporation Method	In this method, lipid and drugs are dissolved in a water immiscible organic solvent with low boiling point. The solution is then emulsified in the aqueous emulsifier solution. Upon evaporation of the solvent under reduced pressure, the organic nanoparticles form.[1,21]

Marketed formulation: [17, 27-30]

Table 2: Currently available cosmetics with lipid nanoparticles in market

Products name	Name of producer or distributors	Market launching
Cutanova Cream Nano Repair Q10	Dr. Rimpler	10/2005
Intensive Serum Nano Repair Q10		10/2005
Cutanova Cream Nano Vital Q10		06/2006
SURMER Crème Legère Nano-Protection SURMER Crème Riche Nano-Restructurante SURMER Elixir du Beautè Nano-Vitalisant SURMER Masque Crème Nano-Hydratant	Isabelle Lancray	11/2006
NanoLipid Restore	Chemisches Laboratorium	04/2006
NanoLipid Q10		07/2006
NanoLipid Basic	Dr. Kurt Richter, CLR Berlin	07/2006
SuperVital -Cream -Serum		09/2006
-Extra moist softener	Amore Pacific	01/2007
-Eye-cream (line: IOPE)		01/2007
NLC Deep Effect Eye Serum NLC Deep Effect Repair Cream NLC Deep Effect	Amore Pacific	12/2006
Reconstruction Serum Hexapeptide-8, highly Active oligosaccharides	Beate Johnen	05/2007
NLC Deep Effect		2007
Reconstruction Body Serum	Beate Johnen	
Regenerationscreme Intensiv Scholl		03/2007

Role of NLC in the Improvement of Stability of Cosmetic Formulations

Vitamin C:

Vitamin C has many favorable effects on the skin due to that it has been used in pharmaceutical and cosmetic preparations for many years. In some situations body cannot be able to produce the adequate amount of antioxidants, so it is necessary to supplement the antioxidants either by topical or oral route. The major problem related to the ozone layer is ozone layer depletion in the atmosphere so; radiation from the sun i.e., UVA & UVB reaches earth very rapidly in higher amount. By this radiation, peoples on earth prone to various skin related problems such as skin cancer, wrinkle, dryness, mottled pigment abnormalities so, to overcome from such skin related disorders it is necessary to give the antioxidants like vitamin C or ascorbyl palmitate.[31] In such type of antioxidants, instability is the major drawback because vitamin C has tendency to undergo oxidation and also get inactivated when exposes to air. It has hydrophilic nature which limits its penetration across the skin as well as when vitamin C used as it is the product formed, it has short half-lives. To increase the stability convenient to use the liposoluble form (ascorbyl-6-palmitate, tetra-isopalmitoyl ascorbic acid etc) so better to prepare the NLC which ultimately improve stability and also product penetration into the skin easily. [32]

Phenylethyl Resorcinol:

Phenylethyl Resorcinol (4-(1-phenylethyl) 1, 3-Benzenediol, PR) is a new lightening agent which has ability to inhibit tyrosinase activity by Schmaus. Tyrosinase found in almost all types of organism which play an important role in pigment biosynthesis. In mammals, tyrosinase catalyzes oxidation of L-tyrosine and L-dopa to form melanin which determines the color of mammalian skin and hair. According to the various investigations, the conclusion made that Phenylethyl Resorcinol is one of the most potent lightening agents ever reported. [33] But it has certain application problems such as its light instability, poor water solubility which affects the absorption and due to low photo-stability may be ineffective when applied topically. To overcome this stability and absorption problem it is beneficial to prepare the Nanostructured Lipid Carriers, the second generation of lipid nanoparticles. When NLC of Phenylethyl Resorcinol was formed it showed improved photostabilty as well as bioavailability. [34, 35]

Lutein: It is one out of 20 carotenoids found in the human body. It is also a lipid soluble pigment in various vegetables (e.g. spinach, kale) & egg yolk. Further, Lutein plays an important role in the skin. It keeps the skin healthy by reducing the UV-induced disorders like erythema and inflammation. So, provide a good link between UV exposure and skin cancer. Lutein also behaves as a protective agent for skin cancer. It is also a filter of blue light. Lutein is a heat sensitive molecule having chances of degradation when it comes in contact with high temperature. To overcome this major drawback, it is suggested to use the lipid nanocarriers of Lutein prepared with carnauba wax lipid which found to show a highest thermostability in increased temperature (85^0C) .[36,37]

CoQ10:

The chemical name of coenzyme Q10 (CoQ10) is 2, 3-dimethoxy-5-methyl-6-decaprenyl-1, 4-benzoquinone and the Q10 also known as ubiquinone or ubidecarenone. This is an oil-soluble vitamin–like substance present primarily in mitochondria & it plays an essential role as a transporter of proton and electron carrier. When its reduced form (ubiquinol) is considered, it acts as an antioxidant. But if its aqueous dispersion is to be used stability, is major drawback for this the complex formation of CoQ10 with cyclodextrin is to be formed which found to be reported an effective method to improve water solubility and thermo as well as photo-stabilities. Along with it, the ultrasonic treatment increases storage stability of CoQ10 dispersion. [38,39,40]

Lycopene:

Lycopene is one of the most potent antioxidants mainly present in tomato, watermelon and pink grape fruit. This antioxidant has very low aqueous solubility, stability problems and not easily diffuses through the epidermis when applied topically. For this, the attractive option is utilization of lipid nanoparticles for cutaneous delivery of Lycopene. As NLC protect the chemically labile drugs from degradation, it ultimately provides sustained release of the active loaded drug. So, when NLC are formed the chemical stability of Lycopene increased and on other hand the degradation of Lycopene was retarded when it has been stored at low temperature.

α-tocopherol:

Nowadays due to depletion of the ozone layer the use of sunscreens is compulsory for the purpose of skin protection from the harmful effects of UV radiation. In cosmetic products α-tocopherol is used as an antioxidant which also has ability to reduce skin damage caused by UV radiation. The most of sunscreens that protect against UVA rays are based on the organic UVA filter butyl-methoxydibenzoylmethane (BMDBM). But this filter has photo-instability problem so, to overcome this stability drawback needs to encapsulate the α-tocopherol & BMDBM together into the lipid-based nanoparticles. This encapsulation proved to be effective in the photo-stabilization of the unstable UVA filter encapsulated into the both NLCs and SLNs exposed to UV radiation.

CONCLUSION

The chemical stability of various cosmetic formulations which are NLC loaded can be improved by selecting suitable types of lipid, surfactant, and proper storage conditions, i.e. cold temperature and flushing with nitrogen gas or inert gas. However, the most of the cosmetic formulation are having antioxidant property, these kinds of drug mainly face instabilities problems and can be found to overcome by various researchers by converting these drugs in suitable drug delivery systems i.e, NLC.

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