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# BREAKTHROUGHS IN TRANSDERMAL NANOSTRUCTURED LIPID CARRIER DRUG DELIVERY SYSTEMS

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**Keywords:**

Nanostructured lipid carriers (NLC), Solid lipid nanoparticles (SLN), Stratum corneum (SC), colloidal drug carriers, Transdermal drug delivery (TDD)

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**ABSTRACT:** The important barrier in transdermal drug delivery (TDD) is the Stratum corneum (SC), the outermost layer of the skin, which acts as an excellent protective physiological barrier. To boost the penetration or permeation of drugs through SC, several tactics have been used including passive and active methods of permeation or both in combination. This unwraps the opportunity to broaden the range of drugs that can be administered through the transdermal route, performed as alternatives to existing products, and overcomes the weaknesses of conventional routes. The Nanostructured Lipid Carriers (NLCs) seem to be excellent candidates over conventional drug delivery systems. NLCs are fastly growing and in increased demand from pharmaceutical research groups globally since the last decade. After development of liposomes and Solid Lipid Nanoparticles (SLN), NLCs were introduced. NLC overcomes the limitations of SLN, like the limited drug loading capacity and drug expulsion during storage. NLCs receive a preferred choice of formulation in the cosmeceutical market and Pharmaceutical market as well. This review is an overview of the different permeation barriers in TDD, focusing on the Nanostructured lipid carriers, as a proof-of-concept of a successful development strategy, formulation additives, Formulation methods, Characterization parameters of NLC, along with till the date breakthroughs in developments of NLC more specifically in transdermal drug delivery systems.

## INTRODUCTION:

**Skin Layers and Appendage:** The safest route of drug administration after the oral route is the transdermal system. Over the period, the skin has become a popular and important route for drug delivery encompassing topical, regional, or systemic effects.

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The transdermal drug delivery is advantageous over other routes, as being non-invasive, painless, and convenient means of drug administration avoids possible infection and compliance issues related to injections, steadier and sustained drug levels over a longer period of time, avoids liver first-pass metabolism and other variables such as gastric irritation, gastric degradation & gastric emptying, also provides an alternative route when oral dosing is not possible (unconscious or nauseated patients), and the ease of dose termination when adverse effects occur [1]. With this background, the potential for transdermal drug delivery is still far from exhausted.

The advances of newer technology such as nanostructured lipid carriers open the opportunity over colloidal, solid lipid nanoparticles, or other multiparticulate drug delivery for new therapeutic areas being explored. This intends to combine improvement over an existing therapy and provide a solution for problems with a current drug. Before proceeding to the approach of NLC delivery of drugs through the transdermal route, an anatomy physiological perspective of the skin and various factors influencing drug permeation are presented.

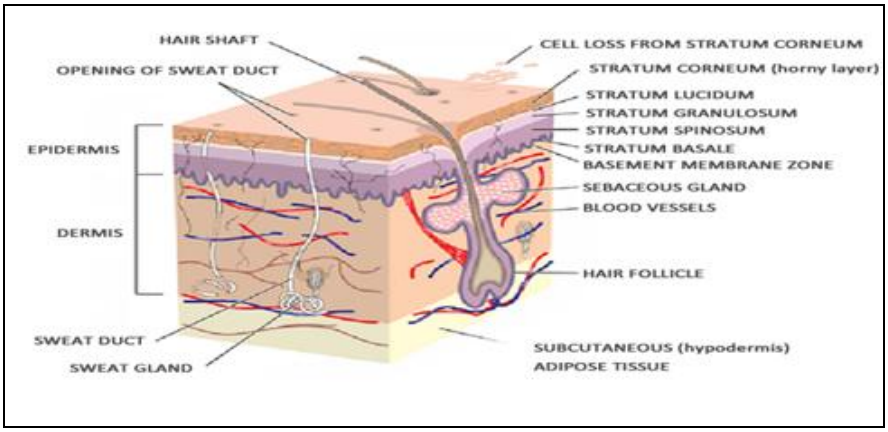


**FIG. 1: SCHEMATIC REPRESENTATION OF THE SKIN LAYERS AND APPENDAGE FROM REFERENCE [8]**

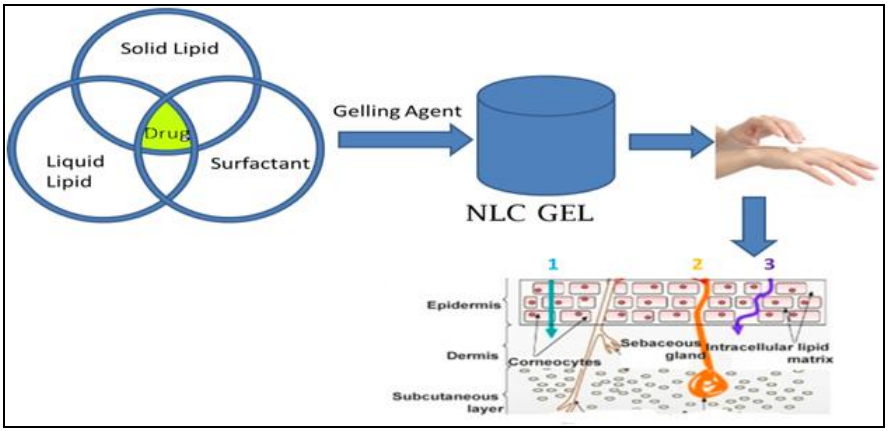


**FIG. 2: SCHEMATIC REPRESENTATION OF DEVELOPMENT AND PENETRATION OF NLC GEL THROUGH SKIN**

Stratum corneum is the outermost layer of the skin, also known as horny layer [15]. The epidermis is a multilayered tissue, with a varying thickness at different regions i.e. on the eyelids 0.06 mm while on the soles and on the palms it is 0.8 mm [1]. The epidermis is composed of keratinocytes (95% of cells) that undergoes constant proliferation, differentiation, and keratinization, being responsible for the constant physiological renewal of the skin [11, 12, 13].

Below the epidermis layer, a thin, separate basement membrane called as dermis, a layer of about 2-5 mm in thickness, made of dense irregular connective tissue [14, 22]. A layer of loose connective tissue, situated beneath to dermis, commonly known as the hypodermis or subcutaneous tissue. It is composed of lipocytes, arranged into fat lobules with interconnecting collagen and elastin fibers [14, 16, 17]. Appendages include Hair follicles, Sebaceous gland, Eccrine (sweat) gland, and apocrine gland. Appendages originate from the dermis layer, each having definite function, but apart from that all acts as a channel for transportation of drug from skin to beneath layers [18, 19, 20]. The process of drug absorption through consecutive skin layers is referred to as a transdermal drug delivery system or percutaneous absorption. So, it starts with the release of the drug from the dosage form, followed by penetration into the SC, and its diffusivity will depend on partition coefficient, lipophilicity, and hydrophilicity; finally, it gets absorbed in the dermis through capillaries [21]. Regardless of the heterogeneity of the skin barrier, steady-state permeation or flux (J) of a drug through the SC can be described by Fick's first law of diffusion,

$$J = Dq / dt = DKCo / h \text{…….1.1}$$

Where Q is the drug permeating a certain unit area of skin, D is the diffusion coefficient of the permeant in the skin, K is the partition coefficient between the SC and the vehicle, C0 is the applied concentration of permeant, and h is the diffusional path length. The drug penetration mechanism can be primarily considered driven by passive diffusion that is dependent on the concentration gradient [22].

**1. Factors Affecting Drug Permeation:** Skin permeability is affected by a large number of physiological factors. Majorly it includes age, gender, anatomical site, ethnicity, and some skin disorders. Intrinsic aging responsible for epidermal thinning, and hence the corneocytes become less adherent to each other [29].

The capability of a drug to cross SC is dependent on its penetrability, the hydrophobicity and hydrophilicity of the skin. From equation (1.1) one is able to predict the ideal properties of a molecule to penetrate and permeate through the SC. This comprises a moderate-high partition coefficient (K), and log P (o/w) between 1 and 4 is pointed as optimal; as the hydrophilicity of drugs increases, it affects partition from the vehicle into SC. In contrast, very lipophilic drugs will be retained in intercellular SC lipids and will be unable to partition to the epidermis, which is more aqueous, thus restricting their skin permeation rate**.** Ionized species have a lower permeability coefficient than the unionized species since the log P value of the former molecule is lower [26].

As the molecular size of the permeant has influence on diffusivity (D) within the SC, a low molecular weight is also desirable. It has been testified that permeant size and skin permeation are inversely proportional to each other. Generally, permeants selected for TDDS must have size less than 500 Da.

Permeants should also have an adequate lipid solubility *i.e.,* possess high diffusion coefficient, D, but also aqueous solubility (> 1 mg/mL) (high donor concentration, Cv, in order to assure a high concentration gradient, acting as driving force for diffusion) to maximize flux. Lastly, a low melting point (<200 ºC) is also one of the characteristics since it signifies good solubility of drugs in the SC lipid layer [37, 38].

**2. Nanostructured Lipid Carrier System-tact to Enhance Permeability:** New technologies have led the Pharma world to find numerous new therapeutic moieties but to develop new drug moightys is not enough to ensure progress in drug therapy. From the beginning of the 20th century, worldwide, pharmaceutical research groups taking an interest in the nano-drug delivery systems. Nanotechnology practically made its impact in all technical fields. Today we have 68-70% drugs that are poorly soluble in water and so less bioavailable; this is a very extensive issue encountered. The lipids component in lipid nanoparticles is generally physiological lipids due to their biocompatibility and biodegradability, and hence this system of drug delivery is safe with drug delivery with low acute and chronic toxicity [40, 41]. Nanotechnology has wide applications in the field of targeted drug delivery, diagnostics, tissue regeneration, cell culture, biosensors, along with some applications in molecular biology. To surpass the limitations associated with traditional colloidal systems (emulsions, liposomes, and polymeric nanoparticles) various nanosystems like Nanostructured Lipid Carrier, fullerenes, nanotubes, quantum dots, nanopores, dendrimers, liposomes, magnetic nanoprobes, and radio-controlled nanoparticles are being developed. Such a carrier used for Drug delivery should have a sufficient pharmaceutical loading capacity, no cytotoxicity and having pharmaceutical targeting and controlled release characteristics [42, 43].

NLCs are the advanced lipid nanoparticles, gaining attention as novel colloidal drug carriers for transdermal applications. NLC has been developed to surpass the problems associated with SLN. SLN is formulated by replacing the oil of an o/w emulsion with a solid lipid or a blend of solid lipid; in this way, the lipid particle-matrix present in the solid phase at room temperature and at body temperature as well. Whereas NLCs are composed of a mixture of specially blended liquid lipid (oil) with solid lipid.

The resulting mixture of the lipid shows a lowering of melting point as compared to the original solid lipid; however, the resultant lipid remains solid at body temperature. Also, the limitations of the SLN delivery technology, such as drug expulsion during storage, reduced particle concentration, reduced

drug loading, are overcome by formulating lipid particles with a controlled nanostructure known as NLC. For most of the drugs, the solubility of liquid lipid is higher than that of solid lipid, which is an important parameter in drug-loading enhancement; NLC enjoys numerous features that lead to a more efficient and promising transdermal route of drug delivery. NLCs contain physiological and biodegradable lipids that help in biocompatibility and low toxicity.

The Nano size ensures increased penetration of the drug into the skin. Additionally, by the use of lipid nanoparticles, an increased skin hydration effect is observed due to its occlusive property. NLCs enhance the chemical stability of compounds which are sensitive to light, oxidation, and hydrolysis. Among the carriers of drug transportation, NLC has arisen as a novel system suitable for topical, dermal, and transdermal administrations for cosmetics and pharmaceuticals [44, 45].

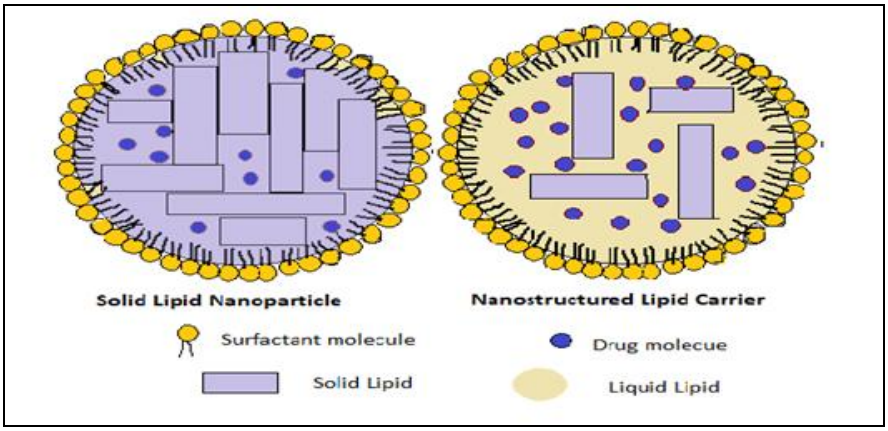


**FIG. 3: DIAGRAMMATIC REPRESENTATION OF SOLID LIPID NANOPARTICLE (SLN) AND NANO-STRUCTURED LIPID CARRIER (NLC)**

The conventional topical preparations reported several problems like low uptake or unwanted absorption to the systemic circulation. The literature review provides detail about new generation NLCs that can deliver an active ingredient across the skin, offering advantages like systemic availability with the least side effects, the bypass of the first-pass metabolism, and control release of a medicament for local and systemic activity as well [45, 46].

**3. Drug Incorporation Model of NLC:** To overcome the limitation associated with old generation SLN, new generation NLCs are developed by incorporating liquid lipid into the solid lipid of SLN. Depending on arrangement and percentage of solid lipid and liquid lipid, NLCs categorized in three types:

**3.1. Type me (Highly Imperfect Matrix) / Imperfect Crystal Model:** In this type, low concentration liquid lipid is used during the high concentration of solid lipid. Oil and Solid lipid are mixed to form o/w nano-emulsion in such a way that when it is cooled to room temperature from its molten stage, it will be in solid form; due to this crystallization process, it leads to a highly disordered structure, so-called as imperfect lipid matrix. This imperfect lipid matrix increases space for drug molecules and the amorphous structure of drugs. NLCs are not able to form a highly ordered structure, as composed of different chain lengths of the fatty acids and the mixtures monoacylglycerols, diacylglycerols, triacylglycerols.

**3.2. Type II Amorphous Type:** NLCs of this type are formulated by mixing special liquids that do not recrystallize anymore after homogenization and cooling, such as isopropyl myristate, hydroxy octacosanyl hydroxy stearate. These liquids are able to generate solid particles of amorphous lipid structure, which can eliminate the occurrence of crystallization, minimizing drug expulsion, because the matrix is maintained in polymorphic form. This amorphous state needs to be preserved.

**3.3. Type III Multiple types:** NLCs of multiple types formulated using high oil concentration. This model improves the loading capacity of several drugs whose solubility in liquid lipids is higher than in solid lipids. Multiple type NLCs are derived from w/o/w emulsions, which are composed of an

oil-in-fat-in-water dispersion. In the process of formulation, melted lipids and hot oil are blended together. During the crystallization process, two lipids phase separates.

At one point of temperature, above which the two phases will be no longer miscible and thus lead to precipitation of oily nano globules. The further addition of liquid lipid into the solid matrix was reported to be advantageous as it prevents drug leakage; also, the higher concentration of liquid lipid responsible for enhanced solubility of lipophilic drugs [46, 47, 48].

## 4. Formulation Additives in NLC:

**4.1. Lipids:** The inner core of NLC composed of Lipids, solid as well as liquid, acts as a carrier for a drug. The commonly used solid lipids for NLCs include triglycerides (*e.g.,* tristearin), glyceryl behenate (Com- pritol® 888 ATO), glyceryl palmitostearate (Precirol® ATO 5), fatty acids (*e.g.* stearic acid), steroids (*e.g.*, cholesterol), and waxes (*e.g.*, cetyl palmitate). These lipids are in solid form at room temperature as having a long chain. They would melt at higher temperatures (*e.g.*,> 80-90 °C) during the formulation process [49].

Liquid lipids, usually used for the construction of NLC, are digestible oils from natural sources. The medium-chain triglycerides, such as Miglyol® 812, frequently used as the liquid lipids because it resembles Compritol®. Apart from these, paraffin oil, 2-octyl dodecanol, propylene glycol dicaprylocaprate (Labrafac®), squalene, isopropyl myristate are also included successfully. On the other hand, fatty acids, such as oleic acid, linoleic acid, and decanoic acid, are added in NLCs as having penetration enhancer property, and oily nature together enhances the efficiency of transdermal delivery [50].

The above-mentioned lipids and many more lipids that are unable to list out in this review are approved by European and American regulatory authorities for clinical applications and for their "Generally Recognized as Safe" (GRAS) status.

There is a requirement of new and biocompatible liquid lipids that are cost-effective, safe, non-irritating, and able to sterilize before the process. Vitamin E (α-tocopherol) and other tocols have been reported as important constituents for nanoemulsions as being biocompatible.

Nowadays, Tocols usage increased in the formulation of NLCs because they exhibit great stability, easily and in a cost-efficient way can be produced on a large scale, and most important, tocols have a good soluble property in lipophilic drugs. Recently NLCs produced by natural origin (plants) are acquiring more attraction. Averina *et a*l. reported that the NLCs prepared by the use of liquid lipid obtained from Siberian pine seed oil and fish oil from Baikal Lake show acceptable physical and chemical stability [51, 52].

**TABLE 1: FORMULATION ADDITIVES WITH EXAMPLE FOR NANOSTRUCTURED LIPID CARRIER DRUG DELIVERY SYSTEM [53, 54]**

| Formulation Additives | Examples |
|---|---|
| Solid lipids | Dynasan®116, Dynasan® 118, Softisan® 154, Cutina® CP, Imwitor® 900 P, Geleol®, Gelot® 64, Emulcire® 61, cetyl palmitate, cholesterol, Precirol® ATO 5, Compritol® 888 ATO, Triglycerides- tricaprin, trimyristin, Tristearin. Hard fat types- Gylceryl monostearate, stearic acid, cetyl alcohol. |
| Liquid lipids | WL 1349, Labrafac® PG, Lauroglycol® FCC, Capryol® 9, Medium-chain triglycerides, paraffin oil, 2-octyl dodecanol, oleic acid, squalene, isopropyl myristate, vitamin E, Miglyol® 812, Transcutol® HP, Labrafil Lipofile® **Natural oils** such as mustard oil, castor oil, cod liver oil, corn oil, sunflower oil |
| Hydrophilic emulsifier | Tween 20, Tween 40, Tween 80, polyvinyl alcohol, Solutol® HS15, trehalose, sodium deoxycholate, Pluronic® F68 (poloxamer 188), Pluronic® F127 (poloxamer 407), Polyvinyl alcohol, sodium glycocholate, Sodium oleate, polyglycerol methyl glucose distearate |
| Lipophilic emulsifiers | Span 20, Span 40, Span 60, Myverol® 18-04K, |
| Amphiphilic emulsifiers | Gelucire® 50/13, phosphatidylcholines, phosphatidylethanolamines, Egg lecithin, soyabean lecithin. |
| Surface modified surfactant | PEGylated lipids - DSPE-PEG, Stearic acid-PEG2000, Solutol® HS15.<br>Ligand conjugated lipid - Folate-PEG-Cholesterol, Folate – stearic acid, Folate-PEG- DSPE, transferrin-PEG-Phosphotidylethanolamine, Mannose-6-cholesterol, MannanPEG-Phosphatidylethanolamine, N-hexadecyllactobionamide |

**4.2. Emulsifiers:** The emulsifiers have been added to stabilize the lipid dispersions. Most of the research work contains the use of hydrophilic emulsifiers such as polyvinyl alcohol, Pluronic F68 (poloxamer 188), polysorbates (Tween), and sodium deoxycholate. Lipophilic or amphiphilic emulsifiers such as Span 80, lecithin are also preferred choices for the fabrication of NLCs. It's reported that the use of a combination of emulsifiers in formulating NLCs prevent particle aggregation more efficiently. Polyethylene glycol (PEG) added in NLCs, as its property to deposit on the shell and thus prevent its uptake by the reticuloendothelial system (RES), leading to prolong the circulation time of drugs. Table 1 gives detailed information relating to the materials used in the formulation of NLCs. Another necessity for NLCs stability is the ability for preservation. The preservatives have an impact on the physical stability of lipid dispersions [53, 54, 55].

**4.3. Stabilizers:** During long-term storage of dispersions, element aggregation can happen and cause destability. NLCs show better stability on storage as compared to SLN as the aggregate formation is rapid in SLN. In the NLC dispersions, the particles behave as "pearl-like networks," so the particles being in a repaired place will avoid collisions and perikinetic flocculation. Stabilizing agents are added in the formulation to stabilize the NLCs. Poloxamers, which are available in different grades in the market, is the preferred choice for numerous formulations. The stability of gel formulation is enhanced by using Poloxamer in combination with organic solvents [56, 57]. In the presence of organic solvents, Poloxamer 407 brings together two liquid crystal structures, namely micellar cubic and hexagonal structures, that build thermodynamic stability. Poloxamer 407 and Poloxmer 188, also used together in liposome formulation, showed increased liposome stability by enlarging half-life, preventing accumulation and fusion of phosphatidylcholine multilamellar vesicles. Poloxamer is less stable in aqueous solution, to overcome this property and to enhance the stability of hydrogels, modified poloxamer is developed in combination with acrylate and thiol groups. A notable rise in the stability of drugs around three to four times its potential is reported in CDDS. Another example of a stabilizer widely used systemically is Polyethylene glycol (PEG). In general, PEG acts by surface modification of particles by leaving a hydrophilic coat. It provides good physical stability and dispersibility of colloids. It acts by enhancing the residence of colloids in the systemic circulation, increasing the stability of colloids in gastrointestinal (GI) fluids, accelerating colloid transport across the epithelium, Modulating the interaction of colloids with mucosa for targeted drug delivery requirements, and improving biocompatibility [58, 59, 60].

**5. Formulation Procedures of Nanostructured Lipid Carriers (NLCs):** There are many methods used to formulate a nanostructured lipid carrier drug delivery system. The selection of appropriate methodology for formulation is based upon the type of drugs mainly its solubility and stability, the lipid matrix and route of administration *etc*.

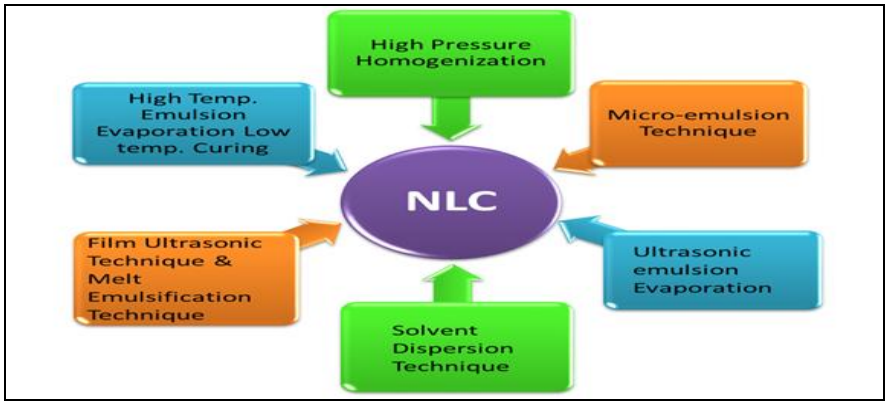


**FIG. 4: FORMULATION METHODS FOR NLC**

**5.1. High-Pressure Homogenization Technique:** High-Pressure Homogenization Technique (HPH) is reported as the most reliable and powerful method for the large-scale formulation of NLCs, SLNs, parenteral emulsions and lipid drug conjugate.

In this technique, lipids are pushed/passed with high pressure (150-200 bars) through a narrow opening of few micron ranges. Thus, the high shear stress and cavitation causes disruption of particles to submicron range. While in other formulation techniques, High-Pressure Homogenization does not show scaling up problems. Basically, two approaches, hot and cold homogenization used for production by high-pressure homogenization [61, 62].

**5.2. Hot Homogenization Technique:** In this method the drug and melted lipid is dispersed in the aqueous medium containing surfactant and temperature maintained equivalent to temperature of melted lipid, with constant stirring by a high shear device. The pre-emulsion formed is further homogenized by using a piston gap homogenizer, and the obtained nanoemulsion is cooled down to room temperature where the lipid recrystallized and leads to the formation of nanocrystals [63].

**5.3. Cold Homogenisation Technique:** Cold homogenisation method involves the use of solid lipid entrapping drugs. This method was developed to overcome the problems associated with the hot homogenization method. Cold homogenization reduces the thermal exposure of sample [64].

**5.4. Microemulsion Technique:** In this method, the drug is incorporated in molten lipid. Simultaneously, on the other side, an aqueous phase is prepared to contain surfactant, cosurfactant water and is heated till the temperature matches with the temperature of molten lipids.

Then, with mild stirring, the aqueous phase is added to the molten lipid. When the compounds get mixed in appropriate ratios, it leads to form a transparent, thermodynamically stable microemulsion system. Thus the basis for the formation of nanoparticles of a requisite size is microemulsion. This micro-emulsion is further dispersed in a cold aqueous with mild stirring. The oil droplets rapidly recrystallize out from the dispersion in cold condition [65].

**5.5. Ultrasonic Emulsion Evaporation Technique:** In this technique, the solid lipid, liquid lipid, and the drug combination stands as an oil phase. This oil phase is further added in an aqueous solution containing surfactant; the dispersion is formed with the help of a probe ultrasonicator. The resultant dispersion was then cooled and solidified to form NLCs. Once a stable dispersion is formed, the oil phase is subjected to evaporation by heating under reduced pressure or by evaporation while stirring continuously. Avoidance of heat during the formulation is the chief advantage of this method. Sometimes toxicological problems may result from solvent residues from the product obtained by this technique [66].

**5.6. Solvent Dispersion Technique:** In the solvent dispersion method, solid lipid, oil, and the drug are dissolved in a water-miscible organic solvent such as ethanol, isopropanol or acetone. Later, the slow addition of organic solution to the aqueous phase containing emulsifier the lead formation of NLCs which are generated by centrifugation technique. NLCs formulated in this way generally show increased drug loading with the mass of the liquid. To further enhance the drug loading of NLCs, a saturated drug solution is usually used as a dispersed phase. Simplicity, speed, and the low requirements of the instruments are advantages of the process as compare to other techniques. This method is not convenient for large scale production. This method has some limitations because of toxicological problems due to residual organic solvent in the product [67].

**5.7. Film-Ultrasonic Technique:** In the technique, the solid lipids, liquid lipids, and drugs are dissolved in an appropriate organic solvent, which is later removed by the vacuum evaporation process. An aqueous surfactant solution is added to form a layer of mixed lipid films. Further, by using an ultrasound probe sonicator, small and uniform NLCs were produced. Most often, this method is used due to its ease and practicality and its yield of small, uniform particles. However, toxicological problems may result from solvent residues from the product obtained by this method, same as that of the Ultrasonic Emulsion Evaporation technique and Solvent Dispersion technique [68].

**5.8. High-Temperature Emulsion Evaporation Low-Temperature Curing:** In this technique, the organic phase and aqueous phase are heated independently. Later that, at the same temperature, organic phase is added to the aqueous phase containing an emulsifier so that an emulsion is produced.

The volatile organic solvent is then evaporated from the system by heating, and the resulting concentrated liquids quickly dispersed in ice water (0-4 ℃). In this way, an NLC dispersion solution is obtained. The advantages of this method include its simplicity and speed, but this technique is not entirely appropriate to get industrialized, and the other limitation involves residual organic solvent.

**5.9. Melt Emulsification Technique:** In this technique, firstly, the solid lipids and liquid lipids are heated and mixed. Then the drugs are added to form an organic phase. The organic phase is added to the aqueous phase containing the surfactant and stirred to form a coarse emulsion. Further, the resultant solution is subjected through high-pressure homogenization to form the NLCs.

This is an advantageous technique because there is no organic solvent residue, no burst release at the initial time as that of SLN, and dispersions with high lipid concentration [69].

**TABLE 2: POLYMERS USED IN TRANSDERMAL DRUG DELIVERY**

| | Polymers | Advantages | Disadvantages |
|---|---|---|---|
| Natural Polymer | Carrageenan (0.1-0.5%)<br>Gellan gum (0.04-4%w/w)<br>Cellulose (1-2% w/w)<br>Starch (3-5% w/w)<br>Chitosan (1-3%w/w)<br>Xantham gum (0.5-1%) | Less toxic Biocompatibility<br>Biodegradable Easily available | Iigh degree of variability in natural materials derived from animal sources tructurally more complex xtraction process very complicated and high cost |
| Synthetic Polymer | Poly (ethylene glycol)<br>Poly (lactic acid)<br>Poly (cyanoarylate)<br>Poly (acrylic acid)<br>Poly Vinyl Alcohol | Biocompatibility | Toxic Non-degradable Synthetic process is very complicated and high cost |

**6. Characterization of NLCs:** Intensive characterization of the structure and mixing behavior of NLCs is essential for studying their behavior.

The physicochemical evaluation for NLCs is critical and very important to confirm quality and stability aspects. Microscopic and Macroscopic evaluation parameters assessed in the development of colloidal systems.

**6.1. Particle Size:** Photon correlation spectroscopy (PCS), laser light diffraction is a suitable method for investigation, and it is effectively applied for particles ranging below 1 µm and up to 100 nm.

For particles below 200 nm, according to Rayleigh's theory, the scattering intensity is proportional to the sixth potency of the particle diameter. With the help of PCS, along with particle size, polydispersity index (PI) can also be determined for NLC.

**6.2. Zeta potential (ZP):** It can be measured by determining the velocity of the particles in an electrical field (electrophoresis measurement) using Zeta sizer assembly.

**6.3. Shape and Morphology:** Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) is the most often used techniques to determine the shape and morphology of NLCs. These techniques can also determine the particle size and size distribution. SEM is not very sensitive to the nanometer size range, so to overcome that, the modified method *i.e.,* field emission SEM (FESEM) can be used to detect nanometer size range.

TEM is an alternative technique where colloidal samples could be visualized at high resolution. Sufficient contrast can be given to a thin film of the frozen sample by use of osmium tetra-oxide. This allows the sample to be viewed directly in the TEM under specific conditions like temperature -196º and very poor pressure so that the examination of the sample is possible by preservation of microstructure/ nanostructure despite the high vacuum [70].

**6.4. Differential Scanning Calorimetry (DSC):** DSC is usually used to get information about both the physical and the energetic properties of an individual compound or formulation. DSC measures the heat loss or gains as a result of physical or chemical changes within a sample as a function of the temperature. Comparative study of the melting enthalpy of the bulk material with the

melting enthalpy of the dispersion helps to estimate the rate of crystallinity [71, 73].

**6.5. Nuclear Magnetic Resonance (NMR):** NMR is used to determine the size and the qualitative nature of nanoparticles as well. NMR techniques are used to check the chemical shift, which complements the sensitivity to molecular mobility to provide information on the physicochemical properties of components within the nanoparticle.

The mobility of the solid and liquid lipids is related to the width at a half amplitude of the signals. Broad signals and small amplitudes are characteristics of ideal molecules with restricted mobility and strong interactions.

The higher line width of NLCs as compared to the physical mixture of the materials added in NLCs indicates the interaction of liquid oil with the solid lipid. NMR studies reported that immobilization of the nanoparticles of NLCs is stronger as compared to SLNs with totally crystallized cores [71, 72].

**6.6. Atomic Force Microscopy (AFM):** AFM technique is ideal for measuring morphological and surface features that are extremely small. AFM does not use photosensor electrons but a very small sharp-tipped probe located at the free end of a cantilever driven by interatomic repulsive or attractive forces between the tip and surface of the specimen.

Although electron microscopy is still frequently used, the AFM technique offers substantial benefits: real quantitative data acquisition in three-dimension view, minimal sample preparation times, flexibility in ambient operating conditions, and effective magnifications at the nano levels [71, 72].

**6.7. X-ray Scattering:** By using this technique, characteristic interferences that are generated from an ordered microstructure are measured. A typical interference pattern generates due to specific repeat distances of the associated interlayer spacing'd'.

According to Bragg's equation 'd' can be calculated by using formula $d= n/\lambda\ 2 \sin \theta$ Where, $\lambda$ is the wavelength of the X- ray being used; n is an integer and nominates the order of the interference and $\theta$ is the angle under which the interference occurs [72, 74].

**6.8. Topical Bioequivalence Study:**

**6.8.1. *In-vitro* Drug Release:** It has been reported that the NLCs show prolonged half-life and retarded enzymatic attack in systematic circulation as compared to SLN and hence achieves controlled or sustained release of the drug.

The drug release behavior from NLCs can be modulated by altering the production temperature, emulsifier composition and oil percentage incorporated in the lipid matrix. As the drug partitioned between the lipid matrix and water composition of NLCs sustained or modulated drug release is observed.

*In-vitro* drug release from nanostructured lipid carriers can be assessed by using dialysis method or franz cell diffusion method. Proper interpretation of *in-vitro* drug release correlating with in-vivo drug release behaviour must be checked [71, 72, 73, 74].

**6.8.2. Tape Stripping (TS):** TS provides information of drug uptake, apparent steady-state levels, and drug elimination from the stratum corneum based on a stratum corneum drug concentration time curve (FDA's Draft Guidance, 1998).

This technique is popularized as a dermato-pharmacokinetic approach similar to that of blood, plasma and urine analysis for drug concentrations as a function of time [75].

**6.8.3. Microdialysis (MD):** This is a continuous sampling technique in which the molecule of interest is collected from the target tissue; thus providing a time course of drug action or biochemical monitoring of the tissue.

The technique involves an artificial capillary, in which a hollow semi-permeable probe is carefully inserted into the site of interest: Brain, muscle, eye, and skin. Therefore, it provides valuable information about unbound drug concentration [76].

**7. Patent Status of NLCs:** Over the previous decade, NLC has been profoundly used as carriers for various bioactive molecules.

**Table 4** presents a brief survey of patents regarding the unique development in the nanostructured lipid carriers.

**TABLE 3: TRANSDERMAL NANOSTRUCTURED DRUG DELIVERY SYSTEM**

| Drugs and Category | Method | Gel (Gelling Agent) / Cream | Remarks | Reference No. |
|---|---|---|---|---|
| Psoralens | High shear homogenization | Carbopol 980 | Enhanced permeation and controlled release were observed | [49] |
| Ketoprofen (NSAID's) | Simple blending and grinding using high energy micro mill | Xanthan hydrogel | Improved drug therapeutic efficacy and safety, improvement in the dissolution stability | [78] |
| Marigold extract (anti-wrinkle) | High-speed homogenization | Cream | NLCs loaded cream stable at 4°C and room temperature conditions, The wrinkles parameters evaluated on 25 healthy volunteers after using creams containing ME-NLCs were significant | [85] |
| FP (NSAID's) | Ultrasonication | Carbopol 934 | Faster effect with prolonged activity | [87] |
| Clobetasol propionate (corticosteroids) | Solvent diffusion method | Carbopol | Improved drug loading capacity was observed | [88, 89] |
| Miconazole nitrate (anti-fungal) | Hot homogenization method | Carbopol 940 | NLC hydrogel to increase the encapsulation efficiency, improved stability with sustained and faster relief from fungal infection | [88, 93] |
| Aceclofenac (NSAID's) | Melt emulsification, Low temp solidification, High-speed homogenization | Carbopol940P, xanthan gum,HPMC, chitosan | The study involves-release rate, permeation rate, and pharmacodynamic activity modulated with a change in the ratio of solid lipid to liquid lipid composition | [89] |
| Minoxidil (anti-hypersensitive) | Ultrasonication technique | Carbopol 934 | NLC gel showed faster onset and elicited prolonged activity up to 16 h | [90, 91] |
| Nystatin (anti-fungal) | Hot homogenization and ultrasonication | Cream | NLCs represent good physical stability, high entrapment efficiency and controlled drug release | [93] |
| Celecoxib (NSAID's) | Microemulsion | Carbopol (Ultrez 10) | NLC based gel formulation- the study showed faster onset and elicited prolonged activity until 24h | [93] |
| CoQ10 (anti-ageing) | Ultrasonication method | Cream | CoQ10-NLC, efficiently counteract UVA-associated mitochondrial depolarization | [96] |
| Lidocaine (local anesthetic) | Ultrasound dispersion method | Polycarbophil | *In vitro* permeation studies indicated that LID SLN gel and LID NLC gel significantly sustained the LID release LID NLC gel resulted in 5-fold and 6-fold increase in duration of anesthesia | [97] |
| Tacrolimus (NSAID's) | Hot homogenization technique by sonication | Carbopol 940 | Lipid modification resulted in high entrapment efficiency and topical delivery | [98] |

NLC: Nano-lipid carrier, NSAIDs: Non-steroidal anti-inflammatory drugs, FP: Flurbiprofen, HPMC: Hydroxypropyl methylcellulose, CT: Capric triglycerides, SLN: Solid-lipid nanoparticle, LID: Lidocaine

**8. Market Concern:** It is observed that in the most recent couple of decades, NLC formulations number in patenting progressively and significantly increased. NlCs are most widely used and patented in the cosmeceutical industry as compared to pharmaceuticals. Many NLC pharmaceutical formulations are in the pipeline to get patented, and some are under clinical phase study to launch in the market.

**TABLE 4: PATENTS PUBLISHED ON NANOSTRUCTURED LIPID CARRIERS DRUG DELIVERY**

| Publication No. | Title | Author | Publication Date | Reference No. |
|---|---|---|---|---|
| WO2018109690 | Production of lipid nanoparticles by microwave synthesis | Soares Sobrinho, Jose Lamartine | 2018-21-06 | [101] |
| KR101777616B1 | Nano-structured lipid carrier comprising α-tocopherol and preparing method thereof | *Geun et al* | 2017-13-09 | [102] |
| WO2017185155A1 | Nanostructured lipid carriers and methods for making and using them | Fabiana Munhoz *et a*l. | 2017-11-02 | [103] |
| CN102283809B | Preparation of nanostructured lipid carriers (NLC) method and products made | Rosner Ismail *et al*. | 2016-12-14 | [104] |
| *WO2012127037A2* | Vitamin D and corticosteroid coloaded into NLC in order to increase drug accumulation in the skin | Louise Bastholm Jensen, Karsten Petersson | 2012-12-27 | [105] |
| WO2011116963 A2 | Lipid nanoparticle capsules | Viladot Petit V et al. | 2011-09-29 | [106] |
| US20110097392 A1 | Antibody bound synthetic vesicle containing molecules for delivery to central and peripheral nervous system cells | Wang KK *et al.* | 2011-04-28 | [107] |
| US20110059157 A1 | Anionic lipids and lipid nano-structures and methods of producing and using the same | Awasthi V and Lagisetty P | 2011-03-10 | [108] |
| US20100247619 A1<br>WO2008000448 A3 | Nanostructured lipid carriers containing riluzole and pharmaceutical formulations containing said particles | Bondi' ML *et al.* | 2010-09-30 | [109] |
| US20100047297 A1 | Nanocrystals for use in topical cosmetic formulations and method of production thereof | Petersen R | 2010-02-25 | [110] |
| US20090238878 A1 | Solid nanoparticle formulation of water-insoluble pharmaceutical substances with reduced Ostwald ripening | Singh CU | 2009-09-24 | [111] |
| EP2229936 A1 | Nanonized testosterone formulations for improved bioavailability | Keck C and Muchow M | 2009-03-09 | [112] |
| US20080020058 A1 | Lipid nanoparticles based compositions and methods for the delivery of biologically active molecules | Chen T *et a*l. | 2008-01-24 | [113] |

**TABLE 5: MOST IMPORTANT PATENTS OF NLC THAT CONCERN TO SPECIfiC THERAPEUTIC / TECHNOLOGICAL AIMS**

| Therapeutic/ Technological aim | Active moiety | Role | Patent No. | Reference No. |
|---|---|---|---|---|
| Cancer | Zerumbone | Treatment of leukemia | WO2014123406A1 | [114] |
| Brain delivery | Riluzole | Medicinal formulations are prepared to treat amyotrophic lateral sclerosis and multiple sclerosis | US2010247619 | [115] |
| | Ubidecarenone | Treatment of neurodegenerative disorders | IN1251/MUM/2012 | [116] |
| Antioxidant and vitamin delivery | Tocotrienols | Lipid compositions that include tocotrienols are engineered | WO2011028757 | [117] |
| | Curcuminoids | Curcuminoid formulations with enhanced bioavailability that are suitable for Alzheimer's disease treatment are produced | WO2010010431 | [118] |
| Arthritis | Celecoxib | Celecoxib encapsulated NLC formulations and Surface Modification for Skin Permeation | US8715736B2 | [119] |
| Occular delivery | Genistein, Pranoprofen, Dexamethason, Econopred, Ofloxacin. | NLC - intraocular lens system, which is loaded with anti-inflammatory drugs and antibiotics, in order to prevent or treat cataract surgery complications | CN105476730B | [120] |

**TABLE 6: NLC DERMAL COSMETICS AVAILABLE IN MARKET [121]**

| Trademark | Active molecule | Manufacturer |
|---|---|---|
| IOPE Line | Ubidecarenone, omega-3, and omega-6 unsaturated fatty acids | AmorePacific |
| NLC deep effect eye serum | Ubidecarenone, highly active oligosaccharides | Beate Johnen |
| NLC deep effect repair cream | Ubidecarenone, TiO2, and highly active oligosaccharides | |
| NLC deep effect reconstruction cream | Ubidecarenone, acetyl hexapetide-8, highly active oligosaccharides in a polysaccharide matrix, and micronized plant collagen | |
| NanoLipid Restore CLR | Black currant seed oil | Chemisches Laboratorium (Dr. Richter) |
| NanoLipid Q10 CLR | Ubidecarenone and black currant seed oil | |
| NanoLipid Basic CLR | Ubidecarenone and black currant seed oil | |
| NanoLipid Repair CLR | Black currant seed oil and manuka oil | |
| Regenerations Creme Intensive | Macadamia ternifolia seed oil, avocado oil, urea, and blackcurrant seed oil | Scholl |
| Swiss Cellular White | Glycoproteins, Panax ginseng root extract, Equisetum arvense extract, Camellia sinensis leaf extract, and Viola tricolor extract | La Prairie |
| Surmer Light Nano-Protection Cream | Kukui nut oil, Monoi Tiare Tahiti®, pseudopeptide, coconut milk and wild indigo | Isabelle Lancray |
| Surmer Rich Nano-Restructuring Cream | Kukui nut oil, Monoi Tiare Tahiti®, pseudopeptide, coconut milk, wild indigo, and tamanol | |
| Surmer Nano-Vitalizing Beauty Elixir | Kukui nut oil, Monoi Tiare Tahiti®, pseudopeptide, coconut milk,and wild indigo | |
| Surmer Nano-Hydrating Cream Mask | Kukui nut oil, Monoi Tiare Tahiti®, pseudopeptide, coconut milk, wild indigo and tamanol | |
| Surmer Nano-Reshaping Eye Cream | Kukui nut oil, pseudopeptide, hydrolyzed wheat protein, Ximenia americana seed oil, and tamanol | |
| Olive Oil Anti Wrinkle Care Concentrate | Olea europaea oil, panthenol, Acacia senegal, tocopheryl acetate | Dr. Theiss |
| Olive oil eye care balm | Olea europaea oil, Prunus amygdalus Dulcis oil, hydrolyzed milk protein, tocopheryl acetate, Rhodiola rosea root extract, and caffeine | |

**CONCLUSION:** NLC is novel carrier systems that have the potential to overcome the limitations of conventional colloidal transdermal drug deliveries. NLC is the advanced generation of the carrier systems after SLNs and liposomes.

They have good perspectives to be developed and marketed very successfully; the reason for this is that they were developing, considering industrial needs and customer needs. The promising results of NLCs prove their potential as versatile carrier systems for application in cosmeceutical formulations and pharmaceutical formulations as well.

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