Abstract:
Lipid based carriers (solid lipid nanoparticles-SLN and nanostructured lipid carriers-NLC) were developed at the beginning of the 90s and has been extensively used for topical and transdermal delivery of pharmaceuticals and cosmeceuticals. Among them, NLC’s are widely accepted for maintaining drug stability, improving drug therapy, solubilizing poorly water soluble drugs, achieving controlled and sustained drug delivery and reduced toxicity. This review article discusses different formulations and characterization techniques and discusses how NLCs can penetrate the skin barrier. Further, overview on the current state of the art of NLCs as therapeutic and cosmetic formulations are also discussed in detail. The study highlights the reported data on oral bioavailability and toxicological studies and how these NLC’s can be employed as promising drug delivery systems for novel treatments in the near future.

Keywords: Nanostructured Lipid Carrier, transdermal drug delivery, topical drug delivery nanoparticles, penetration.

Introduction
Among the various delivery systems, drug delivery through skin can be considered as one of the convenient routes of administration (1). Skin drug delivery can be either dermal (topical) or transdermal. Dermal delivery includes application of drug directly at the site of action (skin surface), resulting in higher localized drug concentration with reduced systemic drug exposure. In transdermal drug delivery, the drug is delivered through the layers of the skin to reach the systemic circulation (2). One of the key advantages of transdermal drug delivery is improved patient acceptance or compliance compared to other routes of administration (3).

The major obstacle associated with the transdermal delivery system is the challenges offered by the Stratum Cornea (SC), whose molecular architecture permits only selected molecules to penetrate through it (4). Hence several new technologies have been developed to increase the transdermal permeation of drugs. Some of the important strategies used to enhance transdermal absorption are by using physical enhancers like ultrasound, iontophoresis, electroporation, magnetophoresis, micronedle, or by using chemical permeation enhancers such as sulphoxides, azones, glycols, alkanols, terpenes etc. or by the most important vesicular systems which include liposomes, niosomes, transfersomes, microemulsion and lipid nanoparticles (5).

The physical permeation enhancement methods are invasive and expensive, whereas the chemical enhancers cause skin irritation which may damage the skin permanently. These facts made the vesicular system more popular than the physical and chemical enhancement methods (5). The conventional vesicular systems like liposomes faces various stability issues which caused formulators to focus on lipid nanoparticles (6). Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are the two lipid nanoparticles which are extensively used for topical and transdermal delivery of drugs (7).
Recently NLCs are gaining more attention as it overcomes the complications connected with SLNs such as drug expulsion during storage and limited drug loading. In addition to this, the occlusive effect and use of lipid components in NLCs reduce the barrier function of SC, thus making them suitable for enhancing transdermal permeability (8).

2. Transdermal skin penetration
Nano lipid carriers penetrate into the skin by three basic pathways.
1. Channeling through the hair follicles and the sweat glands i.e. transappendageal.
2. Transcellular intake by direct permeation through the cell membrane of the epidermis.
3. Intercellular route involving passage through the gaps between the epidermal cells.
   The nano size of these carriers promotes close association with stratum corneum of the skin, which permits topical spreading of the formulation causing occlusion and hydration of the skin. This leads to the widening of the gaps between the corneocytes. In addition, the presence of surfactants in these carriers causes alteration of the skin structures which further accelerates the penetration of the drug moieties. It is also hypothesized that the lipid richness of the epidermis may cause exchange of lipids with the nano carriers, thus adding to the penetration enhancement (10).

3. Advantages of Nanostructured Lipid Carriers (11)
   - Prevention of chemical degradation of encapsulated drugs which improves drug stability.
   - Site specific delivery to obtain control and targeted drug release.
   - Improved drug loading capacity.
   - Biocompatible and biodegradable lipids which results in reduced cyto and systemic toxicity.
   - Holds both lipophilic and hydrophilic drugs.
   - Reduced usage of organic solvents.
   - Cost affective.

4. Disadvantages of Nanostructured Lipid Carriers (12)
   - Polymorphic changes of lipids may lead to drug expulsion on storage.
   - Physical changes like gelation and formation of super cooled melts.
   - Sterilization issues, specially formulations used for parental purpose.
   - Insufficient data on clinical studies related to NLC.

5. Types of NLC (13, 14)
   a) Type I: Highly imperfect solid matrix: In this type of NLCs, a blend of solid and liquid lipids are used. The structural difference of lipids leads to imperfect, disarranged and disordered matrix. This structural disarrangement offers a lot of space for the accommodation of the drug.
   b) Type II: Multiple oil/fat/water carriers: The main drawback of SLNs is drug expulsion due to the poor solubility of drug in the solid lipid. To overcome this, in NLCs, liquid lipids are used in large amounts, based on the fact that drugs are more soluble in liquid lipid than solid lipid. Use of liquid lipids leads to formation of minute nano compartments of oils which can accommodate large amount of drugs.
   c) Type III: Amorphous Matrix: In this type of NLCs, crystallization is avoided by mixing solid lipids with special lipids like medium chained triglycerides, so that the matrix formed is not crystalline but amorphous in nature.

6. Method of preparation (25, 26)
   - High-Pressure Homogenization Method
   - Ultrasonic Emulsion Evaporation Method
   - Solvent Dispersion
   - High-Temperature Emulsion Evaporation-Low-Temperature Curing
   - Microemulsion Method
   - Phase Inversion Temperature (PIT) method
   - Double emulsion technique
   - Melt Emulsification Method

7. Lipids used in NLCs
   Lipids used in NLCs are biocompatible and
biodegradable i.e. lipids which belong to the Generally Regarded As Safe (GRAS) category (10). Nanostructure lipid carriers (NLCs) contain both solid and liquid (oil) lipids in defined ratio. The structural imperfection of NLC is due to the presence of Liquid Lipids (oil), which converts the perfect crystalline structure of the solid lipid to a crystal lattice with many spaces, thus resulting in greater drug encapsulation and drug loading (27).

The solid lipids commonly used for NLCs include glyceryl palmitostearate, glyceryl behenate, steroids (e.g. cholesterol) and waxes (e.g. cetyl palmitate). Liquid lipids used are Caprylic/Capric triglycerides (C8/C10), Vitamin E and its derivatives, Monoacylglycerols, oleic acid, isopropyl myristate, paraffin oil, 2-octyl dodecanol, propylene glycol, dicaprylocaprate (Labrafac®), Soya lecithin, Squalene. Generally digestible oils from natural sources are preferred. For topical delivery, use of oleic acid, linoleic acid, and decanoic acid will give an additional benefit as they are penetration enhancers. Liquid lipids and solid lipids for the preparation of NLCs are selected based on the relative drug solubility (28,29).

Surfactants used to prepare NLCs are usually selected based on their emulsification capacity (12). Hydrophilic, Lipophilic and Amphiphilic emulsifiers are used to stabilize the lipid dispersions.

Hydrophilic emulsifiers used are Pluronic® F68 (poloxamer 188), Pluronic® F127 (poloxamer 407), Tween 20, Tween 40, Tween 80, polyvinyl alcohol, Solutol® HS15, trehalose, sodium deoxycholate, sodium glycocholate, sodium oleate.

Lipophilic emulsifiers used are Myverol® 18-04K, Span 20, Span 40, Span 60 Amphiphilic emulsifiers used are Egg lecithin, soya lecithin, phosphatidylcholines, phosphatidylethanolamines, Gelucire® 50/13 (28, 29, 30).

8. Cosmetic Benefits of NLC

Recognition of NLCs in cosmetic industry is due to its pearlaceous morphology and nano size. Their composition, high drug payload, stability, protective and occlusive property makes them popular in this field (31). Some of the important benefits are mentioned below.

8.1 Occlusive effect: The lipid nano particles form a single layered film on the skin because of its high lipid composition and submicron size. Adhesive action due to the film formation prevents the water loss from the skin thus producing a moisturizing effect (32). This feature is effectively used in anti-aging formulations where moisture retention is the most important requirement (33).

Skin aging can be due to intrinsic or extrinsic factors. Intrinsic aging occurs with age and is inevitable. This is due to decreasing sweat/oil glands, collagen and elastin which makes skin less elastic and more fragile. The occlusive effect of NLCs on skin causes rapid hydration and may improve the elasticity (34).

Lucia Montenegro et al. formulated a gel of NLCs containing rosemary essential oil (EO). Rosemary essential oil (EO) contains flavonoids and terpenes and hence possesses numerous therapeutic activities such as antioxidant, anti-inflammatory, fungicidal, antimicrobial, and anticancer activities. Studies have showed that rosemary essential oil (EO) can be used to treat many skin disorders. Skin hydration and improvement in skin elasticity was proven from the in vivo study, making it a suitable candidate for topical formulations (35).

8.2 Protective action against UV rays: The crystallinity of NLCs aids in the protection of the skin from harmful UV radiations. This property can be attributed to the light scattering property of their crystalline structure. This inherent property can be synergized by inclusion of a sunscreen agent into NLCs (36, 37). UV-blocking materials of ethylhexyl methoxycinnamate, oxybenzone, and avobenzone, were formulated into NLCs as a sunscreen formulation by Chen et al. The Sun Protection Factor (SPF) and UVA-protection factor (PFA) was 51.5 and three stars respectively for...
the optimized formulation. The crystallinity index of the optimized formulation was found to be maximum, further emphasizing its UV blocking ability (38).

8.3. Aesthetic Appearance: The presence of lipid dispersion gives an elegant appearance to these nano carriers. This may be due to the whitening effect of the lipid (39). The undesired pigment of vitamin E was masked by formulating it into SLNs. So, the incorporation of active ingredients of cosmetics into NLCs/SLNs improve the customer acceptance by giving it an attractive appearance (40).

8.4. Stability improvement: The improvement of stability of the active ingredients, incorporated into NLC is attributed to the presence of spatially unlike lipids. These dissimilar lipids lead to a highly disarranged molecular structure which has high encapsulation ability. This uniqueness of the NLC Matrix is used to encapsulate drugs which are unstable or undergo physical or chemical degradation (41,42). Solubility of the drug in the lipids is an important criteria for attaining this stability. So the lipid must be selected based on its ability to solubilize the drug (12,43).

A novel whitening agent Phenylethyl resorcinol was formulated into NLCs to overcome the drawback of photo degradation by Kim et al. The encapsulation efficiency was 93.1 ± 4.2% and loading capacity was 8.5 ± 0.4%. The stability test was performed for 3 months at 4 °C in the dark and 25 °C under daylight and the results showed excellent photo stability of the NLC loaded Phenylethyl resorcinol. The tyrosinase activity was efficiently reduced in melanoma cells indicating development of effective whitening agents (44).

8.5. Use of NLCs in perfumes: Perfumes are sweet-smelling liquids made from essential oils extracted from flowers and spices and are used to give an attractive/pleasant smell to one’s body (45). Rapid loss of perfume action due to evaporation of the solvent is a major challenge in formulation of perfumes. Incorporating perfumes into emulsions containing oils is one approach to prolong their effect. Substituting lipid mixtures for liquid lipids (oil) of o/w emulsions leads to the formation of a solid matrix. This may result in slower release of the perfumes from this matrix compared to the emulsion (46). Hence NLCs could be used for the incorporation of perfumes.

Perfumes like CA, CT and Kenzo was loaded into NLC by Aiman Hommos. Panel nose test was performed to confirm its suitability. Perfume intensity was evaluated for 3, 6, 18, 24, 28 and 48 h. The towels treated with softeners containing the perfume-loaded NLC (Kenzo NLC) showed high intensity (47). Table 2 gives the cosmetic applications of NLCs.

9. Dermal Benefits of NLC: Local delivery of drug to the skin by NLC is a major interest of study; as it is aimed in providing site specific action. The Main advantage of targeted delivery is that it avoids systemic exposure of the drug. Reduced systemic reach of drug reduces the toxicity associated with it. The formulation used for local action should be designed in such a way that the drug must not reach the viable dermis, as it may be absorbed by the capillaries into the blood (53,54, 55).

In order to attain the topical action of NLCs, they must be incorporated into aqueous or semi solid dispersion. Incorporation of viscosity enhancers (hydroxypropyl methylcellulose, xanthan gum, hydroxypropyl methylcellulose, chitosan and Carbopol®) will be useful to attain the required consistency. The popularity of NLCs in topical applications is due to its ability to incorporate huge amount of drugs in the disordered matrix. These nano carriers on application achieve close contact with the stratum corneum due to its nano size. This will increase the drug flux and cause the drug to accumulate in the skin appendages resulting in the release of the drug in a controlled fashion to the site of action (28,56).

Broad range therapeutic molecules which show systemic adverse effects can be delivered through this formulation for obtaining efficient management of the disease, Betamethasone

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Table No 1: Evaluation of NLCs

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Objective/Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size</td>
<td>Photon Correlation Spectroscopy (PCS) based on laser light diffraction</td>
<td>15</td>
</tr>
<tr>
<td>Poly dispersability index</td>
<td>Measures the particle size distribution</td>
<td>16</td>
</tr>
<tr>
<td>Entrapment efficiency</td>
<td>Total drug encapsulated within NLCs can be determined by UV spectroscopy</td>
<td>17</td>
</tr>
<tr>
<td>FT-IR Spectroscopy</td>
<td>Used to determine the compatibility between the excipients and active moiety</td>
<td>18</td>
</tr>
<tr>
<td>Zeta potential</td>
<td>Measures the electric potential of a particle determined by Dynamic Light Scattering (DLS) principle (electrophoresis measurement).</td>
<td>19</td>
</tr>
<tr>
<td>Shape</td>
<td>Involves determination of lamellarity of particles by Scanning electron microscopy (SEM)</td>
<td>20</td>
</tr>
<tr>
<td>Morphology Crystalline index</td>
<td>Atomic Force Microscopy (AFM) Differential scanning calorimetry (DSC) and X ray diffraction</td>
<td>22</td>
</tr>
<tr>
<td>Drug release</td>
<td>In vitro diffusion method</td>
<td>24</td>
</tr>
</tbody>
</table>

Figure 1: Representation of drug accommodation in SLN and NLC (13, 14)
<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Lipids used</th>
<th>Use</th>
<th>Method of preparation</th>
<th>Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbyl palmitate</td>
<td>Witcosol 85, Miglyol 812</td>
<td>Anti-oxidant, Moisturizer</td>
<td>High pressure homogenization</td>
<td>Moisturizing effect and skin penetration effect of Ascorbyl palmitate encapsulated in SLNs and NLCs was studied on 10 female Caucasian volunteers, the results proved to be better compared to the placebo.</td>
<td>48</td>
</tr>
<tr>
<td>1.2 Coenzyme Q10</td>
<td>Cetyl palmitate, Miglyol 812</td>
<td>1.3 Anti-aging</td>
<td>1.4 High pressure homogenization</td>
<td>1.5 Tape-stripping test showed that Coenzyme Q10-loaded NLCs had improved skin penetration compared to the reference emulsion and liquid paraffin</td>
<td>49</td>
</tr>
<tr>
<td>1.6 Coenzyme Q10 and retinol dehydrocoloaded</td>
<td>Compritol 888 ATO, Isopropyl Myristate</td>
<td>Management of wrinkles</td>
<td>high shear homogenization</td>
<td>1.7 Anti-wrinkle effect was studied by applying the formulation on wrinkle induced mice. Reduction in the epidermal thickness and recovery from wrinkle was observed.</td>
<td>50</td>
</tr>
<tr>
<td>CA, CT and Kenzoe</td>
<td>Apifil, Dynasan 116 and Precifac ATO 888</td>
<td>Perfume</td>
<td>high pressure homogenization</td>
<td>Panel nose test confirmed slower release of the perfume with high intensity from the lipid matrix of the NLC.</td>
<td>47</td>
</tr>
<tr>
<td>Oxybenzone</td>
<td>Glycerol monostearate Miglyol 812 and oleic acid</td>
<td>Sun screen</td>
<td>Solvent diffusion method.</td>
<td>Oxybenzone-loaded NLC gel showed higher in vitro sun protection factor and erythemal UVA protection factor with very low irritation tendency to the skin.</td>
<td>51</td>
</tr>
<tr>
<td>Phenylethyl resorcinol</td>
<td>Glycerol monostearate olive oil were</td>
<td>Skin whitening</td>
<td>Hot-melted ultrasonic method.</td>
<td>Tyrosinase activity was significantly reduced by PR-NLCs, skin whitening effect was proven. UV blocking ability was assessed by measuring β-carotene concentration. The concentration was higher in TiO2-loaded NLC cream compared to the conventional</td>
<td>44</td>
</tr>
<tr>
<td>Titanium dioxide (TiO2)</td>
<td>Dynasan 118, Dynasan 114, cetyl palmitate, Compritol 888 carnauba wax Miglyol 812</td>
<td>Sunscreen</td>
<td>High pressure homogenization</td>
<td>The optimum tretinoin NLC formulation showed slow release for about 360 min and lesser skin irritation as compared to the marketed gel formulation.</td>
<td>47</td>
</tr>
<tr>
<td>Decyl olate</td>
<td></td>
<td></td>
<td></td>
<td>cream. Hence it was proved that lesser concentration of TiO2 was required for the activity.</td>
<td></td>
</tr>
<tr>
<td>Tretinoin</td>
<td>stearic acid oleic acid</td>
<td>Skin anti-aging</td>
<td>Hot melt probe sonication method</td>
<td>The optimum tretinoin NLC formulation showed slow release for about 360 min and lesser skin irritation as compared to the marketed gel formulation.</td>
<td>52</td>
</tr>
</tbody>
</table>
Topical and Transdermal Benefits of Nanostructured Lipid Carriers

Dipropionate loaded nanostructured lipid carriers were formulated by Kong X et al., using precirol ATO 5 and oleic oil (OA) through the melt emulsification method. The optimum W/O ointment of BD-NLC showed highest skin retention and with very minimal amount of drug in the blood. Hence it was concluded that topical administration of BD-NLC can be affectively used to treat atopic dermatitis with reduced systemic side effects (57).

Thymol, a constituent of thyme oil from the plants of the Thymus genus is proven to have anti-inflammatory, antibacterial, antioxidant, anesthetic and antipsoriatic activity. Pivetta T et al. encapsulated thymol in NLCs using natural lipids - Illipe butter and Calendula oil through the sonication method. The NLCs were incorporated into gels to give them an appropriate rheological nature. In vivo studies indicated effective anti-inflammatory and anti-psoriatic activity in mouse models of skin inflammation and imiquimod-induced psoriasis (58). Table 3 gives the dermal application of NLC.

### Table No 3: Dermal Application of NLC

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Lipids used</th>
<th>Use</th>
<th>Method used</th>
<th>Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone dipropionate (BD)</td>
<td>Precriol ATO 5, oleic oil</td>
<td>Atopic dermatitis (AD)</td>
<td>Melt emulsification</td>
<td>The skin retention study was proved by the tissue distribution test, which showed order of BD distribution as skin &gt; muscle &gt; blood.</td>
<td>57</td>
</tr>
<tr>
<td>Clobetasol propionate</td>
<td>Compritol® ATO 888 and oleic acid</td>
<td>Eczema</td>
<td>Hot high-pressure homogenization technique</td>
<td>Carrageenan-induced hind paw inflammation method was used to compare the anti-inflammatory activity of C-NLCs with marketed formulation. The formulation showed appreciable reduction in inflammation, in a sustained manner.</td>
<td>59</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>Stearic acid, Phosal® 53 MCT</td>
<td>Benign Prostate Hyperplasia (BPH) to promote hair Growth</td>
<td>Melt-dispersio n &amp; ultrasonication method</td>
<td>A slow release for first 12 h was seen with DST- NLCs coated with CSO-SA. In vivo diffusion studies proved low permeability of the formulation into the blood, indicating good skin retention.</td>
<td>60</td>
</tr>
<tr>
<td>Halobetasol propionate (Hb)</td>
<td>Precirol, LAS</td>
<td>Vitiligo</td>
<td>High pressure homogenization</td>
<td>Larger particles with small polydispersity index were obtained by increasing the lipid composition. The encapsulation efficiency was greater than 90 % and size was less than 200 nm</td>
<td>61</td>
</tr>
</tbody>
</table>
| 2 Lidocaine (LID) | Compritol 888 ATO and Precirol ATO 5 | Local anesthetic | Ultrasound dispersio n | In vivo test included comparison of the guinea pig response to the pinprick test by LID SLN gel, LID NLC gel, and a marketed

10. Transdermal benefits of NLC: Non-invasiveness, easy administration, maintenance of steady plasma drug concentration and avoidance of degradation by GIT are the important features of TransDermal Delivery System (TDDS). These advantages has made TDDS more popular and one of the most patient accepted systems...
as compared to the conventional oral and intravenous systems (67,68,69).

The most important task of TDDS is penetration through the stratum corneum which is a protective barricade of skin. As discussed earlier, NLCs are an effective method for improving the skin penetration. This penetration enhancement is due to the hydration effect caused by the adhesive action of these carriers. In addition, their nano size gives an additional advantage; felicitating it to creep through the skin barriers and reach the systemic circulation (70).

The advent of NLCs owes to the drawbacks associated with the first generation lipid particulate system i.e. Solid Lipid Nanoparticles. NLCs hold good drug loading capacity and prevents drug expulsion and improves the stability. NLCs forms a depot at the site of application and releases the drug in a controlled pattern thus used in chronic disease conditions (41,71,72,73).

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Bhaskar K et al. formulated flurbiprofen loaded NLCs and SLNs for transdermal delivery. The prepared lipid particles were incorporated into a hydrogel to ease topical application. The blood samples were collected from the tail vein of the wistar albino rat at regular intervals and pharmacokinetic and pharmacodynamic parameters of hydrogel and oral formulations were compared. The hydrogels with the NLCs and SLNs of flurbiprofen showed sustained release for nearly 24 hours when compared to the oral formulation. The gel edifice of the formulation was responsible for the slow sustain release and prolonged anti-inflammatory activity (74). Table 4 gives the transdermal applications of NLCs.

11. Conclusion

The advantage of NLCs over the conventional nano systems have made them a promising mode of drug delivery. The cosmetic industry has seen a massive increase in their usage. The number of marketed NLC cosmetics has increased since their invention. Increased patient compliance and improved bioavailability has made transdermally administered NLCs more accepted. NLCs for pulmonary and ocular delivery are gaining importance and has great potential for the near future.

Acknowledgement:

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