ABSTRACT

Background: The advanced development of lipid nanocarrier contributes a lot to the domain of therapeutic effectiveness of the drug. However, the parameter such as drug loading, drug release, stability, and targeting influence much more towards the limitation of many lipid nanocarriers. The Nanostructured lipid carrier, the second generation of lipid carrier has more promising advantages over others and have tremendous targeting ability to skin for drug administration.

Objective: The present review paper focus to understand the different fabrication technique, impact of lipid and surfactant on formulation effectiveness, characterization of formulation, and Crystalinity concept of lipid which have an impact on stability & drug loading. Focus on a parameter such as Transepidermal water loss, skin occlusion, and hydration which determine the ability of the carrier to target the skin. Hence the effectiveness of the drug improved. This review also focused on patents based on Nanostructured lipid carriers.

Method of preparation: many methods have been adopted to prepare Nanostructured lipid carriers and among all High-pressure homogenization method is considered as best one.

Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Conclusion: Because of numerous advantages of this carrier system such as biocompatibility of lipid, high drug encapsulation, stability over others, it is considered as a major focused area for researchers. The new domain of Nanostructured lipid carrier is transdermal drug administration by targeting the skin; hence more research is focused on topical preparation. However, toxicity must have to be studied in humans. So by considering all factors one can rename it as “smart nano lipid carrier”.

Keywords: Nanostructured lipid carrier; skin occlusion; stability; skin targeting; fabrication; safety and toxicity; patent; transepidermal water loss.

ABBREVIATIONS

NLC : Nanostructured Lipid Carrier
SL : Solid Lipid
LL : Liquid Lipid
ZP : Zeta Potential
EE : Entrapment Efficiency
TEWL : Trans Epidermal Water Loss
WAXS : Wide Angle X-ray Scattering
SAXS : Small Angle X-ray Scattering (SAXS)
CCT : Critical Crystalline Temperature
PPI : Proton Pump Inhibitor
NSAID : Non-steroidal Anti-inflammatory Drug

1. INTRODUCTION

In the last decade the nanoparticulate carrier imparting a promising drug delivery system for drugs. Among the nanoparticulate carrier, lipid nanoparticles carrier is the emerging carrier for recent development. As many drugs are structurally designed and well-formulated but their toxicity, low bioavailability, stability make them limited for use. Hence by choosing the route of administration along with lipid nanocarrier removes the boundary of limitation. The various lipid carriers used in the formulation are liposome, niosome, Solid Lipid Nanoparticles (SLN), Nanostructured Lipid Carriers (NLC). Among these, the NLC is now a promising carrier for researchers as it provides more advantages over other lipid carriers for drug delivery. The solid lipid nanoparticles which contain only solid lipid produce more limitations to formulation such as poor drug loading capacity( which is attributed due to lipid crystalline nature), the expulsion of drug content (because of perfect crystalline lattice formation), and stability concern of formulation over long storage [1,2]. However, NLCs are second-generation lipid carriers that consist of solid lipid and liquid lipid enhancing drug entrapment capacity and preventing leakage of the drug during storage [3,4]. Hence the current study is concerned with how NLC is a promising delivery system through the skin by studying the important parameter such as skin barrier & permeability, skin hydration & occlusion, TPEL(Trans Epidermal Water Loss), skin targeting, and stability aspect of the formulation [5,6,7]. Skin's enormous surface area makes drug easy administration and acts as a barrier for drug molecules having a molecular weight greater than 500 Da [8]. The top layer of skin called the epidermis act as a barrier that limits many drugs from their effectiveness. Hence NLC is the approach equipped with nanotechnology and lipid carriers that can make effectiveness through the skin.

NLC has particle diameter ranges from 10-1000 nm consisting of solid lipid & liquid lipid which are biocompatible. The presence of different fatty acid carbon chain in liquid lipids make NLC with a less organized crystalline structure. Hence improving loading capacity for drug accommodation. The presence of Liquid lipids is an excellent solubilizer of drugs than Solid Lipid (SLS). The NLC produces low cytotoxicity/systemic toxicity as it is composed of physiological and biodegradable lipids. The nanosizes of lipid particles enhance drug penetration through the stratum corneum. The controlled release from this carrier is also possible due to the solid lipid matrix [9,10].

Table 1. Type of NLC model along with characteristics

| NLC type       | Characteristics                                                                 | References |
|----------------|---------------------------------------------------------------------------------|------------|
| Imperfect types crystal types | Nanoemulsion is formed by blending SL(solid lipid) & LL (liquid lipid) followed by cooling and highly disorder matrix formed due to crystallization process - characterized by low liquid lipid - Disordered matrix contain more space due to gap between    | [11]       |
### NLC type | Characteristics | References
--- | --- | ---
**Multiple types carrier** | fatty acid chain which will accompany more drug
- NLC matrix does not form a high order structure due to different chain lengths of fatty acid & other glycerol | [12,13]
- It is Oil/fat/water system
- In the solid matrix, the oil compartment distributed
- High drug solubility in nanosized lipid oil compartment
- A high concentration of liquid lipid is used as a drug that has poor solubility in solid lipid
- Drug entrapment is more
- Prolong release is achieved because of being surrounded by a solid lipid matrix
- Drug leakage minimized

**Amorphous types** | Mixing of special lipid to form amorphous state (e.g. hydroxycocatalcohol hydroxyl stearate or isopropyl myristate)
- Drug leakage minimized due to crystallization of lipid matrix | [14]

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![Type of NLC](solid_lipid_carrier.png)  
**NLC(SL+LL)**

Fig. 1. Different types of NLC [15]

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2. **NLC FABRICATION**

2.1 **Ingredients Used for NLC**

The Nanostructured lipid carrier contains major component that are solid lipid, Liquid lipid, surfactants, and water. Normally surfactants are dispersed in water and they add to the lipid mixture followed by homogenization. The ratio of SL and LL is from 70:30 to 99:9:0:1. The concentration of surfactant varies from 0.5-5% [16].

2.2 **Lipids and Surfactants as Component of NLC**

To formulate the NLC lipid is the primary component of the formulation. It influences a parameter such as drug encapsulation, stability, and prolonged action. The lipids used in the carrier are biodegradable and non-toxic, and physiologically acceptable. Even though many lipids are available and they have GRAS (Generally Recognized As safe) status, the choice of suitable lipid for NLC is of more concern. The characteristics such as solubility of the drug in lipid and partition coefficients are extremely vital for the selection of lipid. Most of the study reveals that the solubility of the drug in lipid influences the drug loading/encapsulation efficiency [23]. The research also reveals that drug loading, charge, and size of the particle are also affected by the degree of crystallization of lipid [24]. The melting point of lipid also has a vital role as the higher melting point of lipid leads to an increase in the viscosity of the dispersed...
phase which increases particle size. The other characteristics such as lipid hydrophilicity & crystal shape also influence the NLC quality. The increase in lipid amount 5-10 percent leads to an increase in particle size [25]. Hence it is highly concerning to select the suitable lipid for NLC.

### Table 2. List of the ingredients used in NLC: [17-22]

| Component        | Trade name                  | Chemical name                        | Melting point         |
|------------------|-----------------------------|--------------------------------------|-----------------------|
| **Solid Lipids** |                             |                                      |                       |
|                  | Compriro® 888 ATO           | Glyceryl behenate                    | 69°C - 74°C           |
|                  | Precirol ATO®5              | Glyceryl palmitostearate             | 50°C - 60°C           |
|                  | Crodamol™ CP, Precipac ATO, Cutina CP® | Cetyl palmitate         | 47°C - 54°C           |
|                  | Glycerol tripalmitate       | Tripalmitin                          | 44.7°C - 67.4°C       |
|                  | Octadecanoic acid           | Stearic acid                         | 68°C - 70°C           |
|                  | Glycerin Monostearate       | Glyceryl monostearate                | 57°C - 65°C           |
|                  | Softisan 142                | Hydrogenated coco-glycerides         | 42°C - 44°C           |
|                  | Dynasan 114                 | Glyceryl trimyristate                | 55°C - 58°C           |
|                  | Softemul 165                | Glycerol stearate & PEG 100 stearate | 50°C - 60°C           |
|                  | Dynasan® 116                | Triacylglycerol of palmitic acid     | 62°C - 64°C           |
|                  | Elfacos® C 26               | Hydroxyoctacosanyl                   | 80°C                  |
|                  | Dynasan® 116                | Hydroxy stearate                     | 80°C                  |
|                  | Imwitor 900®                | Mono diglyceride                     | 54°C - 64°C.          |
|                  | Syncrowax ERLC              | Ethylene glycol ester                | 60°C - 68°C           |
| **Liquid Lipids**| Myverol 18-99K              | Monoacylglycerols                    | -                     |
|                  | Gelucire® 44/14             | Lauroyl Polyoxyglycerides            | -                     |
|                  | Epikuron™ 200               | Soy lecithin                         | -                     |
|                  | Miglyol® 812                | Caprylic/Capric triglycerides (C8/C10) |                      |
|                  | Softisan® 378               | Oleic acid (9Z)-Octadecenoic acid   | -                     |
|                  | Labrasol®                   | Linoleic acid                        | -                     |
|                  | Oleic Acid                  | Propylene glycol decaprylate         | -                     |
|                  | Caproyl 90                  | Glyceroyl Caprylate/Caprate          | -                     |
| **Surfactants**  | Tween®20                    | Polyoxylethylene sorbitan laurate    | 16.7                  |
|                  | Tween® 80                   | Polyoxylethylene sorbitan oleate     | 15                    |
|                  | Lutrol® F68                 | Poloxamers 188                       | 29                    |
|                  | Lutrol® F127                | Poloxamer 407                        | 21.5                  |
|                  | Cremophor EL                | Polyoxy castor oil                   | 12-14                 |
|                  | Solutol® HS 15              | Macrogol-15-hydroxy stearate         | 15                    |
|                  | Kolliphor® HS 15            | Phosphatidylcholine                  | 9                     |
|                  | Phospholipon® 80/H          | Soybean lecithin                     | 7-10                  |
|                  | Epikuron® 200               | Soy lecithin                         | -                     |
|                  | Cremophor® RH 40            | PEG-40 Hydrogenated castor oil       | 14-16                 |
|                  | Labrasol®                   | Caprylic capryl macroglycerides      | 8-12                  |
|                  | Gelucire® 44/14             | Lauroyl polyoxy 32                   | 14                    |
|                  | Span 20                     | Sorbitan monolaurate                 | 8.6                   |
|                  | Sodium oleate               | Sodium oleate                        | 18.0                  |
|                  | Polyvinyl alcohol           | Polyvinyl alcohol                    | 15-19                 |
The crystallization, stability, and toxicity of NLC are affected by surfactant type and concentration [26]. The choice of surfactant is also based on the route by which the drug is administered, the effect on particle size, and HLB value. Due to crystallization during NLC formulation particle surface area increases that leading to the whole system being unstable. Therefore, the selection of surfactant becomes necessary to make the formulation stable. Another important parameter of surfactant is rHLB (required HLB) value for lipid can be calculated by dispersing in a mixture of surfactant with different HLB values followed by high-pressure homogenization to find out least particle size [27,28].

Other excipients as a component of NLC: There are other categories of excipients such as counter ion (ionic polymer and organic salts) used to minimize the problem associated with water-soluble drug encapsulation. The surface modifiers were also used to reduce the NLC formulation from phagocytic uptake by macrophages. Various polymers like polyethylene glycol can be used to coat the lipid particle so that drug residence time can be increased in the systemic circulation. This surface modification can also improve the physical stability and drug targeting [23,29].

2.3 NLC Method of Fabrication: The Method is Categorized into 3 Groups Namely [30]

i) High energy method
ii) Low energy method
iii) Organic solvent-based method

2.4 Methods of NLC Preparation

High energy method based on the requirement of equipment that can produce high shear force, distortion of pressure, or the mechanism involved in particle size reduction. The low energy method does not require any specific amount of energy for the reduction of particle size. However, the solvent-based method involves the requirement of organic solvent on a mechanistic basis to the system for the reduction of particle size [30]. Among all the methods high-pressure homogenization method is the most accepted and well-reported method for the research work because of its less production time & easy scale-up process. This method is again categorized into two parts - the hot method and the cold method.

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**Methods of preparation of NLC**

- **High Energy Method**
  1. High pressure homogenization
  2. Ultrasonication
  3. Microwave assisted
  4. Super critical fluid technique

- **Low Energy Method**
  1. Micro emulsion
  2. Double emulsion
  3. Phase inverted Temperature
  4. Membrane Contactor

- **Organic Solvent Based Method**
  1. Solvent Injection Method
  2. Emulsification
  3. Solvent Evaporation
  4. Membrane Contactor
  5. Solvent Diffusion

**Fig. 2. Different methods used for the preparation of NLC**
In the hot method, initially solid lipid has to be melted above 5-10°C of its melting point, then liquid lipid has to be added to it & mixed for a few minutes to ensure proper mixing of it. Then surfactant solution heat at the same temperature as lipid mixture. At the same temperature, surfactant solution was added to lipid mixture followed by homogenization under high pressure (500-800 bar) to form nanoemulsion. Subsequently, the mixture allows cooling below room temperature to give NLC [31,21,32]. In the cold homogenization method, the melted hot mixture of lipid & drug is allowed to cool by using nitrogen of ice. Then the mass is ground into fine particles. The obtained macro particle has to be dispersed in a cold aqueous solution containing surfactant/stabilizer followed by homogenization with high pressure. To get particles with average size & good polydisperse index it is necessary to use high pressure with more number cycles as compared with the hot homogenization method [33,34,35].

Ultrasonication: The cavitation mechanism used for the ultrasonication method. Initially the solid lipid and liquid lipid melted at a temperature higher than the melting point of solid lipid. The drug substance needs to add the lipid mixture. The next step involves preparing the aqueous phase of surfactant heated at the same temperature and adding drop by drop to the lipid mixture with constant stirring. The obtained emulsion is sonicated by using a probe sonicator.

Microemulsion method: Lipid mixture containing drug mixed with surfactant and co-surfactant with proper ratio to form a microemulsion. The prepared microemulsion (hot) is diluted with cold water so that breaking of microemulsion takes place which forms nanoemulsion.

Phase inversion method: This method involves the use of heating as well as the cooling cycles for the formulation component. During this cycle the temperature used in increasing order of 4°C/min from 25°C to 80°C and bring back the temperature to 60°C. Due to this Thermal treatment inversion of emulsion occurs.

Solvent emulsification/Evaporation methods: This method involves the dissolution of solid lipid and liquid lipid with drugs in an organic solvent (water - immiscible). Then it is emulsified in an aqueous phase using high shear homogenization. Instead of using temperature, low pressure (40-50 bar) is used to evaporates the organic solvent. This method is suitable for the thermo labile drug as the method use low - pressure technique. However presence of residual solvent (as heat avoided) makes this method limited for use.

Membrane contractor method: The lipid mixture is placed in a pressure vessel above its MP( melting point). Under applied pressure, the lipids allow passing through the pores of the ceramic membrane to produce tiny droplets. With constant stirring, the aqueous phase allows to flow tangentially inside the ceramic membrane and remove droplets formed at the outlet. Then bring the preparation to room temperature so that lipid particle formed.

3. VARIOUS METHODS OF FABRICATION, PROCEDURE INVOLVED ALONG WITH ADVANTAGES AND DISADVANTAGES OF METHODS

| Methods of fabrication | Procedure involved | Advantages of method | Disadvantages of method | References |
|------------------------|--------------------|----------------------|-------------------------|------------|
| Hot high-pressure homogenization | Drug lipid mixture emulsified in a hot aqueous solution containing surfactant at same temperature followed by homogenization with high pressure then cool to room temp to form NLC | Simple & cost effective method | Not suitable for thermo labile drug | [36,37] |
| Cold high-pressure homogenization | The melted drug–lipid mixture solidified using liquid nitrogen or ice and milled to get microparticles. Then it dispersed in cold aqueous solution containing surfactant, then homogenized at high pressure to form NLC | Suitable for thermo labile drug & large scale production | The presence of macroparticle affect dispersion quality | [37,38] |
| Methods of fabrication | Procedure involved | Advantages of method | Disadvantages of method | References |
|------------------------|--------------------|----------------------|-------------------------|------------|
| Ultrasoundation         | Methods involve direct mixing of melted lipid phase with heated with aqueous surfactant solution using ultrasonication. Probe Sonication is more useful to obtain the narrow distribution of NLC. | Simple & feasible for production as significant available of ultrasonicator | Large polydispersity & moderate product stability | [39] |
| Microemulsion          | The lipid–drug mixture is dispersed in the hot aqueous solution of surfactant at the same temperature to form a microemulsion. Then hot micro emulsion is poured into cold water to form nanoemulsion which will produce NLC upon recrystallization. | Scale-up process easy | Dilution of the particle due to high volume of water, a high concentration of surfactant used | [40,41] |
| Phase inversion technique | Under this method mixture of lipid, drug, surfactant, and water is formed by stirring & exposed to heat & cold cycle (3 cycles). Then dilute with cold water to induce shock which will produce NLC by phase inversion. | Suitable for thermo sensitive drugs, avoid using organic solvents | The process is complex & require more time | [42] |
| Membrane contractor     | This method involves the passing of melted lipid over the membrane to produce tiny lipid particles & at the same time aqueous phase is circulated in the membrane to remove lipid droplets from the pore. Then cool at room temperature. | Simple methodology | It may not be more effective as particles may stick to the membrane | [43,44] |
| Solvent diffusion method | In this method, an organic solvent such as benzyl alcohol is used to dissolve lipid. To maintain the thermodynamic equilibrium organic solvent is saturated with water. The o/w emulsion is diffused into the water with continuous stirring to | Water miscible solvent used | Use of organic solvent | [4,7] |
### Methods of fabrication

| Procedure involved                                                                 | Advantages of method                                                                                                      | Disadvantages of method                                                                 | References |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------|
| Solvent emulsification evaporation                                                | Suitable to thermo sensitive drug                                                                                       | Use of organic solvent, Ultrasonication required                                        | [45]       |
| The lipid dissolves in a water-immiscible solvent like cyclohexane. After that it is emulsified in an aqueous surfactant solution with continuous stirring, then lipid is precipitating on the removal of organic solvent. |                                                                                                                          |                                                        |            |
| Solvent Injection method                                                          | Easy process                                                                                                            | Use of organic solvent                                                                 | [46,47]   |
| Dissolve lipid in water-immiscible solvent & quickly inject the preparation into an aqueous solution containing surfactant through the needle. |                                                                                                                          |                                                        |            |

### 4. DIFFERENT PARAMETERS OF NLC FORMULATION, ITS DESCRIPTION AND TEST METHODS

#### Table 4. Characterization of NLC

| Parameter                          | Description                                                                                                                      | Test method                              | References |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|------------|
| **Morphology (particle size & distribution)** | Stability of NLC mostly affected by Particle size & distribution  
- Particle with smaller size & limited distribution tend to reduce aggregation & improve physical stability  
- Increase amount of liquid lipid may increase particle size  
- Low concentration of surfactant produce larger NLC particle compare with the high surfactant-to-lipid ratio | Transmission Electron microscopy (TEM)  
- Scanning electron microscopy (SEM)  
- Dynamic light scattering (DLS) | [31,50,51] |
| **Zeta potential**                 | This parameter analyze the NLC repulsion of particles & measure the long term stability  
- Greater surface charge increases electrostatic repulsion & decrease aggregation between particles  
- The stable Nanostructured Lipid Carrier should have a minimum ZP of ±30Mv  
- Formulation parameters like liquid lipid & SL concentration and surfactant nature have a significant impact on NLC surface charge  
- Higher LL to SL ratio, the impact is less as LL mostly negative charge | Dynamic light scattering (DLS) | [52,17] |
| **Crystallinity**                  | Lipid crystal lattice structure affect encapsulation efficiency and drug release rate from NLC  
- Amount of drug-loaded, viscosity of preparation, and storage time have an impact on the Crystallinity of NLC  
- More the crystal lattice imperfection, more the encapsulation of drug due to entrapment & | Differential scanning Calorimetry (DSC)  
X-ray Diffraction (XRD) | [53,54] |
| Parameter                        | Description                                                                 | Test method                                      | References |
|---------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------|------------|
| Drug load & Encapsulation       | - The nature and amount of drugs have a significant impact on entrapment efficiency  
                                 | - There is inverse relationship was observed between the amount of drug-loaded and entrapment efficiency  
                                 | - Lipophilic drug uniformly solubilized in LL/SL mixture and entrapped for a long period | Ultracentrifugation & spectroscopic analysis | [55,56] |
| efficiency                      | In vitro drug release                                                       | Dialysis bag method, Franz diffusion cell         | [57]       |
|                                 | - Factors such as liquid lipid quantity, type of solid lipid, the surfactant used, the quantity of drug and location in NLC, pH of medium affect the drug release |                                                  |            |
|                                 | - Release of drug from NLC controlled by diffusion of drug or erosion of matrix which depends on drug entrapped in NLC core, in the matrix or the shell. |                                                  |            |
|                                 | - Due to more surface area & shorter diffusion path, small particle size results in faster drug release compare with larger particle |                                                  |            |

### 4.1 Parameter of NLC Formulation

**Morphology:** The effectiveness of NLC formulation depend on particle size and shape. The study shows that particle of NLC formulation ranges from 10-1000nm. However depending on site-specific action, the range may vary or be specific (50-300 nm for chemotherapeutic agent). The physical stability of NLC formulation depends on particle size & its distribution throughout the formulation. The parameter like entrapment efficiency, cellular uptake, the potential for a target is affected by the shape of particles present in the formulation. The analysis technique such as TEM (Transmission Electron Microscopy) and SEM (scanning Electron Microscopy) is necessary to find out the shape of the particle. Generally, NLC formulation shows the spherical particle with low surface area [31].

**Surface charge:** The surface charge of particles affected by the concentration of lipid mixture and surface active agent. The term ‘Zeta potential’ is used to measure the surface charge. The determination of zeta potential (ZP) of a particle based on electrophoretic mobility. Higher the zeta potential value (> +30 mV) lesser the particle aggregation. Generally, the dispersion should have ZP either more than +30mV or less than -30Mv [52].

**Entrapment Efficiency (EE):** Entrapment efficiency is the percentage amount drug entrapped in particle and determine the efficiency of the formulation. The lipophilic drug entrapped more as compared with hydrophilic one as the drug easily solubilized in lipid. The release rate of the drug in NLC formulation is significantly affected by EE as a high entrapment value changes the concentration gradient [55]. The formula for EE is as below

\[
EE = \left( \frac{WI - WS}{WI} \right) \times 100
\]

Where WI : Initial amount of drug added to the formulation  
WS: Amount of drug present in the supernatant  
WL: Total weight of lipid in formulation

**In vitro drug diffusion study:** A Dialysis bag is used for in-vitro drug diffusion study. Initially the dialysis membrane activated by soaking with distilled water overnight for better results. The prepared NLC formulation is required to be put inside the bag and both ends to be sealed. The total experiment need to conduct under sink condition. At specific time intervals samples are withdrawn and replaced with fresh media. The sample is analyzed with UV-visible spectrophotometer [57].

### 5. SCREENING METHODS FOR SOLID LIPID AND LIQUID LIPID

Liquid lipid: Liquid lipid can be selected depending on the solubility of the drug in it. The excess amount of drug added to 2 ml of various
liquid lipid in a small vial. Then the vial stoppered tightly & continued stirring with the help of a mechanical shaker at 25°C for 24-48 hours followed by centrifugation for 30 minutes at 37°C. The collected supernatant was suitably diluted & analyzed with a UV-Vis spectrophotometer [48].

Solid lipid: one of the methods used to select solid lipid-based on the solubility of the drug in it. This can be performed by incremental addition of the drug to solid lipid at above its melting point until the excess of drug fails to dissolve in it. Usually, solid lipid has to be melted above 5-10°C of its melting point. Then depending on the solubility of drug amount in various solid lipids it can be chosen for NLC formulation [49].

6. LIPID MATRIX CRYSTALLINE BEHAVIOR

The crystalline behavior of the lipid matrix is to be studied as it is fundamental to optimize the formulation. The melting point depression (temperature much below its melting point) of the liquid mixture is responsible for the crystallization of lipid. The crystallization of lipid occurs only when the lipid blend of NLC cooled below its CTT (critical crystalline temperature). The crystallization of the internal structure of lipid determines the shape of the particle, amount of drug incorporation, and stability of the formulation. The characterization of Crystallinity of NLC study utmost importance as encapsulated drug undergoes polymorphic changes leads to leakage of the drug, impact on release rate and encapsulation efficiency [2,58]. There are structural changes of lipid during heating and cooling of the mixture, which lead to different polymorphic formations [59]. Therefore control of transition of the polymorphic form allows the metastable crystalline form to entrap more drugs [60] and stable polymorphic forms of nanoparticles are formed.

Depending on the cooling rate of NLC preparation and solidification of starting material, the nucleation process starts from the inner layer of lipid [61,62]. That is why depending on the preparation process and composition, the internal structure of lipid particle has various conformations like gel, liquid crystal, etc.

The study also reported melting point of the stabilizing agent can affect the lipid polymorphic form of thermodynamic stability. The melting point of stabilizer greater than 50°C maintains the lipid in low thermodynamic stability as compared with lipid having melting point <0°C (which favors stable polymorphic transition) [63]. Two possible ways that the crystallization process modulation is mediated by lipid having low molecular weight. In the first way interaction between molecules of low molecular weight lipid with triglyceride molecules. On the other hand, heterogeneous nucleation process induction leads to organized of minor lipids into the micellar structure.

DSC (Differential scanning calorimetry) and X-ray diffraction are the two possible methods that investigate the crystalline status. DSC gives information about the change in physical & chemical properties as a function of temperature due to heat loss or gain. This information tells about the status of lipid, crystallization, and melting of solid lipid used in NLC [23]. DSC is used to analyze the crystalline nature of lipid in a pure state and after processing (freeze-dried powder). The solid lipid & liquid lipid compatibility identified by DSC and help to analyze the polymorphic transition. The degree of Crystallinity or RI (recrystallization index) can be measured by DSC data.

\[
RI(%) = \frac{\Delta H_{\text{of NLC}}}{\Delta H_{\text{bulk lipid}} \times \text{concentration of lipid}} \times 100
\]

Where,
\[
\Delta H_{\text{of NLC}} = \text{melting enthalpy of 1g NLC preparation}
\]
\[
\Delta H_{\text{bulk}} = \text{melting enthalpy of 1g bulk lipid}
\]
\[
\Delta H \text{ is given in j/g & concentration given in percentage}
\]

XRD is the technique that helps to determine crystal structure & various polymorphic forms and reveals compound polymorphic structural changes. In different ways, lipids may aggregate to give polymorphic forms like micelles, laminar phases. Wide range X-ray scattering (WAXS) and small-angle X-ray scattering (SAXS) give information on layer arrangement, polymorphic behavior, crystal structure. The length of long & short spacing of lattice and drug localization in it can also be studied by X-ray diffraction [64,65].

7. NLC STABILITY CONCERN

The long-term storage of NLC may lead to aggregation due to perikinetoflocculation (flocculation due to Brownian motion of colloidal particles). A pearl-like network arrangement observed with NLC of highly concentrated
dispersion leads to prevent collision and as a result, perikinetic floculation can be avoided. This pearl-like network converts to fine particles once it is in contact with gastric fluid on administration [57].

As NLC formulation possesses less water in comparison with solid lipid nanoparticles, then care must be considered to avoid bacterial growth and changes in initial particle size. There are two possible ways to preserve the stability of NLC. One is to remove water content by freeze-drying (by converting nanoparticles liquid dispersion to solid). The second possible way is to add a preservative to NLC preparation [66,67]. Generally, the freeze-dried nanoparticles should maintain stability by preventing changes in particle diameter, reducing reconstitution time, and maintaining the appearance while maintaining drug activity [68]. As the freeze-drying process leads to aggregation of particles it is necessary to add cryoprotectant. A group of researchers (Beloqui et al.) conducted the study to know the effect of cryoprotectant on NLC formulation by taking different concentrations of trehalose, sucrose, sorbitol (5,10,15% W/V) respectively [69,70,71]. The study concluded that trehalose is effective to prevent the aggregation of particles. Another study was conducted by Varshosaz et al using microcelac, Avicel PH 102, Avicel RC 591, Mannitol, and sucrose at different concentrations and found that Avicel RC 591 at 1% concentration exhibit effective agent to prevent the increase of particle size [66]. So it needs to be attention for the formulator that the lyophilization process only does not improve stability but required adding cryoprotectant for it. Another way to prevent the instability of NLC is the use of preservatives. Obeidat et al conduct a study by using eleven different preservatives and study their influence on particle size, ZP (zeta potential) & other physical stability of NLC formulation loaded with Q10. They collected the sample at 3,6,12 month intervals (sample store at room temp.) and the result found that seven preservatives out of 11 show efficacy for the stability of NLC formulation (Hydrolite 5 was the best effective preservative) [67].

In topical NLC preparation preservative is added to maintain physical stability but preservative also causes destabilization of NLC. So preservatives are categorized into various types based on their impact on NLC preparation.

A multifactorial phenomenon is related to physical stability or the effect of destabilization. Examples of such factors are the nature of particle stabilizer, the affinity between particle surface and preservative, a preservative with stabilizer layer interaction, anchoring of stabilizer onto/into the surface, preservative ability to reduce zeta potential, surface hydrophobicity of particle [67].

![Fig. 3. stabilization effect A) particles collide to form an aggregate in low lipid concentration dispersion B) in high concentration NLC dispersion, pearl-like network dispersed into fine particles upon dilution](image-url)
Table 5. Different preservatives & their impact on NLC stability

| Example of preservative | Impact on stabilization of NLC                      |
|-------------------------|-----------------------------------------------------|
| Ethanol                 | Preservative causing major stability problem        |
| Caprylyl glycol         | Minor stability issue by preservative               |
| Pentylene Glycol (pentylene + propylene glycol) | Preservative with stabilizing effect               |
| Propylene glycol        | Have no impact on the stability                     |

8. SKIN AS TARGETING ORGAN FOR NLC

8.1 Skin Barrier

Human body covers the skin as the largest organ having a surface area of approximately 2 sq.m. It serves as a permeability barrier against the transdermal absorption of many biological agents [72]. Skin acts as a major factor to determine drug delivery aspect such as permeation & drug absorption through the dermis. The skin is composed of mainly three layers such as epidermis, dermis, and lower layer of adipose tissue. The stratum corneum (SC), the outermost layer of skin is the rate-limiting barrier for the movement of various chemical substances. The coenocytes of the stratum corneum embedded in a lipid matrix have a significant role in the permeability of substance. Lipids that are present in SC are ceramide, phospholipids, sterol ester, cholesterol-3 sulfate & free fatty acid. The stratum corneum also contains sebaceous lipid (composed of triglyceride, wax ester & squalene). This organized structure of lipid is completely related to barrier properties of skin [73]. The factors which are responsible to target skin for NLC are skin permeation, skin hydration & elasticity, skin occlusion, Transepidermal water loss.

8.2 Skin Permeation

The Transepidermal pathway contains intercellular and transcellular routes as micro pathways for the transport of drugs. As two pathways involved in the transport of drugs through intercellular lipid, more research work focused on to understanding the organization of the structure and composition in the SC. The following mechanism involves drug penetration through the skin:

i) Lipid present in formulation mediating increased transdermal drug delivery through the appendageal route.

ii) By skin fluidizing property lipid acts as a penetration enhancer.

iii) Direct skin-carrier drug exchange through ‘collision complex transfer’.

![Drug penetration through the different route of the skin](image-url)
Among the appendageal route, the hair follicle is the most penetration pathway for NLC. As NLC contains more lipid as a component it may exchange with skin lipid and facilitate drug penetration. However other factors responsible for drug permeation are particle size, aggregation form, the solubility of a particle in skin lipid, particle surface charge, and capacity to form a film over skin [7].

8.3 Skin Hydration

The hydration state of the stratum corneum normally ranges from 10-20%. The content of lipid and water has a significant influence on the skin frictional resistance. The presence of biocompatible lipid in NLC produces occlusive action which enhances skin hydration. Due to skin hydration, cornocyte packing is loosened and an expanded gap leads to more drug penetration [74]. As a particle of less size in NLC, the capillary channel of nanometer pores will be very smaller. Hence decrease the hydrodynamic evaporation of water [75]. When the concentration of lipid is more in formulation leads to more occlusion resulting in increased hydration. Corneometer is the instrument used to measure skin hydration. This instrument measures the conductance of the dielectric medium. The dielectric properties changes as the skin hydration level increases.

8.4 Transepidermal Water Loss (TEWL)

It is a good indicator to know the impaired barrier function of SC. It is the passive evaporation of water to the environment through the skin due to vapor pressure gradient. The increase in TEWL indicates disruption of SC and depletion of intercellular fluid [6]. When NLC is used in topical the TEWL is lesser due to skin occlusion resulting in skin hydration. The nanosizes of the particle of NLC have more surface area and improve the particle contact with the stratum corneum. The lipid particle forms a thin film over the skin and reduces the evaporation of water. The other factor responsible for TEWL is the size of the particle, amount of lipid, and presence of emollients in the formulation [76,77].

8.5 Skin occlusion: occlusion involves hydration skin due reducing of TEWL. The presence of lipid in formulation produces film over skin leads to occlusion effect. With lipid formulation like NLC ‘controlled occlusion effect’ can be achieved by i) at a given lipid concentration the occlusion effect can be increased by reducing the particle size or ii) at a given particle size by increasing the lipid concentration [76]. The characteristics of lipid such as low melting point & high Crystallinity can attribute more occlusion effect.

Fig. 5. Skin as a target organ for NLC
Table 6. Literature survey on the drug used in NLC topical formulation for targeting skin

| Name of drug | Category | Dosage form | Method used | Composition of formulation (solid lipid, liquid lipid, surfactant) | The particle size & Zeta potential | Encapsulation efficiency | Research output | References |
|--------------|----------|-------------|-------------|---------------------------------------------------------------|-----------------------------------|--------------------------|-----------------|------------|
| Aceclofenac  | Non-steroidal Anti-inflammatory drug for rheumatoid arthritis | Gel | Ultrasonic high-speed homogenization | Stearic acid, oleic acid, Tween 80 | < 500 nm | 75-85% | Optimized formulation converted into topical gel & shows the sustained release profile | [78] |
| Betamethasone | Glucocorticoids for treatment of atopic dermatitis | Ointment | Melt emulsification method | Precirol ATO 5, oleic acid, Tween 80, span 80 | 169.1 nm, -23.4 mV | 85% | Topical ointment NLC formulation shows high skin retention (35.43 μg/g) and low penetration (0.87 μg/ml). More advantage for skin retention as it was better for drug release | [79] |
| Clindamycin  | Antifungal treatment for acne | Gel | High-pressure homogenization | Stearic acid, oleic acid, Pluronic F-68 | 258.83 nm, -19.0 mV | - | Topical gel formulation shows stability with short term stability study. No change of pH, viscosity & consistency | [80] |
| Clotrimazole | Antifungal drug for skin occlusion effect | Semi-solid | Hot high-pressure homogenization | Dynasan 116, tyloxapol, Miglyol 812 | <1 μm | >50% | Research carried out for both SLN & NLC for topical delivery. Particle diameter same after 3 months for SLN & NLC. NLC shows a faster release profile than SLN | [81] |
| Dexamethasone | Corticosteroid for allergic reaction and skin inflammation | Hydrogel | Ultrasonic homogenization | Compritol ATO 888, Mygriol 812, Tween 80 and Span 80 | 224.4 nm | - | Research shows hydrogel containing NLC was 7.3 times higher than dexamethasone ointment. Skin deposition of hydrogel was 3.8 times more than solution | [82] |
| Diclofenac   | Non-steroidal | Gel | Hot high-pressure homogenization | GMS, lanolin, PEG-75 | <126 nm | 78.26% | Research reported that | [83] |
| Name of drug | Category | Dosage form | Method used | Composition of formulation (solid lipid, liquid lipid, surfactant) | The particle size & Zeta potential | Encapsulation efficiency | Research output | References |
|--------------|----------|-------------|-------------|---------------------------------------------------------------|-----------------------------------|----------------------------|-----------------|------------|
| Anti-inflammatory drug for pain and inflammatory condition | pressure homogenization | Phospholipon® 90G, preciros ATO 5, Tween 80 | high drug loading achieved by smaller particle size which improved drug penetration & in vivo efficacy improved |
| Etoricoxib | COX-2 inhibitor for treatment of inflammation & allied condition | Gel | Melt emulsification & low-temperature solidification method | Stearic acid, oleic acid, Tween 80 | 244 nm, -11.9 mV | 69-76% | high drug loading achieved by smaller particle size which improved drug penetration & in vivo efficacy improved |
| Flurbiprofen | Platelet aggregation inhibitor for treatment of gout, rheumatoid arthritis | Hydrogel | Hot high-pressure homogenization | Dynasan114, Epikuron 200, cpax 355, polysorbate 80 | 150-300 nm, 21.7 mV | >90% | Invitro drug release pattern experience burst effect & prolong release -Zeta potential value predict good stability |
| Ibuprofen | NSAID for treatment of osteoarthritis and other musculoskeletal diseases | Gel | Hot high-pressure homogenization | Witpepsol E85, Miglyol 812, Lutrol F68 | 106 nm, -18.4 mV | 98.51% | NLC gel is of great potential to increase drug permeation through the skin and enhance the efficacy |
| Ketoprofen | NSAID for treatment of musculoskeletal disorders | Gel | Melt emulsification & low-temperature solidification method | Compritol 888 ATO, Labrafac Lipophile, LutrolF68 | 298 nm | 77% | Drug-cyclodextrin complex loaded to NLC -NLC hydrogel exhibit better permeation than plain drug-loaded NLC |
| Lansoprazole | PPI (proton pump inhibitor), objective to protect drug form gastric degradation | Hydrogel | Ultrasound | GMS, Stearyl amine, Pluronic F65 | 90-210 nm, -61.9 to +3.2 mV | - | NLC hydrogel showed that drug elimination significantly reduced and prolong the mean residence time |
| Lidocaine | Local anesthesia | Gel | Ultrasound | Compritol 888 ATO | 72.1 nm | 95.9% | Formulation prepared with |
| Name of drug | Category | Dosage form | Method used | Composition of formulation (solid lipid, liquid lipid, surfactant) | The particle size & Zeta potential | Encapsulation efficiency | Research output | References |
|-------------|----------|-------------|-------------|---------------------------------------------------------------|----------------------------------|------------------------|-------------------|-----------|
| Methotrexate | Used for Rheumatoid arthritis | Hydrogel | Hot micro-emulsion method | Phospholipon S 100, Gelucire® 50/13, Transcutol®P | 181.5 ± 11.5 nm, −16.58 ± 1.8 mV | - | NLC gel resulted in a six-fold increase in the duration of anesthesia compared with a market gel product | 90 |
| Minoxidil | used in case of Alopecia | Gel | Melt dispersion Ultrasonication | Tristearin, Oleic acid, Tween 80, soya lecithin, Pluronic F-68 | 280 nm, 42.40 mV | 86.09% | A biphasic release pattern was observed in NLC gel and provided a fast release initially for skin saturation followed by a slow-release profile to maintain the skin concentration. | 91 |
| Nebivolol | Used for hypertension (Selective β1-blocker) | Gel | High-pressure homogenization | Glyceryl monostearate, oleic acid, Span 80, Cremophor EL | 228 nm, -29mV | 95% | -Increase encapsulation efficiency along with stability and sustainable transdermal effect has been observed. | 92 |
| Pioglitazone | Antihypertensive | Gel | High-pressure homogenization | Apil, labrasol, Carbopol, Tween 80 | 81.33 to 181.87 nm, 27.5 mV | 63.46–87.56%, | - The pharmacokinetic study showed 2.17 times enhanced bioavailability in comparison to oral tablet. | 93 |
| Quercetin and Resveratrol | Anti-cancer | Gel | Melt emulsification and ultrasonication | Precirol ATO 5, Compritol ATO 888, Labrasol, Labrafil M2125CS, Labrafil M1944CS, Captex GTO | 191 nm ± 5.20 mV ± 0.30 a | 92.85 ± 0.25% | -NLC gel formulation evaluated for permeability study - The enhanced drug deposition in the epidermal layer was observed through dermatokinetic and CLSM studies. | 94 |
| Name of drug | Category | Dosage form | Method used | Composition of formulation (solid lipid, liquid lipid, surfactant) | The size of particle & Zeta potential | Encapsulation efficiency | Research output | References |
|-------------|----------|-------------|-------------|---------------------------------------------------------------|--------------------------------------|------------------------|----------------|------------|
| Sildenafil  | Phosphodiesterase type 5 inhibitor, used for erectile dysfunction | Gel | Modified high-shear homogenization technique | Cetyl palmitate, Glycerol monolinoleate, Cremophor® RH 40, Span 85 | <1µm | 97.5% | - Formulation was prepared with both SLN & NLC - Improved SC transdermal permeation & prolonged action | [95] |
| Tadalafil  | Phosphodiesterase-5 inhibitor, used for erectile dysfunction | Gel | Hot-melted ultrasonic method | Glyceryl monostearate, Oleic acid, Tween 80 | <0.5 µm | 89.6% | - The Tadalafil-loaded NLC dispersion with skin permeation enhancers (ethanol and limonene) exhibited the highest flux - Tadalafil-loaded NLC gel with selected permeation enhancers showed tolerance against toxicity in HaCaT cells. | [96] |

Table 7. List of patents for Nanostructured lipid carrier formulation

| Patent number | Patent publication date | Title of the patent | Description | Applicant of patent | References |
|---------------|------------------------|---------------------|-------------|-------------------|------------|
| RO135202      | 30.09.2021             | Process for dual encapsulation of two categories of bioactive plant-based principles in the same nanostructure distribution system | The invention comprises a dual nanocarrier. The NLC formulation contains licorice extract & wild yam extract which provide sustained release and enhance antioxidant & anti-inflammatory effect. | Ac helcors.r.l. | [97] |
| EP3876913     | 15.09.2021             | Artificial tears | It involves the preparation of NLC consisting of solid lipid outer shell & liquid lipid as the liquid core. It used for dry eye disorder | Waterford institute of tech | [98] |
| AU2021104317  | 19.08.2021             | An Artemether-Loaded Nanostructured Lipid Carrier (NLC) Nanogel Composition and A | The research involves the preparation of lyophilized NLC formulation and covert into a gel for the treatment of | Nnamani, Petra Obioma | [99] |
| Patent number | Patent publication date | Title of the patent | Description | Applicant of patent | References |
|---------------|-------------------------|---------------------|-------------|--------------------|------------|
| AU2021104270 | 19.08.2021              | Desvenlafaxine succinate loaded Nanostructured lipid carrier (NLC) for brain targeting via nasal route | The NLC preparation improved the bioavailability of the lipophilic drugs by crossing the Blood - Brain Barrier through the nasal route and producing an antidepressant effect | Fatma, Bushra Kumar, Vikram Kushwaha, Swatantra K S Mantry, Shubhrajit Mohanto, Sourav Srivastava, Dipti Tiwari, Pallavi | [100] |
| CN113041234  | 29.06.2021              | Cannabidiol lipid nanoparticles, freeze-dried powder, and preparation method | Encapsulation of Cannabidiol in NLC for improvement of bioavailability & sustained release | Shanghai normal university, East china university of science and technology | [101] |
| AU2021102817 | 17.06.2021              | Novel formulations of 5-fluorouracil against diabetic retinopathy and process thereof. | Present research involved for preparation of 5-Fluorocil loaded NLC with enhanced drug absorption and molecular targeting for diabetic retinopathy | Lovely Professional University | [102] |
| CN112641727  | 13.04.2021              | Antioxidant water-in-oil-in-water type micro-nano multiple emulsion as well as preparation method and application thereof | Modification of lipoic acid into water-soluble derivative and incorporated in NLC formulation. The obtained preparation has better antioxidant activity & improve bioavailability | Beijing Technology and business university | [103] |
| US20210085618 | 25.03.2021             | Ocular drug delivery | An Ocular delivery system was prepared where the outer shell is solid lipid and liquid lipid in the core. Therapeutic agent present in core used for an eye disorder | Waterford Institute Of Technology | [104] |
| IN202141009486 | 12.03.2021         | Ant psoriatic effects of clobetasol loaded nano structured lipid carriers | Preparation of novel NLC loaded with clobetasol for Psoriasis treatment | Mr. Ramesh reddy kudamala, prof.venkata | [105] |
| Patent number   | Patent publication date | Title of the patent                                                                 | Description                                                                                                                                                                                                 | Applicant of patent                                                                                           | References |
|-----------------|-------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------|
| MYPI 2019005424 | 19.03.2021              | Nanostructured lipid carrier composition and method for enhanced trans-epidermal absorption of Ficus deltoidea extract | The NLC preparation contain Ficus-deltoidea extract improve epidermal absorption so that antioxidant & anti-inflammatory action improved                                                                 | Universiti Teknologi Malaysia                                                                               | [106]       |
| KR102020011734  | 14.10.2020              | Nanostructured lipid carrier containing econazole and film-forming topical pharmaceutical composition containing same | Topical film-forming NLC formulation containing econazole for long term anti-bacterial effect                                                                                                               | The Industry & Academic Cooperation InChungnam National University (IAC)                                      | [107]       |
| KR102020005199  | 14.05.2020              | Cosmetic composition for delaying skin aging containing active ingredient stabilized with nanostructure lipid carrier | NLC preparation contains retinol, tocopherol and glutathione as core active ingredient for the treatment of skin wrinkle with enhanced stability                                                                 | Coreana Cosmetics Co., Ltd.                                                                                   | [108]       |
| IN201811021213  | 13.12.2019              | Novel nanostructured lipid carrier-based ophthalmic controlled release formulation for treatment in fungal keratitis | The poor solubility & low permeability nature of the drug is used to formulate NLC for the treatment of fungal keratitis. The research aim was to improve retention time & increase solubility in intraocular tissue. | Manish Kumar Ajay Pathania Vipin Saini A. Pandurangan Shailendra Bhatt Prerna Sarup                             | [109]       |
| MYPI 2018300001 | 22.07.2019              | A Nanostructured solid lipid carrier encapsulates bromelain extract                   | The objective of the invention was to prepare Bromelain extract loaded NLC for better penetration and stabilize the physicochemical properties of extract                                                                 | Universiti Teknologi Malaysia                                                                                | [110]       |
| CN109602706     | 12.04.2019              | Ferulic acid lipid carrier and nanostructured preparation                             | The objective was to prepare Ferulic Acid (FA) loaded NLC with a lipid                                                                                                                                   | Shaanxi University of Chinese medicine                                                                       | [111]       |
| Patent number | Patent publication date | Title of the patent | Description | Applicant of patent | References |
|---------------|------------------------|---------------------|-------------|---------------------|------------|
| AU2018285694  | 20.12.2018             | Nanostructured lipid carriers and stable emulsions and uses thereof | To prepare NLC containing lipid phase along with other oil core which delivers the active ingredient to cell for generating of immune response like the vaccine | Infectious Disease Research Institute | [112] |
| CN108853054  | 23.11.2018             | Cyclic peptide modified gambogic acid nanostructured lipid carrier and preparation method thereof | The prepared NLC formulation with modified gambogic acid is able to target tumor & strong penetration effect in tumor tissue. | Tianjin University of traditional Chinese medicine | [113] |
| CN107115531  | 01.09.2017             | Nanostructured lipid carrier modified by glycolipid polymer as well as preparation method and application of Nanostructured lipid carrier | The method involves for encapsulation of hydrophobic drug A-317491 in NLC by using modified glycolipid polymer. The concentration of drug has improved in ectopic endometrium tissue. | Zhejiang University | [114] |
| US15163724   | 26.01.2017             | Topical nano drug formulation | The prepared NLC gel contains spironolactone as a biomolecule for acne vulgaris disorder. The formulation shows improved skin penetration and drug release. | Hamidreza Kelidari Majid Saeedi | [115] |
| CN106176677  | 07.12.2016             | N-acetyl-L-cysteine modified curcumin nanostructured lipid carrier used for oral administration | Work-based on the preparation of NLC load with curcumin. The formulation contains N-acetyl-L-cysteine modified accelerator which improves the solubility of curcumin in water & improves oral bioavailability. | China Pharmaceutical University | [116] |
| WO2016065444 | 06.05.2016             | Method for producing nanostructured lipid carriers on | The Present invention related to producing NLC with triblock | UniversidadeEstadual De Campinas | [117] |
| Patent number | Patent publication date | Title of the patent | Description | Applicant of patent | References |
|---------------|-------------------------|---------------------|-------------|---------------------|------------|
| IN276/MUM/2014 | 11.09.2015 | Idebenone lipid nanocarrier composition for the treatment of neurodegenerative disorders | The nanoprecipitation technique is used for formulating NLC by the solvent evaporation method. The preparation containing Idebenone as biomolecule for treatment of Alzheimer’s disease | Unicamp [BR]/[BR] | Sachin Subhash [118] Salunkhe |
| CN104367549 | 25.02.2015 | Psoralen-doxorubicin-loaded composite nanostructured lipid carrier preparation and preparation method thereof | The investigation includes Psoralen-doxorubicin as two active biomolecules used to prepare NLC. The formulation contains 40-120 part of SL & 10-30 part of LL. The preparation used for multi-drug resistance of leukemia cells. | Liaoning University [119] |
9. LIST OF THE DRUGS USED TO PREPARE NLC TOPICAL FORMULATION ALONG WITH THEIR RESEARCH OUTCOMES

As the NLC remains an excellent lipid carrier, many researchers put their effort to find out the alternate route of administration. A different category of the drug such as antihypertensive, anticancer, NSAID, antidiabetic, local anesthesia, etc. is used to prepare topical NLC formulation with the aim to enhance bioavailability & avoid unwanted side effects. The lists of drugs formulated for topical use are presented in Table 6.

10. LIST OF DIFFERENT PATENTS BASED ON NANOSTRUCTURED LIPID CARRIER

In the era of nanotechnology, lipid carrier is attractive for formulation scientist. The researcher from academia and industry are eager to protect their invention related to NLC formulation. Every year many formulations of NLC is patented. The various patented NLC formulation is depicted in Table no 7.

11. SAFETY AND TOXICITY

A group of researchers (C Vario et al) conducted experimental work for the safety of NLC formulation in topical route. They used Compritol ATO, Migloyl 182 as lipid, and Tween 80 and polaxomer 188 as a surfactant for formulation. The prepared formulation was applied to the skin of the rat. It was observed that formulation remains 24 hr. in application site & no systemic absorption. Hence indicate the safety of formulation. Rahman et al carried-out research work using Zerumbone loaded NLC to know the toxicity of formulation. The oral route used for the experimental work uses mice as the animal. The formulation was composed of palm oil, Lipoid S 100, thimeosal, olive oil. The histopathological study report that the formulation does not have a toxicity effect on the kidney, liver & lungs. Bruge et al conducted research work to know the effect of various lipid carriers of NLC formulation on cytotoxicity in human dermal fibroblast using Precirol ATO 5,compritol 888 ATO, GMS, Dynasan 118, migloyl 812,softisan 100, and polaxomer 188 as ingredients for formulation. From the study, they found Compritol 888 ATO was the safest lipid as it has a neutral cytotoxic effect. V.R Salvi and P.Pawar with their research study found that because of biocompatible lipid, nonionic & biocompatible surfactant of NLC formulation without the use of organic solvent, lipid nanoparticles are non-toxic & relatively safe for ocular drug delivery [120].

12. CONCLUSION

NLC, a new generation of lipid carrier gaining more popularity as it has numerous advantages over others. The vigorous institutional research also progresses remarkably owing to its stability &effectiveness. The biocompatibility of lipid, high drug loading, prolonged-release, and non-use of organic solvent made the NLC more numerous areas for researchers. Among all the routes of administration skin targeting of NLC is the new domain for cosmetic research as well as topical formulation due to its occlusion and skin hydration effect. From the various methods of preparation HPH (High-pressure Homogenization) is considered as the most used method because of its scalability. The factor considered is its toxicity in humans to be evaluated. As day by day NLC formulation occupies more places in the market, we can predict its prospectiveness with more advancement in near future. Therefore by considering the above NLC can be termed as ‘smart nano lipid carrier’.

CONSENT TO PARTICIPATE AND ETHICS APPROVAL

It is not applicable.

AVAILABILITY OF DATA AND MATERIAL

The data and material that support the finding of this manuscript are available on request.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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