International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Nanostructured Lipid Carrier for Hyperpigmentation Treatment: A Dermal Prospective

Ajeth G[1], E. Gopinath[2], Ganesh N S[3], Adlin Jino Nesalin[4], Vineeth Chandy[5]

[1]Student, Department of Pharmaceutics, T. John college of Pharmacy
[2]Associate Professor, Department of Pharmaceutics, T. John college of Pharmacy
[3,4]Professsor, Department of Pharmaceutics, T. John college of Pharmacy
[5]Principal, T. John college of Pharmaceutics

ABSTRACT:
The normal human skin is exposed to different types of infection like wrinkles, pigmentation, acne, pimples in which pigmentation is most common in women over 30-40 years. The field of nanotechnology is currently intensely exploited for drug delivery technology for passive and active targeting via various routes of administration, such things can be effectively treated by incorporating the drug, loaded in a Nanostructured lipid carrier (NLC). NLCs have shown potential in delivering poorly soluble active components and in depigmenting. NLC springs up as the second generation of lipid nanoparticles to overcome the shortcomings of first generation through the topical route. NLC in topical administration provides some added advantages like increasing skin hydration and modified release profile and increase in skin penetration leading to avoidance of systemic absorption. NLCs are composed of biocompatible lipids, surfactants, and cosurfactants which help enhance drug loading capacity and stabilize the formulation. NLC's remarkable physicochemical and subsequently biocompatible qualities have created an ongoing need for the development of beneficial and safe drug delivery methods. The key attributes of NLC that make them a promising drug delivery system are ease of preparation, biocompatibility, the feasibility of scale-up, non-toxicity, improved drug loading, and stability Their ingredients have a special impact on the end product's physicochemical characteristics and efficacy. The present review aims to focus on the recent advancement in the preparation, characterization, and applications of NLC in treating hyperpigmentation.

Keywords: Dermal, Carriers, Penetration, Stability

1. INTRODUCTION:

Topical and dermatological dose forms are designed to distribute medication molecules over specific skin regions, considering factors such as flow, retention, reservoir capacity, and patient tolerance [1]. Dermo-cosmetics have been introduced more frequently to treat skin conditions like hyperpigmentation, psoriasis and eczema [2]. Topical delivery of active pharmaceutical ingredients (APIs) is advantageous for treating musculoskeletal and cutaneous conditions, as it reduces systemic side effects and maintains a consistent

level of plasma API levels. This is particularly beneficial for APIs that need frequent administration and rapid elimination [3]. Skin disorders can cause severe emotional and psychological distress, especially in the younger generation, who are more aware of their physical appearance. Factors influencing the pattern and prevalence of cutaneous illnesses in young people include food, environmental factors, personal hygiene, skin care practices, gender and ethnicity, and patients using skin lesions to release tensions from interpersonal disputes or unresolved emotional issues [4]. The human skin in Figure-1 is characterized by the presence of different layers which act as the barrier for the drug to penetrate it.

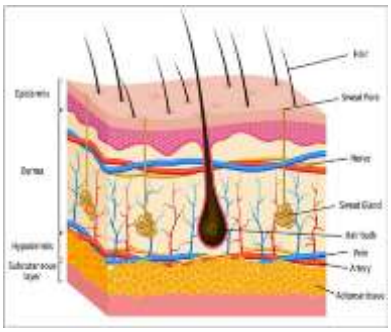


Figure 1: structure of skin

2. PIGMENTATION:

The pigmented biopolymer known as melanin is produced by melanocytes and is endogenously transported to nearby keratinocytes after being enclosed in melanosomes. For thermoregulation and photoprotection of the epidermis, the packed cutaneous pigment is then applied [5]. The amount of melanin the body produces a process known as skin pigmentation determines the color of the skin. Melanocytes in the skin's epidermal layer create the two primary forms of melanin, eumelanin and pheomelanin. Eumelanin is the pigment that gives darker skin tones, whereas pheomelanin provides lighter skin tones [6]. The synthesis of melanin pathway descripted in figure-2,

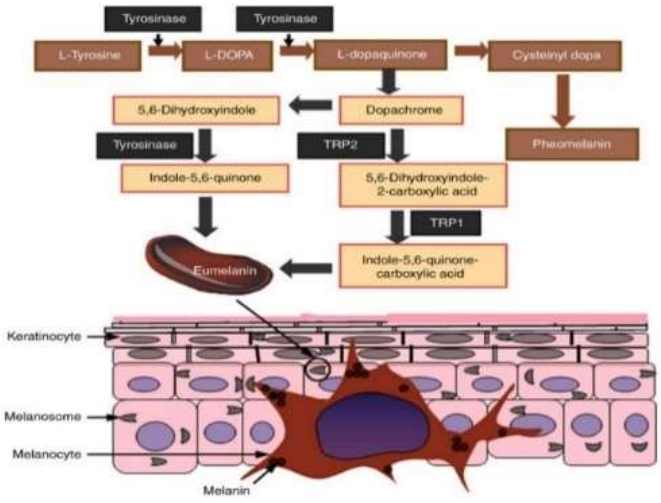
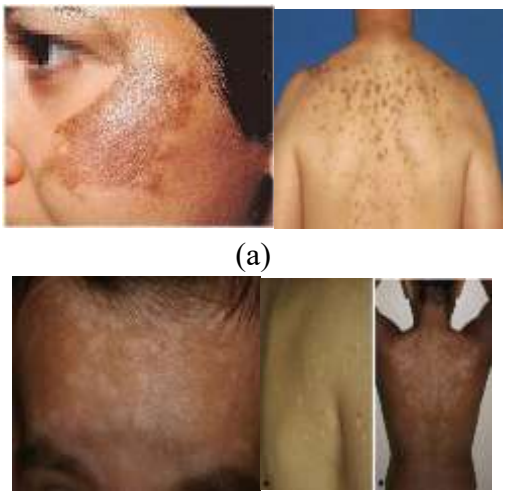


Figure 2: Synthesis of melanin

2.1. Types of pigmentation:

A person's skin tone can change while they are sick, going from being lighter (hypopigmentation) to darker (hyperpigmentation. Hypopigmentation is caused by the body producing less melanin, the pigment that

controls skin colour, on an infrequent basis. Conversely, hyperpigmentation results from an increase in the production of melanin [7]. The appearance of hypopigmentation and hyperpigmentation were illustrated in Figure 3 a and b,



(a)

(b)

Figure 3: A) Hypopigmentation on Face and Body B) Hyperpigmentation on Face And Body

2.2. Causes of hypopigmentation:

Hypopigmentation, a condition causing low melanin concentration, is often caused by prior skin damage, such as blisters, infections, burns, or exposure to chemicals [8]. Other hereditary illnesses can also cause hypopigmentation, including vitiligo, pityriasis versicolor, pityriasis alba, melasma, albinism, and fungal infections [9]. Low melanin concentration is a genetic defect that causes albinism at birth, with dark blue eyes, white hair, and white skin. Melasma can cause brown or blue-grey blotches on the face or arms [10].

2.3. Causes of hyperpigmentation:

Hyperpigmentation is a condition resulting from increased melanin synthesis, often caused by factors such as sun exposure, hormonal changes, age, inherited traits, skin inflammation, acne, and hormonal changes. Sun exposure is the most common cause, with dark spots appearing worse due to exposure [11]. Melasma and chloasma are two examples of hyperpigmentation caused by progesterone and oestrogen, which increase melanin production when exposed to sunlight. Hyperpigmentation is often a side effect of hormone replacement treatment [12].

2.4. Treatment of hyperpigmentation [13]:

Mechanism of action	Drug
Tyrosinase inhibition	Hydroquinone Azelaic acid Resveratrol
Stimulation of keratinocyte turnover	Retinoids
Reduction in melanosome transfer	Soyabean trypsin inhibitors
Interaction with copper	Kojic acid, ascorbic acid
Inhibition of melanosome maturation	Arbutin, deoxy arbutin
Inhibition of protease activated receptor 2	Soyabean trypsin inhibitors

Inhibition of plasmin	Tranexamic acid

3. Challenges on the available therapy:

Despite the availability of dermatological treatments, many skin conditions remain untreated due to inadequate drug concentration at the disease site. Topical and dermal therapies are increasingly preferred as initial treatments, and for chronic invasive skin diseases, they may be combined with oral or systemic therapy. Physical and chemical strategies have been developed to increase drug permeation, such as high voltage, sound waves, laser light, and electric current. However, these methods are limited by safety concerns. Topical formulations like creams, gels, ointments, and lotions improve efficacy but have poor permeation through the stratum corneum and require high doses and repeated applications, which may cause severe side effects and poor patient compliance for long-term therapy [14].

4. NANO-FORMULATIONS:

In 1986, oral nano pellets were prepared, leading to the development of solid lipid nanoparticles and nanostructured lipid carriers. These carriers offer biocompatibility and targeted delivery, and have been used in cancer treatment, allergies, and COVID-19 vaccine development. However, multistep production can affect their physicochemical characteristics [14].

Innovative drug delivery aims to maintain a constant drug level in the body or deliver sustained action at a set rate using carriers to deliver medication to specific targets. Nanotechnology is extensively used in transdermal drug delivery, particularly for therapeutic agents. Nanocarriers, such as silicon, polymers, magnetic nanoparticles, dendrimers, carbon materials, lipid-based systems, and silicon, are effective in delivering medication to the intended location [15]. Encapsulating the drug in a nanocarriers-based formulation has become a suitable alternative to overcome the challenges of available therapies and facilitate the permeation of the drug through the skin [16].

The Greek word "dwarf" is where the word "nano" comes from, and nanotechnology is the general term for material manipulation at the nanometre (10^{-9} m) scale. Even though nanotechnology may seem like a relatively new field of study, nanoparticles (NP) were initially created as a means of delivering drugs more than 40 years ago. Since then, significant advancements have been made in the engineering of nanoscale materials and the assessment of these carriers' potential for improving human health [17]. The approach of developing Solid lipid nanoparticles and Nanostructured lipid carrier are illustrated below in Figure-4,

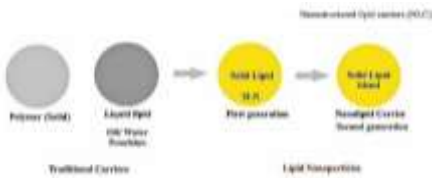


Figure 4: Lipid carriers

4.1. Nanoparticles and Nanostructured lipid carrier:

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are promising drug delivery vehicles ue to their appealing characteristics. SLN, similar to oil-in-water emulsions, can be produced on an industrial scale but may face issues like drug leakage and inadequate drug load [18]. To create solid lipid nanoparticles, replace liquid lipid with solid lipid at room temperature. The first generation of solid lipid nanoparticles (SLN) consisted of solid lipids. In the second generation of nanostructured lipid carriers

(NLC) technology, solid lipids are combined with solid liquid lipids, making NLC a significant advancement over previous emulsification techniques. NLCs (Figure 5) typically range from 10-500 nm and contain medication dissolved or melted within a mixture of liquid and solid lipids [19].

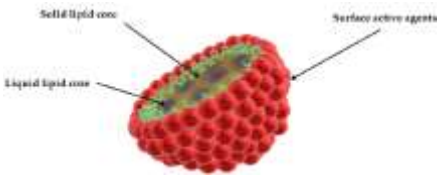


Figure 5: Nanostructured lipid carrier

4.2. Advantages of lipid carriers [20-24]:

1. Their small size and narrow distribution enable site-specific drug delivery.
2. Controlled and Sustained release of active drugs can be achieved.
3. Incorporated drug is protected from the onslaughts of biochemical degradation.
4. By shielding the chemically labile medications from the outside world, their stability can be increased (to protect the drug from biochemical destruction).
5. In terms of physical stability, NLCs outperform SLNs.
6. Increased hydrophilic and lipophilic drug trapping as well as increased dispersibility in an aqueous media.
7. Possibility of combining medications that are both hydrophilic and hydrophobic
8. Solid lipids immobilize drug molecules, protecting labile and sensitive pharmaceuticals against oxidative, photochemical, and chemical degradation.
9. Because their lipid components are permitted or used as excipients in commercially available topical cosmetic or pharmaceutical preparations, they are one of the preferred transporters for medications applied topically.
10. Biodegradable lipids can be used to lessen severe and chronic toxicity.

4.3. Types of lipid carriers:

The composition of the various lipid mixes and the various production techniques determine how NLCs are made. Giving the lipid matrix a particular nanostructure is the major objective in order to enhance the pay-kind for active substances and reduce the ejection of drug molecules during storage. The following summarizes the three types of NLCs,

4.3.1. NLC type I (Imperfect NLCs):

A partial substitution of liquid lipid or oil for solid lipid results in an incomplete crystal lattice or matrix. This occurrence indicates that there is more room for drugs to be accommodated and permits increased drug loading. A highly structured or ordered matrix would have forced the drug out of the core, whereas the development of an imperfect crystal core allows for additional space for drug integration. Imperfect type of NLC were mention below in Figure-6

Figure 6: Imperfect NLC

4.3.2. NLC type II (Amorphous NLCs):

Combining liquid lipids with solid lipids that retain their α polymorph after solidification and storage often results in the formation of an amorphous core. Compared to type I NLCs, this is better since the medication stays entrenched in the amorphous matrix and no crystallization happens. Solid lipids with the β polymorph form a matrix with a crystalline structure. Figure-7 shows the structure of Amorphous type NLC of NLC.

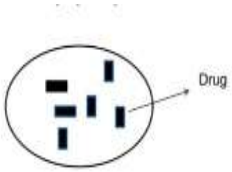


Figure 7: Amorphous NLC

4.3.3. NLC Type III (Multiple O/F/W NLCs):

It is essentially NLC of the oil-in-solid or fat-in-water kind, which can only be produced via the phase separation method. Using this method in the formulation of NLCs can increase drug loading capacity and stability when the medication exhibits higher solubility in oil. A solid lipid matrix contains evenly distributed tiny oil droplets, and this system is distributed in an aqueous medium [25]. Such type of NLC were shown below in Figure-8.

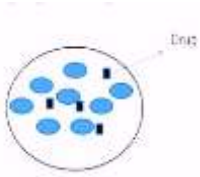


Figure 8: Multiple NLC

4.4. COMPOSITION OF NLCs:

The NLC is composed of lipids, surfactants, and water in an aqueous medium. Factors affecting its size, loading capacity, drug release profile, and stability include lipid content, matrix, and production process. The NLC combination consists of a long and short chain of liquid and solid lipid, with varying lipid content from 5 to 40%. Surfactants stabilize NLC formulations in aqueous mediums at 0.5 to 5% w/w concentrations [26].

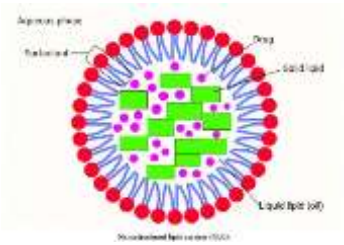


Figure 9: Composition of NLC

The main components of NLC includes as follows,

1. Lipids
2. Surfactants
3. Other excipients

4.4.1. Lipids: Lipids are crucial in New Life Cycle Cells (NLCs), regulating drug loading capacity, action duration, and formulation stability. The inner cores consist of both liquid and solid lipids, with the best lipids being physiologically acceptable, biodegradable, non-toxic, and generally recognized as safe (GRAS) status.

a) Solid lipids:

NLC is a blend of chemical substances with a melting point over 40°C, biodegradable *in vivo*, and a GRAS rating. Lipids used in NLC are chosen based on their high solubility, determined by dissolving the component in liquified solid lipids in increasing amounts to achieve the maximum amount of activity [27].
Ex: Glyceryl tristearate/tristearin, Stearic acid, Glyceryl monostearate, Propylene glycol monostearate, Cetyl palmitate, Cholesterol, Beeswax, Carnauba wax, Preciface, Emulcire,

b) Liquid lipids:

Natural sources of digestible oils are the most often utilized liquid lipids for NLCs. These liquid lipids have a GRAS (Generally Recognized as Safe) rating and are well tolerated. The lipophilic excipients utilized to integrate the solid lipid core and lessen its crystallinity are called liquid lipids, or oils [28].
Ex: Soyabean oil, vitamin-E/tocopherol, Castor oil, Corn oil, Oleic acid, Palm oil, Olive oil, Squalene, caprylic/capric triglyceride, Propylene glycol dicaprylate/caprate, Miglyol.

4.4.2. Surfactants:

Surfactants are used in the preparation of NLC to stabilize the structure of lipid nanoparticles in dispersion media. They lower the interfacial energy between the lipid phase and aqueous phase, reducing the particles tendency to accumulate in the binding interface. This creates a layer around the particles, supporting the dispersion's physical stability during storage and formulation. Two emulsifiers with lipophilic and hydrophilic properties can improve results. Surfactants stabilize the structure of lipid nanoparticles in dispersion media, stabilizing the dispersive system. High surfactant concentrations in drug delivery systems present challenges. The appropriate surfactant should be chosen based on the surfactant's HLB value and the molecules molecular weight [29].

a) Ionic surfactants: Sodium Tauro deoxycholate, Sodium oleate, Sodium dodecyl sulphure, Polysorbate 60 & 80.etc.

b) Non-Ionic surfactants: Polyoxyethylene, sorbitan monolaurate (Polysorbate 20, Tween 20), Polyoxyethylene, sorbitan monostearate (Polysorbate 60, Tween 60) Polyoxyethylene, sorbitan monooleate (Polysorbate 80), Poloxamer 188 Poloxamer 182 Ethoxylated p-tert-octylphenol formaldehyde polymer (Tyloxapol).

c) Amphoteric surfactants: Egg phospholipid (Lipoid E 80, Lipoid E 80 S) Soy, Hydrogenated soy phosphatidylcholine (Lipoid S PC-3), Hydrogenated

d) Co-surfactants: Butanol, Butyric acid, Polyvinyl alcohol (PVA), Propylene glycol, Polyethylene glycol.

4.4.3. Other excipients:

In the creation of nanostructured lipid carriers, organic salts and ionic polymers may be used as counter-ions to overcome the challenge of encasing water-soluble medication molecules. Surface-modifiers are another kind of excipients used in the formulation of NLC; its purpose is to lessen the phagocytic absorption of the excipients by macrophages in the reticuloendothelial system (RES). Lipophilic particles are coated with hydrophilic polymers such as PEG, poloxamines, or poloxamers to prolong the duration of medicinal compounds' residency in the systemic circulation. Increased drug targeting is one of the possible additional advantages of surface modification. enhanced physical stability, enhanced transit via the epithelium, and enhanced biocompatibility [30].

4.5. METHODS INVOLVED IN FORMULATION OF NLCs:

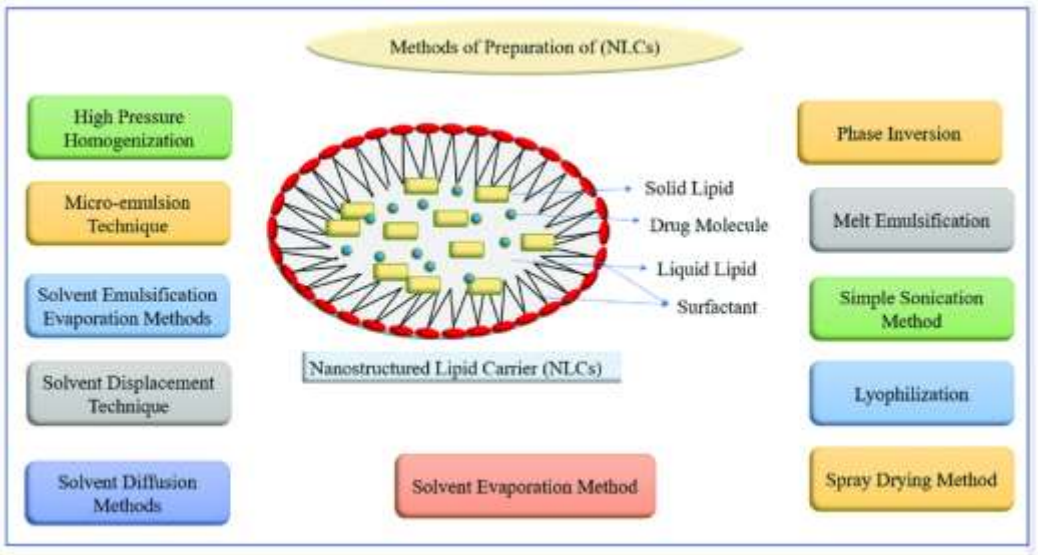


Figure 10: Method of preparation

4.6. CHARACTERIZATION OF NANOSTRUCTURED LIPID CARRIER:

To ensure NLC's functionality, quality, and stability, its physicochemical qualities must be characterized using appropriate methods. The viability of NLCs as drug delivery systems is demonstrated through factors like crystallinity studies, drug entrapment efficiency, interfacial characteristics, particle shape and size, *in vitro* drug release, surface charge, etc [31].

4.7. APPLICATIONS OF NLC:

4.7.1 NLCs in dermal application:

These days, a number of NLC formulations are sold for medical and cosmetic purposes, most likely as a result of their well-established biocompatibility thanks to the usage of lipids. The work of developing and characterizing NLCs and investigating potential remedies for different illnesses and conditions is continuous. Here, several recent studies that took into account different delivery methods and physiological problems are reviewed.

Oral drugs are broken down through intestinal metabolism, hepatic first pass metabolism, and stomach acid, leading to medication loss and decreased bioavailability. This necessitates frequent dosage administration and adverse effects. Applying NLC formulation to the stratum corneum allows efficient

drug penetration, creating an occlusive barrier, lowering transepithelial water loss, and hydrating the skin [32].

Lansoprazole's NLC-incorporated hydrogel was created, with permeation enhancers added to the hydrogel to help with negatively charged NLC's resistance to permeation. Drug accumulation in the skin was seen, which resulted in the drug's extended-release duration [33].

According to certain research, medication penetration may result via the electrostatic interaction of positively charged NLC with the negative skin surface and the aggregation of negatively charged NLC at hair follicles. Chitosan-coated NLC loaded with clobetasol propionate developed for treating psoriasis, etc. [34].

In NLC, Guo *et al*. included two alkaloids from *Aconitum sinomontanum,* lappaconitine and ranaconitine, which demonstrated less cytotoxicity than alkaloid solutions and increased *in vivo* BA in comparison to SLN [78]. When spironolactone was created as NLC, it was noted that follicular delivery and localization may be helpful in the management of androgenic alopecia [35].

Increase in skin hydration and elasticity: The study found that occlusion from SLN, NLC, or formulations reduces trans epidermal water loss, resulting in increased skin hydration. An *in vivo* study showed that SLN-containing o/w cream significantly increased skin hydration compared to conventional cream. Repeated application of these creams for 28 days also increased skin hydration [36].

Enhancement of skin permeation and drug targeting: The stratum corneum, which acts as a barrier against the absorption of external substances, typically has a water content of 20% in healthy skin. Applying SLN or NLC to the skin increases skin hydration, which in turn reduces the packing of corneocytes and enlarges the gaps between them. This facilitates the absorption of substances through the skin and enhances drug penetration into deeper skin layers [37].

Waghule et al. proposed the use of NLC embedded in a topical gel to administer the anti-fungal voriconazole (VCZ) in order to decrease the severity and frequency of its adverse effects. The optimized formulation showed suitable mean particle size, high encapsulation efficiency, and drug loading. The VCZ-loaded NLC demonstrated a prolonged release of the drug for a duration of 10 hours. This specific formulation was incorporated into a Carbopol gel and ex vivo permeation studies were conducted. The results revealed an improved permeation of 66.45% and sustained release for up to 11 hours compared to a gel containing the free drug. The findings indicated that the NLC embedded gel retained more drug in the skin layers, preventing its systemic permeation and thus reducing the adverse effects associated with the free VCZ. *In vitro* evaluation of the antifungal activity against Aspergillus flavus showed a significantly larger zone of inhibition (22.5 ± 0.5 mm) for the NLC formulation compared to the free drug counterpart (14.5 ± 0.5 mm). This study contributes to the understanding of the relationship between formulation and process variables. Additionally, it was reported that the VCZ-loaded NLC gel, which can target the skin, holds promise as an alternative treatment for managing topical fungal infections [38].

Moghddam et al. conducted a study in which they developed a nimesulide NLC for topical delivery. They utilized a Box-Behnken design to optimize the ratio of stearic to oleic acids and the concentrations of Poloxamer 188 and lecithin as independent variables. The dependent variables, particle size, and encapsulation efficiency, were also optimized. The researchers conducted various tests, including a skin permeation assay, *in vitro* release, confocal laser scanning microscopy (CLSM), and stability evaluation. The optimized nimesulide NLC exhibited reasonable encapsulation efficiency, particle size, and skin permeation. Initial investigations indicated a delayed drug release for the optimized batch, following Higuchi release kinetics. CLSM demonstrated enhanced penetration of rhodamine-loaded NLC into

deeper skin layers. These findings suggest that NLC has the potential to serve as a carrier for the topical application of nimesulide. [39].

Jain et al. conducted a separate study where they formulated and characterized a topical NLC gel containing both adapalene (Ada) and vitamin C (AP-Ascorbyl-6 palmitate). The NLC gel was prepared using HPH and then incorporated into a gel. The drug-loaded NLC gels were evaluated for their ability to permeate the skin, biodistribution, and effectiveness in treating testosterone-induced acne in male Wistar rats. The NLC gel demonstrated improved targeting of the epidermis and reduced absorption into the systemic circulation. These research findings not only suggested the potential application of NLC for dermal delivery of Ada but also emphasized the synergistic effect of vitamin C in topical acne treatment [40].

The therapeutic outcome in cutaneous disorders can be enhanced through the use of a drug targeting approach. Over the past decade, the benefits of lipid nanoparticles in targeting drugs have been recognized. These nanoparticles possess a small particle size and controlled release property, resulting in a low concentration gradient in the epidermal layer. This leads to the accumulation of the drug and prevents its further penetration into deeper layers [41]. Additionally, the occlusive property of SLN/NLC, along with the lipids and surfactants composing the nanoparticles, further contributes to their advantages in drug targeting [42].

Recently, Mendes et al. conducted a study where they developed and characterized a transdermal gel containing donepezil (DPB) NLC. The NLC was prepared using the microemulsion technique, and the selection of excipients was based on their potential for skin permeation. Stearic acid was chosen as the solid lipid, oleic acid as the liquid lipid, and lecithin and sodium Tauro deoxycholate as the surfactant and co-surfactant, respectively. The *in vitro* permeation assays showed enhanced skin permeation of DPB, which was attributed to the excipients and lipid nanocarriers used. The DPB-NLC gel was considered an interesting formulation for improving the treatment of Alzheimer's disease [43].

In another study by Chauhan and Sharma, they developed a transdermal carrier for rivastigmine based on NLC to improve its bioavailability. They employed the Box-Behnken design for the optimization of NLC formulations, which were engineered using castor oil, Span 80, and Tween 80. After routine characterization, the NLC formulations were loaded into transdermal patches. The *in vitro* release behavior showed sustained drug release compared to a commercial patch. Pharmacokinetic studies demonstrated higher Cmax and AUC0-72 values in plasma treated with NLC transdermal patches compared to conventional patches. These findings validated the potential of NLC transdermal patches for enhancing the bioavailability of rivastigmine in dementia [44].

Yue et al. also conducted a study where they produced hyaluronic acid (HA) modified NLC for transdermal delivery of bupivacaine (BPV) and evaluated their *in vitro and in vivo* performance. They prepared HA-PEG-LOA and added it to the NLC during production. In addition to physicochemical characterization, they also performed *in vitro* skin permeation, drug release, and *in vivo* therapeutic activity assessments. The NLC that were prepared had a small size of 150 nm and a zeta potential of -40 mV. BPV-NLC demonstrated a high encapsulation efficiency of 90%. The *in vitro* release assay showed a sustained profile for 72 hours. When compared to free BPV, BPV-NLC and HA-BPV-NLC exhibited a 1.6 and 2.5-fold enhancement in percutaneous penetration, respectively. These results demonstrate the effectiveness of HA modified BPV-NLC in prolonging and improving the action of the anesthetic drug [45].

Medha Joshi et al. developed a topical gel containing celecoxib for the treatment of inflammation and related conditions. The gel was formulated using nanostructured lipid carriers (NLC) prepared through the

microemulsion template technique. The size of the NLC was determined using photon correlation spectroscopy, and their structure was examined through scanning electron microscopy. The efficiency of drug encapsulation was assessed using a Nanosep® centrifugal device. The NLC dispersion was then transformed into a gel and tested for its release and permeation properties using rat skin *in vitro*. The efficacy of the NLC gel was evaluated through a pharmacodynamic study using a rat paw edema model induced by aerosil. The permeation of the gel through the skin and its pharmacodynamic effects were compared to those of a micellar gel with a similar composition, except for the solid lipid and oil components. The NLC-based gel demonstrated a faster onset of action and prolonged activity for up to 24 hours [46].

In a study conducted by Donatella Paolino et al, NLC of lutein were investigated as an alternative to a 20% suspension of lutein in safflower oil (FloraGLO® Lutein) for the production of creams and other semisolid formulations. However, the high viscosity of FloraGLO® and the poor chemical stability of lutein in the suspension posed practical limitations. NLC were prepared using different percentages of FloraGLO® as the liquid phase. The physical stability of the NLC was evaluated through storage at room conditions and Turbiscan accelerated analysis. Application of the produced nanocarriers on the skin was well-tolerated. In an *in vivo* model of UV-induced skin erythema, the lutein-loaded NLC demonstrated enhanced photo-protective effects compared to the commercial suspension when applied prior to erythema induction. This study also demonstrated the possibility of converting a liquid formulation into a solid, modified release nanocarrier with improved manageability [47].

4.7.2. NLCs in treating hyperpigmentation:

Banna et al. evaluated MHY908-loaded nanostructured lipid carriers for hyperpigmentation treatment. They found that MHY908 NLC had a higher skin penetration rate and occlusion effect than MHY908 solution, and effectively prevented UVB-induced hyperpigmentation. It also reduced UVB-induced hyperpigmentation without damaging skin fibroblast cells, indicating its potential for hyperpigmentation treatment [5].

Sharifmakhmalzadeh B., et al. evaluated 8 different formulations of Hydroquinone NLC. They found that the 2nd formulation had maximum drug release and increased penetration in rats, while the 8th formulation reduced melanosome percentage compared to HQ cream [48].

Khezri K., et al. characterized eight Kojic acid-loaded nanostructured lipid carrier formulations, concluding that the third formulation effectively treats photoaging and hyperpigmentation, releasing the drug in a prolonged and controlled manner [49].

Cheon and colleagues conducted a study where they formulated a Nanostructured Lipid Carrier (NLC) to deliver velutin topically. Their findings demonstrated that the loaded velutin exhibited enhanced inhibitory activity of up to 56.5%. This suggests that lipid-based NLC nanoparticles can be efficacious in the treatment of various skin conditions such as hyperpigmentation, acne, and wrinkles [50].

Vaziri et al. conducted a study where they developed and analysed five distinct variations of Undecylenoyl Phenylalanine loaded NLC. These formulations contained varying concentrations of solid and liquid lipids. The results indicated that the entrapment efficiency increased up to 90.81±3.75%, and the NLC exhibited a tyrosinase inhibition rate of approximately 72%. Based on their findings, the researchers proposed that the formulated NLC could be efficiently utilized for sustained action on the epidermal layer of the skin, making it a promising option for skin brightening purposes [51].

Krambeck and colleagues conducted a study where they developed and examined NLC and NLC-based hydrogels that contained Passiflora edulis seed oil. These formulations were then analysed for their long-term stability over a period of 12 months. The size of the NLC particles ranged around 150nm, and the zeta potential was approximately -30mV. The NLCs that were encapsulated in the hydrogels demonstrated improved tyrosinase inhibitory action, enhanced skin retention, and showed no cytotoxic effects on HaCat cells. Additionally, the NLC formulations exhibited suitable viscosity and texture properties for skin application. In conclusion, the researchers stated that NLCs have great potential as depigmenting agents [52].

Kumari S et al. conducted a study to analyse and assess the use of nanostructured lipid carriers (NLC) for delivering an antiacne drug topically. The study revealed that the incorporation of azelaic acid into NLC resulted in improved targeting of specific sites, such as melanocytes. This improvement can be attributed to the small size of the NLC particles and their occlusive effect, which enhances penetration through the stratum corneum. In terms of permeation capabilities, the release rates of azelaic acid-NLC, azelaic acid gel, and azelaic acid in water were found to be 21%, 38%, and 78% respectively. Despite the slower release rates, azelaic acid-NLC exhibited a higher initial burst release of up to 5%. The sustained release and high initial burst release of azelaic acid-NLC offer advantages for topical application, as it allows for a rapid onset of action and creates a localized drug depot effect. [53].

Wu et al. formulated and evaluated Hydroquinone NLC by homogenization emulsification method whose result were found to be 393.30 ± 28.23nm particle size and 22.13 ± 2.66% entrapment efficiency and -30 mV zeta potential. They also carried out tyrosinase inhibition assay and found that the inhibitory action increased to some extent, and also show improved light stability and permeability through skin through which they concluded that HQ loaded NLC can be potentially used as vehicle for transdermal application [54].

Siti Maria Abdul Ghani et al. conducted a study on the encapsulation of *Ficus deltoidea* extract in NLC for its anti-melanogenic activity. They employed two different methods, namely thin film ultra sonication dispersion and double-emulsion solvent diffusion. The latter method resulted in the production of NLC with a size of 155.9 ± 7.11 nm. Additionally, the zeta potential of NLC produced using the latter method was lower compared to the former method. Moreover, the entrapment efficiency of NLC through the latter method was higher than that of the former method. The researchers also evaluated the efficacy of the drug in inhibiting melanin production and found that it effectively reached the melanocytes by enhancing its delivery into the viable epidermis layer. [55].

Hengfeng Fan et al. have devised an innovative approach to enhance the skin whitening effect using NLC. The product they developed exhibited a spherical morphology and had a charge of -65.4 ± 4.3 mV. In addition, they conducted studies on melanin measurement and observed that the NLC formulation demonstrated improved skin whitening and inhibition of melanogenesis. The NLC formulation displayed a stronger ability to inhibit melanin and tyrosinase at a higher concentration of 2.4 ng/ml-1. Based on these significant findings, they concluded that NLC is a potent carrier for skin whitening agents [56].

Faizatun Faizatun and colleagues conducted a study where they developed a NLC gel using mulberry root extract (Morus alba) for its whitening properties. They used zebrafish as a model and compared the effects of the root extract with the loaded NLC. Through morphological observations, they found that the melanin levels in the eye decreased. The concentration of mulberry root extract directly influenced the reduction in melanin levels. Similarly, an increased concentration of mulberry root extract in the NLC resulted in a

decrease in melanin levels. Based on their findings, the researchers concluded that mulberry root NLC has effective whitening properties as it reduces melanin content [57].

4.7.3. Other applications of NLC:

a) Oral drug delivery:

Oral medication administration is the most convenient method, as it can overcome reduced bioavailability of poorly water-soluble drugs due to gastrointestinal barriers and biochemical processes like enterocyte transporters' efflux, hydrophilic environment, enzymes, gut wall metabolism, and hepatic first pass metabolism [58].

The HPH technique was used to synthesize spironolactone (SPN), a medication with low water solubility. Its primary metabolites, canrenone and 7α-TMS, were responsible for its action. Pharmacokinetic data revealed very low amounts of SPN, with plasma containing more 7α-TMS. SPN was biodistributed in the kidney, liver, and small intestine, and its solubilization and binding affinity from micelles were likely improved by mixed micelles [59].

The milk thistle plant extract, Silybum marianum, was used in NLCs for improved drug effectiveness. *In vitro* lipolysis experiments suggest mixed micelle production, while a canine *in vivo* oral BA study showed a lower t max, indicating improved gastrointestinal tract absorption [60].

The study utilized N-acetyl-L-cysteine-polyethylene glycol (100)-monostearate (NAPG) to functionalize the surface of curcumin NLCs, enhancing their absorption and retention in the stomach [61]. Amphotericin B coated with chitosan, NLC, also improved oral BA by delaying gastrointestinal transit and exhibiting muco-adhesion due to its positive surface charge [62].

Tacrolimus, an immunosuppressant, was improved by its NLC formulation, resulting in greater aqueous solubility and enhanced half-life and plasma concentration, compared to other NLCs made using other methods [63].

Vinpocetine loaded NLC have been found to improve oral blood pressure (ABB) compared to traditional formulations [64]. NLC loaded with calcium rosuvastatin showed better drug penetration in deeper intestinal tissues, increasing antihyperlipidemic potential [65].

b) Ocular drug delivery:

Due to the numerous barriers found in the eyes, a variety of innovative drug delivery technologies, including liposomes, nanoparticles, microemulsions, and micelles, were created to overcome the limits of conventional ocular treatments. Among all carriers, polymeric systems are the most popular.

However, NLCs were created with the potential for foreign body responses and local toxicity in mind, taking into account their lipid-based biocompatibility and lack of toxicity. The use of cationic surfactants or polymers increased the carriers' retention in the eyes for the duration of the medication's effect by enabling them to interact with the negatively charged mucosal surface through electrostatic forces [66].

Mira et al. improved flurbiprofen NLC formulation using a central composite factorial design, resulting in a safe, non-irritating, and prolonged ocular administration [67].

c) Drug delivery to central nervous system

Drug delivery to the central nervous system is challenging due to the Blood Brain Barrier (BBB), which restricts drug passage due to capillary tightness. Only lipophilic drugs can pass, and essential nutrients are taken up through active transport. The BBB disruption mechanism is invasive and painful, but non-

invasive approaches like intranasal drug delivery, nanoparticles, prodrugs, and vector-mediated chimeric peptides can replace it [68].

d) Intranasal route: Drugs for central nervous system problems must be administered orally and intravenously, which necessitates repeated dosages and increases the drug's exposure to the systemic circulation, increasing the risk of organ toxicity and related adverse effects. In order to avoid these effects, the trigeminal and olfactory nerve routes are used to deliver drugs directly to the brain through the intranasal route [69]. For the Intra nasal way of treating epilepsy, lamotrigine (LMT) loaded NLCs were created, demonstrating constant drug release at zero order. Higher drug penetration of NLC was demonstrated *ex vivo* by goat nasal mucosa permeability, and *in vivo* pharmacodynamic experiments in animals produced with maximal electroshock demonstrated greater effectiveness of IN given LMT-NLCs for monitoring epileptic situations [70].

e) Intravenous route: When treating CNS disorders, oral medication distribution causes physiological issues. Thus, parenteral NLC treatment is created, which targets the brain specifically while overcoming organ toxicity and adverse effects. Researchers developed an intravenous NLC therapy using artemether and Lumefantrine, which effectively targeted CNS-resident malarial parasites for four consecutive days, completely reversing cerebral malaria symptoms in animals without any organ toxicity [71].

f) Pulmonary drug delivery: Because the lungs have a higher surface area accessible for medication absorption, drugs are given there in formulations appropriate for treating local disorders or for systemic drug administration. Particles must have a mean aerodynamic diameter of 1-3 µm in order to be disposed of deeply in the alveolar area during systemic drug administration through the pulmonary route. Particle characteristics must be changed or tweaked if local delivery is anticipated in order to increase medication disposal in the appropriate infected/targeted area [72].
Mannose-coated, rifampicin-loaded NLCs were created with the goal of reducing the duration of TB therapy and preferentially targeting the medication to alveolar macrophages. This was accomplished by a passive strategy that maintained the aerodynamic diameter of the carriers at or above 200 nm. By way of macrophage phagocytosis. Mannose-coated NLCs were actively targeted by mannose receptor-mediated absorption, which resulted in a reduction in bacilli's intracellular proliferation [73].

g) In Cosmetics: Nanostructured liquids (NLCs) are a type of cosmetic product that offer significant advantages in terms of load-bearing capacity and long-term stability. They are used in various formulations like gels, creams, lotions, and ointments, offering benefits like enhanced skin absorption, UV protection, improved permeation, targeted transdermal delivery, enhanced physical and chemical stability, and skin hydration *in vivo*. These advantages make NLCs a valuable product in the cosmetics industry. [74].

h) In Gene delivery: Viral and non-viral vectors are the two main categories of gene delivery technologies. While non-viral gene therapy offers advantages such as reduced antigenicity and simplicity in production, viral vectors have gained significant attention due to their high transfection effectiveness. However, there is room for improvement in their effectiveness. Lipopolyplexes, which are composed of lipids, polycations, and genes (RNA/DNA), are utilized as nanomedicines for successful and efficient gene delivery. The ability of PNLC combined with triolein to transfer genes *in vitro* in human lung

adenocarcinoma highlights the importance of NLC in gene transport. Recently, the enhanced efficacy of NLC has been demonstrated in the localized distribution of anti-cancer medications for tumour treatment via inhalation. Additionally, the combination of siRNAs has shown promising results in reducing tumour growth and minimizing adverse effects on sensitive organs in the treatment of pulmonary cancer [75].

i) In Nutraceuticals: Nutraceuticals are substances with bioactive properties that provide pharmacological or health benefits, including the ability to treat and prevent diseases. In the case of NLC, Hesperetin, a flavanone, was directly included, resulting in NLC with satisfactory acceptability, uniformity, excellent flavour, and enhanced medicinal properties. Hesperetin has demonstrated effectiveness in chemically induced breast malignancy, colon carcinogenesis, cardiac arrest, and hypertension [76].

5. Future prospectus:

NLCs are lipid-based structures that provide protection and sustained drug release through hydrophobic drug coverage. They are approved by the FDA for oral administration and can be formulated using surfactants and biocompatible lipids. Formulating NLCs is straightforward and can be scaled up to larger batch sizes. Continuous improvements in NLC formulations have significantly impacted the pharmaceutical and cosmetic industries. The potential of NLCs as pharmaceutical carriers is demonstrated through topical administration. With the increasing number of patented NLC-based formulations and research papers, it is expected that clinical trials related to NLC will expand in the future.

6. Conclusion:

To summarize, recent research has revealed the immense potential of a nano-based delivery system in enhancing the bioavailability of poorly soluble lipophilic drugs and effectively targeting the intended site of action on the topical route. The smart NLC, as the next generation, offers even greater versatility in drug loading, modulation of drug release, and improved efficiency in developing various dosage forms like pills, creams, capsules, and injectables. The utilization of NLCs for exploring alternative treatment routes and addressing other medical conditions should be further expanded. Based on the wealth of knowledge gathered from recent literature, it can be concluded that NLC represents an exceptional advanced drug carrier system in treating the skin ailments.

Reference:

1. Bhaskar, K., Mohan, C. K., Lingam, M., Mohan, S. J., Venkateswarlu, V., Rao, Y. M., Bhaskar, K., Anbu, J., & Ravichandran, V., 2009.Development of SLN and NLC enriched hydrogels for transdermal delivery of nitrendipine: *in vitro* and *in vivo* characteristics. Drug Development and Industrial Pharmacy, 35(1): 98-113.
2. Eroglu, C., Sinani, G., & Ulker, Z. 2023.Current state of lipid nanoparticles (SLN and NLC) for skin applications. Current Pharmaceutical Research, 29(21): 1632-44.
3. Mahant, S., Rao, R., Souto, E. B., & Nanda, S. 2020.Analytical tools and evaluation strategies for nanostructured lipid carrier-based topical delivery systems. Expert Opinion on Drug Delivery,17(7): 963-92.
4. Joseph, N., Kumar, G. S., & Nelliyanil, M. 2015.Skin diseases and conditions among students of a medical college in southern India. Indian dermatology online journal,5(1): 19.

5. Banna, H., Hasan, N., Lee. J., Kim, J., Cao, J., Lee, E. H., Moon, H. R., Chung, H. Y., & Yoo, J. W. 2018.*In vitro* and *in vivo* evaluation of MHY908-loaded nanostructured lipid carriers for the topical treatment of hyperpigmentation. Journal Drug Delivery Science Technology,48: 457-65.
6. Thawabteh, A. M., Jibreen, A., Karaman, D., Thawabteh, A., & Karaman, R. 2023.Skin Pigmentation Types, Causes and Treatment-A Review. Molecules,28(12): 4839.
7. Nicolaidou, E., Katsambas, A. D. 2014.Pigmentation disorders: hyperpigmentation and hypopigmentation. Clinics in dermatology,32(1): 66-72.
8. Bohm, M. 2021.Disorders of Melanin Pigmentation. InBraun-Falco´ s Dermatology, Berlin, Heidelberg: Springer Berlin Heidelberg, 1-35.
9. Ma, E. Z., Zhou, A. E., Hoegler, K. M., & Khachemoune, A. 2023.Oculocutaneous albinism: epidemiology, genetics, skin manifestation and psychosocial issues Archives of Dermatological Research,315(2): 107-16.
10. Hill, J. P., & Batchelor, J. M. 2017.An approach to hypopigmentation. BMJ, 356: 356–362.
11. Silpa-Archa, N., Kohli, I., Chaowattanapanit, S., Lim, H. W., & Hamzavi, I. 2017.Post-inflammatory hyperpigmentation: A comprehensive overview: Epidemiology, pathogenesis, clinical presentation, and non-invasive assessment technique. Journal of the American Academy of Dermatology,77: 591–605.
12. Sheth, P. B., Shah, H. A., & Dave J. N. 2014.Periorbital hyperpigmentation: A study of its prevalence, common causative factors and its association with personal habits and other disorders. Indian Journal of Dermatology,59: 151–157.
13. Pinheiro, M., Ribeiro, R., Vieira, A., Andrade, F., & Reis, S. 2016.Design of a nanostructured lipid carrier intended to improve the treatment of tuberculosis. Drug design, development and therapy,2467-75.
14. Müller, R. H., Mader, K., & Gohla, S. 2000.Solid lipid nanoparticles (SLN) for controlled drug delivery–a review of the state of the art. European Journal of Pharmaceutics and Biopharmaceutics,50(1): 161-77.
15. Lopez, K. L., Ravasio, A., Gonzalez-Aramundiz, J. V., & Zacconi, F. C. 2023.Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) Prepared by Microwave and Ultrasound-Assisted Synthesis: Promising Green Strategies for the Nanoworld. Pharmaceutics,15(5): 1333.
16. Sathyanarayana, T., Sudheer, P., Jacob, E., & Sabu, M. M. 2023.Development and Evaluation of Nanostructured Lipid Carriers for Transdermal Delivery of Ketoprofen. Fabad Journal of Pharmaceutical Science,48(1):105-24.
17. Kakkar, V., & Scope, S. K. Scope of nano delivery for atopic dermatitis. Ann Pharmacol Pharm.2017; 2(27): 2-5.
18. Lane, M. E., Nanoparticles and the skin–applications and limitations. Journal of microencapsulation. 2011 Dec 1;28(8):709-16
19. Shekhawat, P. B. Preparation and evaluation of clotrimazole nanostructured lipid carrier for topical delivery. Int. J. Pharm. Bio. Sci. 2013;4(1):407-16.
20. Müller, R. H., Petersen, R. D., Hommoss, A., & Pardeike, J. 2007.Nanostructured lipid carriers (NLC) in cosmetic dermal products. Advanced Drug Delivery Reviews,59(6): 522-30.

21. Aliasgharlou, L., Ghanbarzadeh, S., Azimi, H., Zarrintan, M. H., & Hamishehkar, H. 2016.Nanostructured lipid carrier for topical application of N-acetyl glucosamine. Advanced pharmaceutical bulletin,6(4): 581.
22. Müller RH, Alexiev U, Sinambela P, Keck CM. Nanostructured lipid carriers (NLC): the second generation of solid lipid nanoparticles. Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Nanocarriers. 2016:161-85.
23. Patel, D. K, Tripathy, S., Nair, S. K., & Kesharwani R. 2013.Nanostructured lipid carrier (NLC) a modern approach for topical delivery: a review. World Journal of Pharmacy and Pharmaceutical Science,2(3): 921-38.
24. Gowda, D., Tej., Karamsetty., Moin., Afrasim., Anjali., Godugu., Karanakar., Patel., Nikhil., Kamal., & Samudrala. 2016.Nano structured lipid carrier-based drug delivery system. Journal of Chemical and Pharmaceutical Research,8(2): 627-643.
25. Javed, S., Mangla, B., Almoshari, Y., Sultan, M. H., & Ahsan, W. 2022.Nanostructured lipid carrier system: A compendium of their formulation development approaches, optimization strategies by quality by design, and recent applications in drug delivery. Nanotechnology Reviews,11(1): 1744-77
26. Sanap, G. S., & Mohanta, G. P. 2013.Design and evaluation of miconazole nitrate loaded nanostructured lipid carriers (NLC) for improving the antifungal therapy. Journal of Applied Pharmaceutical Science,3(1): 046-54.
27. Wissing, S., & Muller, R. 2002.The influence of the crystallinity of lipid nanoparticles on their occlusive properties, International Journal of Pharmacy,242(1-2): 377-9.
28. Liu, Y., Wang, L., Zhao, Y., He, M., Zhang, X., Niu, M., & Feng, N. 2014.Nanostructured lipid carriers versus microemulsions for delivery of the poorly water-soluble drug luteolin. International Journal of Pharmaceutics.476(1-2): 169-77.
29. Chaudun, L., Yasir, M., Verma, M., & Singh, A. P. 2020.Nanostructured Lipid Carrien. A Groundbreaking Approach for Transdermal Drug Delivery. Advanced Pharmaceutical Bullitin,10(2): 150-165.
30. Soni, K., Kukereja, B. K., Kapur, M., & Kohli, K. 2015.Lipid nanoparticles: future of oral drug delivery and their current trends and regulatory issues. International Journal of Current Pharmaceutical Research,7: 1-18.
31. Purohit, D. K., Nandgude, T. D., & Poddar, S. S. 2016.Nano-lipid carriers for topical application: Current scenario. Asian Journal of Pharmaceutics,10: 1-9.
32. U. Nagaich, & N. Gulati. 2016.Nanostructured lipid carriers (NLC) based controlled release topical gel of clobetasol propionate: design and *in vivo* characterization, Drug Delivery and Translational Research,6 :289-298.
33. Lin, W. J., & Duh, Y. S.2016.Nanostructured lipid carriers for transdermal delivery of acid labile lansoprazole. European Journal of Pharmaceutics and Biopharmaceutics,108: 297-303.
34. Silva, L. A., Andrade, L., M, de Sá, F. A., Marreto, R. N., Lima, E. M., Gratieri, T., & Taveira SF. 2016.Clobetasol-loaded nanostructured lipid carriers for epidermal targeting. Journal of Pharmacy and Pharmacology,68(6): 742-50.
35. Guo, T., Zhang, Y., Zhao, J., Zhu, C., Feng, N. 2015.Nanostructured lipid carriers for percutaneous administration of alkaloids isolated from *Aconitum sinomontanum*. Journal of Nanobiotechnology,13:1-14.

36. Loo, CH., Basri, M., Ismail, R., Lau, H. L., Tejo, B. A., Kanthimathi, M. S., Hassan, H. A., & Choo, Y. M. 2012.Effect of compositions in nanostructured lipid carriers (NLC) on skin hydration and occlusion. International Journal of Nanomedicine,27 :13-22.
37. Patel, D. K., Tripathy, S., Nair, S. K., & Kesharwani, R. 2013.Nanostructured lipid carrier (NLC) a modern approach for topical delivery: a review. World Journal of Pharmacy and Pharmaceutical Sciences;2(3): 921-38.
38. Waghule, T., Rapalli, V. K., & Singhvi, G. 2019.Voriconazole loaded nanostructured lipid carriers based topical delivery system: QbD based designing, characterization, *in-vitro* and ex-vivo evaluation. Journal of Drug Delivery Science and Technology 52: 303–315.
39. Moghddam, S. M., Ahad, A., & Aqil, M. 2017.Optimization of nanostructured lipid carriers for topical delivery of nimesulide using Box-behnken design approach. Artificial Cells, Nanomedicine, Biotechnology.;45(3):617–624.
40. Jain, A., Garg, N. K., Jain, A., Kesharwani, P., Jain, A. K., Nirbhavane, P., & Tyagi, R. K. 2016.A synergistic approach of adapalene-loaded nanostructured lipid carriers, and vitamin C co-administration for treating acne. Drug Development and Industrial Pharmacy, 42(6): 897-905.
41. Wu, X., & Guy, R. H. 2019.Applications of nanoparticles in topical drug delivery and in cosmetics. Journal of Drug Delivery Science and Technology,19(6): 371-84.
42. Choi, W. S., Cho, H.I., Lee, H. Y., Lee, S. H., & Choi, Y. W. 2010.Enhanced occlusiveness of nanostructured lipid carrier (NLC)-based carbogel as a skin moisturizing vehicle. Journal of Pharmaceutical Investigation,40(6): 373-8.
43. Mendes, I. T., Ruela, A. L. M, & Carvalho, F. C.2019. Development and characterization of nanostructured lipid carrier-based gels for the transdermal delivery of donepezil. Colloids Surfaces B: Biointerfaces,1(177): 274–281.
44. Chauhan, M. K., & Sharma, P. K.2019. Optimization and characterization of rivastigmine nanolipid carrier loaded transdermal patches for the treatment of dementia. Chemistry and Physics of Lipids,224: 104794.
45. Yue, Y., Zhao, D., & Yin, Q.2018 Hyaluronic acid modified nanostructured lipid carriers for transdermal bupivacaine delivery: *in vitro* and *in vivo* anaesthesia evaluation. Biomedicine and Pharmacotherapy,98: 813–820.
46. Joshi, M., & Patravale, V.2008. Nanostructured lipid carrier (NLC) based gel of celecoxib. International Journal of pharmaceutics,346(1-2): 124-32.
47. Donatella Paolino., Annalisa, H. S., Stancampiano., Felisa Cilurzo., Donato Cosco., Giovanni Puglisi., & Rosario Pignatello.2012. Nanostructured Lipid Carriers (NLC) for the Topical Delivery of Lutein. Drug Delivery Letters,1(1): 32-39.
48. Sharifmakhmalzadeh, B., Javadi, M., & Salimi, A.2022. The depigmentation effect of hydroquinone-loaded nanostructured lipid carriers (NLCs) on the rat skin. Journal of Reports in Pharmaceutical Sciences,11(1): 71-8.
49. Khezri, K., Saeedi, M., Morteza-Semnani, K., Akbari, J., & Hedayatizadeh-Omran, A.2021. A promising and effective platform for delivering hydrophilic depigmenting agents in the treatment of cutaneous hyperpigmentation: Kojic acid nanostructured lipid carrier. Artificial Cells, Nanomedicine, and Biotechnology,49(1): 38-47.
50. Cheon, S. H., Park, S. Y., Sung, J. H., Lee, J. G., Choi, S. H., Jang. J. W., Kim, H. C., Kim, S. T., Jeong, S., Lee, K., & Jang, D. J.2021. Preparation and Evaluation of Nanostructured Lipid Carrier for Topical

Delivery of Velutin: Synthetic Tyrosinase Inhibitor. Journal of Nanoscience and Nanotechnology,21(7): 4093-7.

51. Vaziri, M. S, Tayarani-Najaran, Z., Kabiri, H., Nasirizadeh, S., Golmohammadzadeh, S., & Kamali, H.2023. Preparation and Characterization of Undecylenoyl Phenylalanine Loaded-Nanostructure Lipid Carriers (NLCs) as a New α-MSH Antagonist and Antityrosinase Agent. Advanced Pharmaceutical Bulletin,13(2): 290.
52. Krambeck, K., Silva, V., Silva, R., Fernandes, C., Cagide, F., Borges, F., Santos, D., Otero-Espinar, F., Lobo, J. M., & Amaral, M. H.2021. Design and characterization of Nanostructured lipid carriers (NLC) and Nanostructured lipid carrier-based hydrogels containing *Passiflora edulis* seeds oil. International journal of pharmaceutics, 600-120444.
53. Kumari, S., Pandita, D., Poonia, N., & Lather, V.2015. Nanostructured lipid carriers for topical delivery of an anti-acne drug: characterization and *ex vivo* evaluation. Pharmaceutical Nanotechnology,3(2): 122-33.
54. Wu, P. S., Lin, C. H., Kuo, Y. C., & Lin, C. C.2017. Formulation and characterization of hydroquinone nanostructured lipid carriers by homogenization emulsification method. Journal of Nanomaterials,2017.
55. Ghani, S. M., Roslan, N. Z., Muda, R., & Abdul-Aziz, A.2021. Encapsulation of *Ficus deltoidea* extract in nanostructured lipid carrier for anti-melanogenic activity. Bionanoscience,11: 8-20.
56. Fan, H., Zhou, H., Ma, C., Huang, Y., Li, Y., & Xia, Q.2014. A novel method for the improved skin whitening effect based on nanostructured lipid carrier. Molecular Crystals and Liquid Crystals,593(1): 232-42.
57. Faizatun, F., & Murti, II.2023. Formulation of Nanostructured Lipid Carrier Gel from Mulberry Root Extract *(Morus alba L.)* as Whitening Agent using Zebrafish Modelling. JOURNAL ILMU KEFARMASIAN INDONESIA,21(2): 209-14.
58. Beloqui, A., Solinís, M. Á., Delgado, A., Évora, C., Isla, A., & Rodríguez-Gascón, A.2014. Fate of nanostructured lipid carriers (NLCs) following the oral route: design, pharmacokinetics and biodistribution. Journal of microencapsulation.1;31(1):1-8.
59. Shamma, R. N., & Aburahma, M.H.2014. Follicular delivery of spironolactone via nanostructured lipid carriers for management of alopecia, International Journal of Nanomedicine,9: 5449-5460.
60. Shangguan, M., Lu, Y., Qi, J., Han, J., Tian, Z., Xie, Y., Hu, F., Yuan, H., & Wu, W.2014. Binary lipids-based nanostructured lipid carriers for improved oral bioavailability of silymarin. Journal of biomaterials applications. 2014 Feb;28(6):887-96.
61. Li, J., Liu, D., Tan, G., Zhao, Z., Yang, X., & Pan, W.2016. A comparative study on the efficiency of chitosan-N-acetylcysteine, chitosan oligosaccharides or carboxymethyl chitosan surface modified nanostructured lipid carrier for ophthalmic delivery of curcumin, Carbohydrate polymers,146: 435-444.
62. Ling Tan, J. S., Roberts, C. J., & Billa, N.2019. Mucoadhesive chitosan-coated nanostructured lipid carriers for oral delivery of amphotericin Breau Pharmaceutical development and technology,24(4): 504-12.
63. Khan S, Shaharyar M, Fazil M, Hassan MQ, Baboota S, Ali J.2016. Tacrolimus-loaded nanostructured lipid carriers for oral delivery-in vivo bioavailability enhancement. European Journal of Pharmaceutics and Biopharmaceutics.109:149-57.

64. Zhuang, C. Y., Li, N., Wang, M., Zhang, X. N., Pan, W. S., Peng, J. J., Pan, Y. S., & Tang, X. 2010. Preparation and characterization of vinpocetine loaded nanostructured lipid carriers (NLC) for improved oral bioavailability. International journal of pharmaceutics,394(1-2): 179-85.
65. Rizwanullah, M., Amin, S., & Ahmad, J.2017. Improved pharmacokinetics and antihyperlipidemic efficacy of rosuvastatin-loaded nanostructured lipid carriers. Journal of drug targeting,2;25(1): 58-74.
66. Li, D., Liu, G., Tan, Z. Zhao, X. Yang, W. Pan.2016. A comparative study on the efficiency of chitosan-N-acetylcysteine, chitosan oligosaccharides or carboxymethyl chitosan surface modified nanostructured lipid carrier for ophthalmic delivery of curcumin, Carbohydrate polymers,146 :435-444.
67. Gonzalez-Mira, E., Egea, M. A., Souto, E. B., Calpena, A. C., & García, M. L.2010. Optimizing flurbiprofen-loaded NLC by central composite factorial design for ocular delivery. Nanotechnology,22(4): 045101.
68. Selvaraj K, Gowthamarajan K, Karri VV.2018, Nose to brain transport pathways an overview: Potential of nanostructured lipid carriers in nose to brain targeting. Artificial cells, nanomedicine, and biotechnology,46(8): 2088-95.
69. Nance, E., Pun, S. H., Saigal, R., & Sellers, D. L.2022. Drug delivery to the central nervous system. Nature Reviews Materials,7(4): 314-31.
70. Alam, T., Pandit, J., Vohora, D., Aqil, M., Ali, A., & Sultana, Y.2015. Optimization of nanostructured lipid carriers of lamotrigine for brain delivery: *in vitro* characterization and *in vivo* efficacy in epilepsy, Expert Opinion on Drug Delivery,12: 181-194.
71. Prabhu, P., Suryavanshi, S., Pathak, S., Patra, A., Sharma, S., & Patravale. V.2016. Nanostructured lipid carriers of artemether-lumefantrine combination for intravenous therapy of cerebral malaria, International Journal of Pharmaceutics,513: 504-517.
72. Labiris, N. R., & Dolovich, M. B.2003. Pulmonary drug delivery. Part I: physiological factors affecting therapeutic effectiveness of aerosolized medications, British Journal of Clinical Pharmacology,56: 588-599.
73. Vieira, A. C. C., Magalhaes, J., Rocha, S., Cardoso, M. S., Santos, S., Borges, G. M., Pinheiro, G. M., & Reis. S. 2017. Targeted macrophages delivery of rifampicin-loaded lipid nanoparticles to improve tuberculosis treatment, Nanomedicine,12: 2721-2736.
74. Puglia, C., & Bonina, F. 2013. Lipid nanoparticles as novel delivery systems for cosmetics and dermal pharmaceuticals, Expert Opinion on Drug Delivery,9: 429-441
75. Han, X., Xu, K., Taratula, O., & Farsad, K.2019. Applications of nanoparticles in biomedical imaging. Nanoscale,11(3): 799-819.
76. Paolino, D., Mancuso, A., Cristiano, M. C., Froiio, F., Lammari, N., & Celia, C.2021. Nanonutraceuticals: The new frontier of supplementary food. Nanomaterials (Basel),11(3): 792.