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NANOSTRUCTURED LIPID CARRIERS: A NOVEL TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT: Over the previous decade, several drug delivery systems have come into view, and an alluring part of this is the advancement of nanoparticle systems. Lipid drug delivery systems has considered as one of the emerging technologies and obtained attention due to features like biocompatibility, lipophilic characteristics. Among nanoparticle Nanostructured lipid carriers (NLC) have numerous advantages than emulsions, liposomes, microparticles, and solid lipid nanoparticles (SLN). NLC is a second-generation nanoparticulate system and has solid nature at ambient temperature. It comprises mainly of solid lipid, liquid lipid, surfactants, and water. It is approved by regulatory authorities to use as drug delivery systems. Due to ease in formulation, the practicability of large scale production, biocompatibility of components used, non-toxicity, and improved targeting efficiency, NLC has a number of applications in the cosmetic industry and pharmaceutical industry. This review highlights its types, the various formulation techniques, and evaluation techniques. The review also provides an application of NLC as a targeted delivery system.

INTRODUCTION: Targeted delivery systems are rapidly growing drug delivery systems with intense research in progress in both the academic sector and industrial sector. The nanoparticulate system, with its small diameter and unique characteristics, has showed great assurance as delivery systems. Colloidal drug carriers *viz*. liposomes, micro-emulsions, polymeric nanoparticles, and micelles can solve solubility related problems of a lipophilic drug.

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But these dosage forms are linked with many disadvantages such as stability problem, aggregation, drug leakage, expensive large-scale production and cytotoxicity caused by organic solvent, *etc*. [1] Lipid drug delivery systems have considered as one of emerging technologies and gained a lot of attention over recent years due to features like biocompatibility, lipophilic characteristics. The low-cost formulation method, productivity on a large scale, and permeability to penetrate the blood-brain barrier make lipid delivery systems more fascinating.

Lipid containing systems like lipid drug conjugate (LDC), nanostructured lipid carriers (NLC), and solid lipid nanoparticles (SLN) can be effectively utilized to solve customary delivery systems issues such as low bioavailability and low drug loading [2].

LDC system contains drug linked to lipid particles enhances drug loading up to 33%. However, LDC suffered from few demerits such as aggregation, uncertain gelation tendency, sudden polymeric transitions, and low drug loading [3, 4]. In order to address LDC disadvantages, the SLN system was developed in the year 1991, an effective alternate [5]. SLN can be characterized as small lipid-containing preparations which possess large surface area and have been considered as biocompatible and biodegradable systems [6, 7].

Even more, the SLN strategy has been designed and practiced efficiently for oral use of cyclosporine and paclitaxel drugs [5]. NLCs are a new generation or second generation of SLN which were designed to solve issues concern with SLN. For the formulation of NLC, a small portion of solid lipid is substituted by liquid lipid. It results in a highly disordered lipid structure, which provides more space for drug loading and prevents drug leaching during storage [8, 9]. NLC is a solid structure of lipids at ambient temperature.

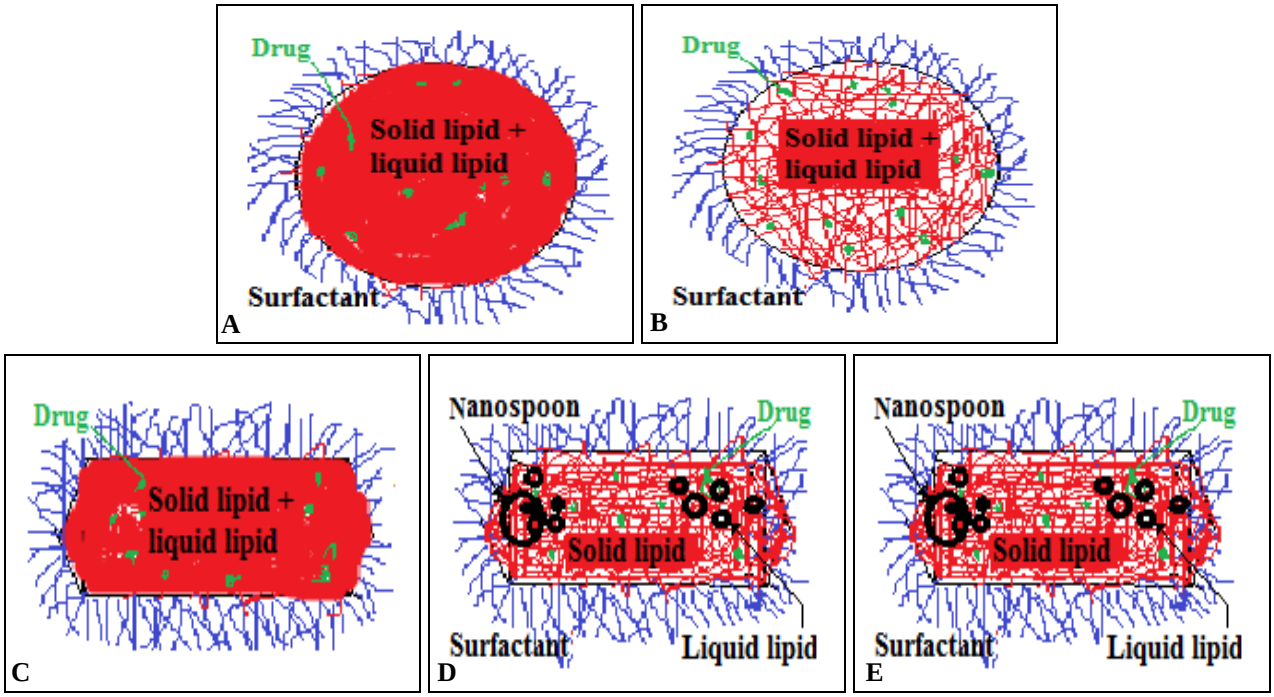

FIG. 1: STRUCTURE OF NLCs. A. Liquid lipid uniformly distributed in spherical solid lipid matrix of α-polymorph B. Liquid lipid nanocompartment within a spherical solid lipid matrix of α-polymorph**.** C. Liquid lipid uniformly distributed in platelet solid lipid matrix of β* or β-polymorph. D. Liquid platelet with multiple liquid lipid droplets on the surface of β* or β-polymorph. E. Liquid platelet with hybrid structure like nanospoon with sticking liquid lipid droplets on the surface of β* or β-polymorph

Pros of Nanostructured Lipid Carrier:

- More physical stability.
- More space to accommodate drug.
- Appropriate for loading of lipophilic drug and hydrophilic drugs.
- Easy for large scale production.
- Provide controlled release of encapsulated drugs.
- Avoidance of first pass metabolism [10].
- Reduction in chances of burst release of drug.
- Better control over release of drug [11].
- By passing p-glycoprotein efflux pumps.
- Protecting drug from intra-enterocyte metabolism [12].

Cons of Nanostructured Lipid Carrier:

- May cause discomfort by some surfactant.
- May cause cell damage.
- Deficiency of adequate preclinical and clinical study [13].
- Polymorphic transition of some lipid.
- Particle size growth during storage time [12].

Structure of the NLC: For triglycerides, the polymorphic forms are α, β', and β, as shown in **Fig. 1**. Mostly blend of molten solid lipid, and liquid lipids crystallize with α, β' form, and finally with most stable β polymorph. Based on the study like 1H-NMR and DSC, the first two structures of NLC were proposed.

Structure A, B assumes that due to an increase in the portion of liquid lipid (oil) to a solid lipid can cause a disturbance in the structure of crystal to a greater extent. Thus, the increment of oil can lead to disorderliness in the structure of solid lipids, which dependent on the quantity of oil added to solid lipids. If the oil proportion is low, both the lipids are accommodated uniformly in solid matrices of low crystallization degree, as showed in **Fig. 1A**. If the oil proportion is high, liquid nano-compartments are formed, as showed in **Fig. 1B**.

By application of methods such as field-flow fractionation and cryo-TEM method, other three models were proposed. With low oil proportion, oil molecules get arranged in the disordered structure of the crystal lattices developed by the β' or β polymorphic forms, as showed in **Fig. 1C**. As the liquid lipid proportion increases to 10% of the solid lipid, oil gets positioned on the solid lipid surface **Fig. 1D**. But as the oil proportion rises to 30% of the solid lipid phase nanospoon gets positioned on the surface, near corner of the solid particle [14, 15].

Composition of NLC: The important constituents of NLC are lipids (solid and liquid lipid), surfactants, and water. The solid lipid and oil are blended in the proportion of 70:30 to 99.9:0.1. The stabilizer (surfactants) used in concentration of 0.5% to 5%. [16]

1. Solid Lipid Table 1:

TABLE 1: LIST OF SOLID LIPID

S. no.	Solid lipid	Examples
1	Fats (hard)	Stearic acid, palmitic acid, behenic acid, theobroma oil
2	Triglycerides	Hydrogenated palm oil, trilaurin, trimyristin Tristearin, tripalmitin, tribehenate
3	Waxes	Elfacos C 26, beeswax, cetyl palmitate, carnauba wax 2442, apifil
4	Partial glycerides	Glyceryl Monostearate
5	Monoglyceride	Glyceryl monobehenate, glyceryl palmitostearate
6	Mixture	Mixture of glyceryl mono, di and tribehenate Medium-chain triglycerides caprylic/capric

Solid Lipid Selection: The Selection of solid lipid was depended upon dissolution of the drug in solid lipid for preparation of NLC. This is done by mixing increasing quantities of the drug in molten solid lipid. Determine the highest quantity of the drug that could be dissolved in solid lipid. Mostly used solid lipids are Compritol 888, Precirol ATO, stearic acid, glyceryl monostearate [17].

2. Liquid lipid Table 2:

TABLE 2: LIST OF LIQUID LIPID

S. no.	Liquid lipid
1	CremerCOOR MCT 60/40 EP (caprylic/capric/triglyceride)
2	CremerCOOR MCT 70/30 EP (caprylic/capric/triglyceride)
3	Miglyol 810 N (caprylic/capric/triglyceride)
4	Miglyol 808 (tricaprylin)
5	Miglyol 8108 (caprylic/capric triglyceride)
6	Miglyol 812 N (caprylic/capric/triglyceride)
7	Oleic acid (9Z-Octadecenoic acid)
8	Soya bean oil
9	Palm oil
10	Coconut oil
11	Olive oil
12	Castor oil

Liquid Lipid Selection: Liquid lipid should be selected according to the highest solubility of the drug. The trial batches should be prepared to fix the proportion of liquid lipids and solid lipids. The most used liquid lipids were oleic acid and propylene glycol dicaprylate/caprate.

3. Surfactants Table 3:

TABLE 3: LIST OF SURFACTANT

S. no.	Surfactant
1	Poloxamer-188
2	Polysorbate 20
3	Polysorbate 80
4	Egg lecithin
5	Cremophor EL
6	Soy lecithin
7	Solutol HS
8	Tego Care 450
9	Span 65

Surfactant Selection: Surfactant is used to stabilize the NLCs. They depend upon surfactant HLB and molecular weight. The surfactant affinity for the various lipids also differs. Based upon these factor, suitable surfactants should be selected [17, 18, 19]. Mostly used surfactants are poloxamer-188, tween 80, egg lecithin, and soya lecithin.

Methods for Fabrication of NLC:

1. High-Pressure Homogenization (HPH):

a. Hot Homogenization: In this method, solid lipid and liquid lipids are melted and blended (over the melting point of solid lipid) along with medicament

and emulsified with stabilizer (surfactant) solution. The temperature of the lipid phase and aqueous phase should have the same temperature at the time of mixing. Blending should be carried out with high shear, which results in a pre-emulsion stage. This emulsion is then handled in an HPH. During cooling to ambient temperature, the emulsion formed and recrystallizes to form NLC [20, 21].

Advantages: It is a simple and economical method.

Disadvantages: Temperature may be raised during homogenization [22].

b. Cold Homogenization: In cold HPH, the medicament is dispersed or dissolved in melted solid lipid and liquid lipid. Solidify the drug-loaded lipids by using dry ice and then milled quickly. The particles are distributed in a relatively cool surfactant solution prior to applying it to HPH at or below ambient temperature.

Advantages:

1. Feasibility of large-scale production.
2. No organic solvent in the formulation.
3. Useful for heat-sensitive drugs.

Disadvantages: Presence of microparticles along with NLCs [23].

2. Microemulsion: In microemulsion, the medicament is dispersed or dissolved in molten solid lipid and liquid lipid. Then this is emulsified with a hot surfactant solution. The microemulsion formed is put quickly in cold water, which results in a nanoemulsion. Recrystallized the solution to forms NLC.

Advantages: Feasibility of production on large-scale.

Disadvantages: It uses a high percentage of surfactants.

3. Solvent Diffusion Method: Both the lipids are dissolved in an organic solvent such as tetrahydrofuran and benzyl alcohol. This solution is dispersed in water with constant stirring, which results in solidification of the lipid.

Advantages: Use of solvents, which are water-immiscible [24].

Disadvantages: Lyophilization is required for stability.

4. Solvent Emulsification Evaporation Method: It utilizes solvent such as chloroform to dissolve the lipids. The lipid solution is then added in aqueous stabilizer phase with constant mixing on a magnetic stirrer. Then the organic phase is evaporated, which results in precipitation of lipid.

Advantage: Suitable for incorporation of heat sensitive drugs.

Disadvantages:

1. Use of water-immiscible solvents.
2. Evaporation of the organic phase required.

5. Emulsification Sonication Method: The pre-emulsion produced by the HPH method is sonicated using probe sonicator for ultrasonication.

Advantages: Excellent shear mixing.

Disadvantages: Metal contamination may occur by probe [25, 26, 27].

6. Phase Inversion Technique: The lipids, drug, water, and stabilizers are blended with constant stirring and made to heat and cool (85–60–85 °C) after this the shock is persuaded by diluting the mixture with cool water (0 °C) which results in the formulation of NLC after inversion of phase [25].

Advantages:

1. Mostly used for heat sensitive medicaments.
2. No utilization of the organic phase.

Disadvantage: Tiresome procedure.

7. Solvent Displacement Method: Solid and liquid lipids are mixed in an organic solvent and quickly injected to stabilizer or surfactant solution through a needle.

Advantages: Fast process.

Disadvantages: Use of water-immiscible solvents.

8. Membrane Contractor Technique: Solid and liquid lipids molten mass is run through a porous membrane with pressure, which results in minute lipid drops. At the same time, water is circulated

inside the porous membrane module, which passes away lipid droplets from the pore. NLCs are formed by cooling at ambient temperature.

Advantages: Easy method [2].

Process Parameter:

1. Melting: Solid lipid should be melted at 5-10 ºC over solid lipid's melting point to ensure the complete dissolution of the drug in lipid.

2. Mixing by Stirring: Blending should be carried out at 5-10 ºC over the melting point of the solid lipid and stir at 8000 revolutions per min for 20-30 seconds to confirm the blending of drugs with lipids.

3. Cooling: Cooling should be carried out at ambient temperature to convert it into solid-state.

4. Temperature: Both lipids and the surfactant solution were heated to 5-10 ºC above the solid lipid's melting point. The surfactant solution should have equal temperature as that of the oily phase. Temperature also influences the zeta potential. NLC should be stored between 5 °C to 25 °C temperature. The particle size of NLC varies according to temperature, at which NLC stored.

5. Homogenization Temperature: Mixing should be carried out at high temperatures *i.e.,* 80-90 ºC.

6. Sonication Time: The sonication time should be selected based on the trial batches and their particle size. Longer sonication time should be avoided because of metal contamination may cause. It should be between 5-15 min [17].

Evaluation and Characterization of QF loaded NLCs:

Polydispersity Index and Particle Size: Particle size was calculated using a photon correlation spectrometer. Particle size is very important as it influences solubility, stability, drug release rate, and efficacy of the NLC. For targeted drug delivery, particles with 50-300 nm particle size are preferred. The polydispersity index was determined to get a clear estimation of the distribution of particle size.

Zeta-Potential (ZP): Zeta potential gives information about an electric charge on the surface of the particle, which indicates the stability of NLC nanoparticle. For better stability of a minimum of ±30 mV, zeta potential is desired.

Entrapment Efficiency and Drug Loading: Entrapment efficiency (EE) is referred to like the % of medicament present in the NLC corresponding to the medicament added. Drug loading (DL) is defined as the % of medicament present in the NLCs corresponding to the total lipid added.

Morphological Study (Scanning Electron Microscopy, SEM): SEM study give information on three-dimensional morphology of the particle and the surface characteristics of a particle. For SEM, the freeze-dried product is used.

Differential Scanning Calorimetry (DSC): DSC study gives information about the dissolution of the drug in lipids.

X-ray Diffraction (XRD): The crystal nature of NLCs studied by X-ray diffraction.

***In-vitro* Drug Release:** The amount of medicament release from NLC depends upon the type of solid lipid used, a quantity of liquid lipid, the quantity of surfactant, and production temperature in the formulation of NLC [2].

Factors affecting the Release of Drug from NLCs:

1. Temperature,
2. Temperature and pH of the medium,
3. Quantity of drug and location of the drug in the NLCs,
4. Shape and size of the NLCs,
5. Crystal lattice formulated by drug and lipids in NLCs,
6. Surfactants used and their arrangement over the internal phase in NLCs.
7. Production method of the NLCs.

Stability of NLC: Two methods used to assure stability of the NLCs:

1. Freeze drying process,
2. Addition of preservatives.

A lyophilized product should maintain free-flowing ability, easy to redisperse ability in the water, and should not produce an aggregation of particle. But, the aggregation has observed in lyophilized powder without cryoprotectants. Different cryoprotectants

utilized for NLC production are lactose, sucrose, sorbitol, microcelac, trehalose, avicel, mannitol and dextrose [28].

Physical stability can be maintained by preservatives. Various preservatives are propylene glycol, rokonsaPB5, euxylPE1090, phenoni, euxylK700, ethanol, pentylene glycol.

The preservative should be hydrophilic, non-ionic. It should not interact with the surface of the particle and should not influence the zeta potential of the particle to form stable NLCs [2, 29].

Applications:

Topical Application: Topical application is mostly favored for skin problems because of less systemic side effects. It also prevents pre systemic metabolism and preserves medicament concentration at the targeted site. NLC showed faster onset, excellent sustained release, no irritation, and excellent security for different skin diseases.

Oral Delivery: The oral administration of NLCs have introduced with an aim to improve the bioavailability of drugs through oral administration by increasing the uptake by lymphatic system through microfold cell in the membrane of intestine and avoids the pre systemic metabolism [30, 31].

Pulmonary Delivery: Pulmonary delivery is for local as well as systemic effects. The advantages of pulmonary routes are rapid absorption because of large area (ca. 100 m^2), slow drug metabolism, prevents the pre systemic metabolism. Thus this way is ideal for several diseases, such as cancer, diabetes, acute pain, and autoimmune diseases [32, 33].

Ocular Delivery: The mucoadhesive property of NLC enhances action with the cornea and causes prolonged retention time, improves permeability to the backside of eye, more bioavailability, and less side effects. NLCs have investigated for disorders, namely eye inflammation, infections, glaucoma, and for diseases of posterior of eye [34].

Brain Delivery: It is a great challenge for the medicament to cross blood-brain barrier [35, 36]. However, NLCs showed excellent results in medicament delivery to the brain due to higher retention of NLCs than that of pure drugs. This improved holding of medicament and enhanced adsorption causes a higher quantity, which causes enhanced uptake of NLCs in the brain.

Other mechanisms are tight junctions opening of endothelial cells of the brain and fluidization of endothelial cell membrane lipids because of the surfactant of NLCs [37].

Intranasal Delivery: Intranasal drug delivery route showed a safe, reliable, and noninvasive method for CNS medicament delivery [2].

TABLE 4: NLC APPLICATION

Drug	Particle size in nm	Excipients (Solid lipid, liquid lipid and surfactant)	Conclusions
Topical delivery			
Aceclofenac	360.36 ± 1.20	Stearic acid, oleic acid, tween 80	Prolonged action and avoided the first-pass metabolism of aceclofenac [38]
Mometasone furoate	163.2±0.522	Stearic acid, oleic acid, tween 80 and transcutol P (2:1)	Reduced the risks of both local and systemic side effects associated with topical corticosteroids [39]
Dithranol	<300	Trimyristin, labrafac, tween 20	Removed irritation, stain and burning sensation on normal and diseased skin [40]
5-Fluorouracil	<200	Glyceryl palmitostearate, labrasol poloxamer 188 and Solutol HS15	Improved the penetration of drug through skin layer, with utmost skin retention [41]
Betamethasone dipropionate	<200	Glyceryl monostearate, oleic acid, tween 80, cremophor RH 40	Penetrated to different skin layers and improved absorption [42]
Methotrexate	239.12±3.65	Stearic acid, oleic acid, tween 80	Exhibited sustained release of drug [43]
Oral delivery			
Exemestane	<500	Precirol ATO 5, flax seed oil, poloxamer 188, tween 80, tween 20	Improved oral bioavailability and enhanced intestinal permeability of drug [44]
Amisulpride	184.9	Triplalmitin, capryo 90, tween 80,	Enhanced oral absorption of drug [45]

		sodium deoxycholate	
Ticagrelor	87.6 ±6.6	Glycerol monostearate, capmul, poloxamer 188, tween 80	Enhanced antiplatelet activity and oral bioavailability [46]
Epigallocatechin-3-gallate	<500	Precirol ATO 5, miglyol 812, tween 60	Exhibited increased oral bioavailability [47]
Amphotericin B	<200	Beeswax, coconut oil, lecithin and tween 80	Exhibited improved oral bioavailability of [48]
Pulmonary delivery			
Montelukast sodium	181.4±6.5	Precirol ATO 5, Capryol-90, DL-Pyrrolidonecarboxylic acid salt of L-cocyl arginine ethyl ester)	Exhibited improved the efficacy with reduced toxicity of drug [49]
Itraconazole	114	Precirol ATO 5, oleic acid, eumulgin SLM 20	Improved bioavailability by pulmonary application [50]
Itraconazole	106 ± 5	Precirol ATO 5, superrefined oleic acid NF, polysorbate 20,	Obtained a high drug quantity at site of infection [51]
Mefenamic acid	<200	Cetyl palmitate, caprylic acid, tween 80, polyethylene glycol	Found biphasic pattern of drug release rapid initially sustained finally, improved stability of medicament [52]
Buparvaquone	<350	Softisan 154, miglyol 182, kolliphor P188, tween 80	Achieved high therapeutic efficacy and safety of drug [53]
Dacarbazine	155 ± 10	Precirol ATO 5, isopropyl myristate, tocopheryl polyethylene glycol succinate, lecithin, Poloxamer 188	Improved the drug solubility and prolonged drug release [54]
Ocular delivery			
Flurbiprofen	228.3	Miglyol 812, castor oil, tween 80	Reduced toxicity on ocular tissue, provided sustained release action [55]
Myriocin	86.25 ± 1.53	Gelucire 44/14, mygliol 812 tween 80	Increased solubility of medicament and delivered medicament to the posterior part of the eye [56]
Amphotericin B	218 ± 5	Precirol, castor oil, cremophor EL	Increased efficacy and stability of drug [57]
Indomethacin	~40	Cetyl palmitate, squalene, Emulmetik 900, Lexol GT865, Tween 80	Improved the mucoadhesive property of drug on the ocular surface [58]
Brain delivery			
Artemisinin	145 ± 12.5 nm	Compritol, oleic acid, tween 80	Increased water solubility, site-specificity, selective targeting, efficient penetration, glioma cell distribution and internalization and decreased the possibility of neurotoxicity [59]
Itraconazole	313.7±15.3 nm	Precirol ATO 5, transcutol HP, tween 80, solutol HS15	Increased drug concentration in the brain by almost two-fold [60]
Curcumin	214	Tripalmitin, oleic acid, tween 80	Improved targeting effect of medicament at brain [61]
Baicalein	~100	Tripalmitin, Gelucire48/9, vitamin E, phospholipids, poloxamer188	Improved stability and the ability of drug to penetrate the brain [62]
Intranasal delivery			
Curcumin	146.8	Precirol ATO5, capmul MCM, tween 80, soya lecithin	Enhanced anti-cancer activities through nasal administration [63]
Temozolomide	41.28	Gelucire 44/14, vit E, tween 80, transcutol	Enhanced brain targeting via nasal route [64]
Quercetin	118.2	Glyceryl monostearate, capmul GMO, polaxomer 188, soya lecithin	Exhibited sustain release behavior, improved bioavailability at target site [65]
Teriflunomide	99.82 ± 1.36	Compritol 888 ATO, maisine 35-1, gelucire 44/14, tween 20	Enhanced nose to brain delivery of drug [66]
Lurasidone Hydrochloride	205.4±2.0	Gelot 64, capryol 90, tween 80, transcutol	Enhanced bioavailability [67]

CONCLUSION: Nanoparticles have been widely used over the last decade in the biomedical field. Among these nanoparticles, NLC showed great assurance in the effective delivery of drugs by different routes, namely topical, pulmonary, intranasal, ocular, and oral. Due to nanoscale

particle size and capacity to cross BBB, NLCs becomes an ideal dosage form for brain delivery. The additives used for NLC production are biodegradable, biocompatible, and with approved GRAS status. Feasibility to scale up, modulation to get the desired particle size, improved drug loading, and higher stability made NLCs as the centre of attraction for the researcher. But many cosmetic dermal NLC products have not gained approval from the regulatory authorities. Now-a-days NLCs were broadly studied for their potential as targeted delivery systems. But, their toxic effect due to accumulation at non-target organs must be studied. Therefore, the potential of NLC needs to be investigated broadly at the preclinical as well as clinical level.

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