Ind. J. Pharm. Edu. Res., 2025; 59(3s):s788-s801.
https://www.ijper.org

Review Article

Nanostructured Lipid Carrier to Improve Oral Bioavailability

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ABSTRACT

Oral administration is the best way to administer both traditional and novel drugs because it decreases patient non-compliance and can also relieve the pain and discomfort associated with parenteral preparations. However, despite many benefits of oral formulations, a number of disadvantages significantly impair bioavailability. By helping with site-specific targeting, nanoparticles can stop drugs from breaking down across different physiological barriers. Lipidic systems are regarded as the most evident among all the emerging nano drug carriers. Lipid carriers that are nanostructured are thus created. As these consist of liquid and solid lipid mixes, which make up the safe lipidic colloidal systems. Surfactants are used in system for stabilization. This lipidic formulation offers improved penetration, longer half-life, decreased clearance and greater drug solubility and improves oral bioavailability of various classes of drugs. A type of lipid-based carrier called Nanostructured lipid carrier replaces a certain amount of solid lipid with liquid lipid to get over some of the main drawbacks associated with Solid Lipid Nanoparticles. Research using Nanostructured lipid carriers show that they may be the most advantageous carrier for improving the oral bioavailability of both hydrophilic and lipophilic medications. The article provides a brief overview of the different types, components and fabrication methods of that are employed in formulations, with a primary focus on typical barriers that affect the bioavailability of drugs delivered orally. The article provides advantages with respect to oral bioavailability enhancement are highlighted in this review.

Keywords: Nanostructured Lipid Carrier, Solid Lipid Nanoparticle, Bioavailability, Nanocarriers, Nanoparticles.

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Received: 27-12-2024;
Revised: 06-02-2025;
Accepted: 12-05-2025.

INTRODUCTION

Oral administration accounts for around 60% of medication administration in commercially accessible medicines. Approximately 70% of chemicals that are being studied are poorly soluble and 40% of medications that are currently in the market are also poorly soluble.

Certain medications exhibit weak solubility, falling into the second class in the BCS classification, whereas others have substantial first pass metabolism effect.

Therefore, it's critical to improve the drug's solubility and rate of dissolution, as these factors eventually affect the drug's oral bioavailability.[1]

Significant efforts have been undertaken in the last 10 years to create dosage forms based on nanotechnology in order to increase the bioavailability of bioactive molecules. Because of its unique benefits, including their highly stable structure, biodegradability, biocompatibility, effective drug loading and sustained release qualities, lipid nanoparticles have drawn more attention than other types of nanoparticles.[2] Because of the unique components of lipid nanoparticles; it is widely known to improve drug absorption when taken orally. Lipid nanoparticles can be broadly classified into three types.

- Solid Lipid Nanoparticles (SLN),
- Nanostructured Lipid Carrier (NLC),
- Lipid Drug Conjugates (LDC).

A nano-particulate carrier system called Nanostructured Lipid Carriers (NLCs) is based on oil-in-water nano-emulsions. Emulsifying agents, fat and water are its main constituents.

At room temperature, the lipid phase is composed of both liquid (oil) and solid (fat) lipids. Because the drug dissolves in oil and simultaneously encapsulates in solid lipid, the goal of NLC-based formulation is to produce particles with a solid lipid core and integrated oil for increased loading capacity and regulated drug release. NLCs offer a number of advantages, including decreased

DOI: 10.5530/ijper.20255950

polymorphic transition, a low crystalline index, enhanced drug loading, encapsulation efficiency, physical stability, enhanced chemical stability, bioavailability and the controlled release of encapsulated components.[3]

Advantages of NCL's

Improve physical stability.

Targeted medication release and regulated particle size.

The potential of transporting hydrophilic and lipophilic drugs with high lipophilic drug entrapment efficiency.

Easier to validate.

Better drug loading in contrast to SLNs.

Since this technique is based on water, organic solvents can be left out.

Delivers excellent and more medicine content than other carriers.

The majorities of lipids degrades and are biocompatible.

Economic than other polymeric or surfactant-based delivery system.

Easy for large scale production.[4]

Disadvantages of NLC's

Because of the concentration and matrix characteristics, cytotoxic effects are seen.

Some surfactants exhibit irritative and sensitizing actions.

Clinical and preclinical studies lacked in the preparation of NLCs.[5]

Types of NLC's

NLCs are classified into 3 types:

- The Imperfect Type.
- The Amorphous Type.
- The Multiple Types.

The Imperfect Type

By chemically combining liquid and solid lipids, an imperfect type of NLCs is formed that increases drug loading. The imperfect type of NLCs contains small amounts of liquid phase lipid or oil. The production's crystallization procedure will cause drugs to be expelled from the defective NLCs.[6]

The Amorphous Type

The Amorphous type of NLCs is produced by carefully combining specific kinds of liquid and solid lipids. This particular kind of NLCs produces solid lipid with no crystalline structure.[7]

The Multiple Types

The multiple types of NLC's have oil micro-compartments encapsulated in solid lipid. The drug is loaded in the oil chambers. Combining high concentrations of liquid lipids within the lipid matrix get an advantage in preventing the drug expulsion commonly observed in imperfect types of NLCs. When the cooling effect occurs, oil approaches its solubility limit and precipitates into micro compartments.[8] The type NLCs described in Figure 1.

Ideal properties that possess NLC's

It should possess higher drug loading and entrapment potential.

It should possess modulation of drug release pattern.

It should maintain long-term stability of incorporated drug during storage.

It should have minimum level of surfactant with maximum drug loading potential.

The capacity to convey both lipophilic and hydrophilic medications, as well as the high trapping of lipophilic medications.[9]

Components of NLC's

The components for the development of NLCs are solid lipid, liquid lipid, surfactant and water. Chemicals that are used in NLCs to transport drug molecules must be safe, non-toxic and suitable for systemic administration.[10] commonly used components of NLCs describe in Tables 1 and 2.

METHODS OF PREPARATION OF NLC'S

In order to produce NLCs, a lipophilic phase in a mixture of Liquid and Solid Lipids (LL and SL) is usually nano-emulsified using an aqueous solution that contains water-soluble surfactants and emulsifiers.[27] Different types of technique used for NLC's preparation describe in Tables 3 and 4.

Based on the amount of energy needed, there are three different types of NLC production processes. Types of method of preparation of NLC's are described in Figure 2.

High pressure homogenization

One of the most used methods for large-scale manufacturing is High Pressure Homogenization (HPH). Lipids are forced through a small opening at a high pressure using the HPH technique, Shear stress and cavitation forces cause particles to fragment into small fragments. Both the hot and cold methods are available for HPH. These techniques dissolve the drug in the lipid (5-10%) and melt it at 5-10°C temperature above its melting point.[28,29]

Hot homogenization method

Using high shear equipment, a drug and melted lipid are combined with an identically-temperature aqueous surfactant solution in this method. The resultant emulsion is stirred using a piston gap homogenizer and the resulting nanoemulsion is then cooled to room temperature to produce nanoparticles.[29]

Demerits

Degradation of thermolabile actives due to heat.

The decrease in certain surfactants' emulsification power at higher temperatures.

Low drug encapsulation efficiency.[30]

Cold homogenization method

By using high shear equipment, the drug and melted lipid are combined with an aqueous surfactant solution at the same temperature in this procedure as well. For drug distribution in lipid, the lipid melt and drug are quickly cooled using ice or liquid nitrogen.With this strategy, some of the disadvantages of hot homogenization such as drugs and surfactants that are heated should be avoided.[31]

Demerits

Costly.

Lipid in its unmelted state must be verified by efficient temperature control and modulation.

Larger particle size distribution and size in comparison to hot homogenization.[32]

Table 1: Commonly Used Solid - Lipid, Liquid- Lipid for development of NLC's.

Components	Excipients with their melting point	Drugs used	Role of ingredient
Solid-Lipid.[11,12]	Steric acid (67-69°C).	Simvastatin Diacerein Carvacrol Testosterone Undecanoate.	For topical administration-controlled release and acidic protection for the medication.
	Glyceryl monostearate (54-64°C).	Tamoxifen, Silybin, raloxifene, Atorvastatin.	Enhancement of orally bioavailability.
	Glyceryl Tripalmitate (61-65°C).	Ranolazine	Enhanced entrapment efficiency and sustained released property.
	Precirol ATO 5 (50-60°C).	Lovastatin, Spironolactone, Saquinavir.	Improved bioavailability.
	Cetyl palmitate (51.9-55.9°C).	Coenzyme Q (10).	Can help in providing your skin with deep moisture.
	Compritol 888 ATO (65-77°C).	Glipizide, Vinpocetin.	Viscosity inducing agent.
	Dynasan 114 (55-58°C).	Domperidone, raloxifene.	Used as an adjuvant, seeding agent in solidification.
Liquid-Lipid.[12,13]	Oleic acid (13 to 14°C).	Glipizide, Testosterone, Undecanoate, Ranolazine, Repaglinide.	Utilized throughout the nanoparticle's solution phase production. It regulates the nanoparticles' size and shape.
	Squalene (-4.8°C)	Lovastatin	It keeps skin hydrated and protects its moisture barrier.
	Labrafac_CC (<-5, 0°C).	Clotrimazole	Used as emollient.
	Miglyol 812(6°C).	Spironolactone, Saquinavir, Vinpocetine.	Having excellent spreadability.
	Capmul MCM C8 (60-65°C).	Diacerien	Emollient Demulcent Analgesic, Improved solubility and oral bioavailability.
	Labrafil WL 2609 BS	Tamoxifen	
	corn oil (-11°C)	Beta carotene	lubricant

High Shear Homogenization/Sonication

Liquid and melted solid lipid were combined with drug. The temperature of the water phase and surfactant is also raised to the same level as that of lipid phase. Using a probe sonicator, the resulting emulsion was ultrasonically treated. Throughout the procedure, the manufacturing temperature was maintained at least 5-10ºC above the lipid melting point to avoid recrystallization. The emulsion should flow through a 0.45 μm membrane in order to eliminate contaminants.[33]

Table 2: Some Commonly Used Surfactant in NLC's Formulation.

Components	Examples	References
Surfactant	Poloxamer 188	14
	Tween 80	15,16
	Pluronic F-188	17
	Myverol 18-04 K	18,19
	Sodium Dodecyl Sulfate (SDS)	20
	Sodium Deoxy Cholate (SDC)	21
	Polyvinyl alcohol	22
	Lecithin	23,24
	Dynasan 118	25
	Solutol HS 15	26

Microemulsion Techniques

A surface-active compound is combined with melted lipid that contains a drug. The aqueous phase co-surfactant is prepared in a ratio that produces a small emulsion at the same temperature as the lipid. In addition, more water is used to dilute the hot microemulsion than cold. When the temperature drops unexpectedly, the microemulsion breaks and becomes a nanoemulsion, which then produces lipid molecules when the lipid component recrystallizes.[34]

Double emulsion

In this process, the generated microemulsion is added to cold water (between 2-10°C), which helps the equally distributed NLCs particles precipitate.[35]

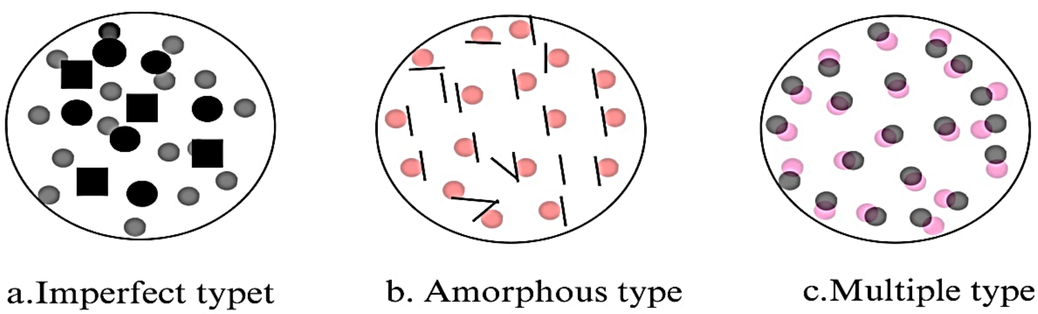

Figure 1: Types of NLC's a: Imperfect type, b: Amorphous type, c: multiple type.

Table 3: Different types of technique used for NLC's prepration.

Sl. No.	Technique used	Drug	References
1.	Hot homogenization	β sitosterol, Candesartan Cilexetil (CC), nisoldipine, 5-fluorouracil.	39-42
2.	High pressure homogenization method.	Vinpocetine, Axitinib, Nobiletin (NOB).	43,44
3.	High shear homogenization/ ultrasonication.	Combination of calcipotriol and methotrexate, Asenapine (ASM), Salicyclic acid, Atorvastatin, Carbamazepine, Felodipine, Rosuvastatin Ibuprofen, Diacerein.	45-52
4.	Solvent diffusion technique.	Tamoxifen citrate paclitaxel,	53,54
5.	Microemulsion technique.	Triptolide (TP), Carvacrol, donepezil.	55-57
6.	Modified ultrasonic solvent evaporation-emulsification technique.	Amisulpride	58
7	Emulsification-solvent evaporation technique	Simvastatin (SIM), Artemisinin, lercanidipine hydrochloride, silybin.	59,60
8.	Double emulsification	Zolmitriptan	61

Table 4: Some recently used nanostructured lipid carrier with loaded drug and excipients.

Sl. No.	Drug	Excipient	Evaluation	Outcomes	References
1	Silybin	Silybin, Glycerol monostearate (GMS, Medium chain triglycerides, Lecithin, Pluronic F68, Mannitol, sodium hydroxide, potassium dihydrogen phosphate, Nitrogen gas, methanol.	The final NLC had a mean size of 232.1 nm and a zeta potential of -20.7 mV.	In comparison to silybin solution, silybin-NLC exhibited greater AUC (area under tissue concentration-time curve) values and circulated in the bloodstream for a longer period of time. 1 of the potential silybin targeted and sustained release method is NLC.	66
2	Breviscapine	Egg yolk lecithin 80 (E80), Medium-chain fatty acid esters, Octadecylamine (ODA), Ethanol and methanol dichloromethane and acetonitrile.	A zeta potential of around 20 mV, a high entrapment effectiveness of about 89% and a mean particle size of about 170 nm.	Breviscapine is significantly protected by the NLC from being broken down by liver enzymes.	67
3	Methotrexate (MTX),	Methotrexate (MTX), Witepsol1 E85, Miglyol1 812, Polyvinyl Alcohol (PVA).	NLCs that were loaded with MTX had a 252-nm spherical shape, a polydispersity of 0.06-0.02, a zeta potential of -14 mV and 87% entrapment efficiency.	Improvement in bioavailability and absorption rate as well as an increase in entrapment efficiency.	68
4	Phenytoin Sodium	Acetone, methanol, potassium di hydrogen ortho phosphate, ortho phosphoric acid, Pluronic-F-188, phenolic acid, sodium phenytoin, cholesterol, oleic acid, diethyl ether, acetone and acetonitrile.	The average particle size 32.59 nm (PDI-0.289), 80.0 nm (PDI-0.256) and 124.56 nm (PDI-0.303) and the zeta potential ranged from -16.5 to -28.0 mV was found to be for three different formulation of NLC's.	Not only may NLCs hold more drugs in place during manufacture and storage, but they can also prevent drugs from being expelled by preventing lipid crystallization.	69
5	Repaglinide	Repaglinide, Cetyl alcohol, Oleic acid, Lecithin and Tween80.	NLC exhibits entrapment efficacy and a significant particle size of 157.8±15.8 nm. The formulation is in a stable state for an extended period of time, as the Zeta potential analysis further clarified.	The capacity of NLC dispersion to regulate release and make nano formulation appropriate for overcoming repaglinide's low bioavailability.	70
6	Dexamethasone	DXM, Apifil, Labrasol, Miglyol 812N, Kolliphor (or Cremophor), Polyoxyl 35 hydrogenated castor oil and Cremophor RH60 (PEG-60 hydrogenated castor oil).	The NLC system has particle sizes of less than 300 nm and PDIs of less than 0.2. NLC's ZP is -12 mv.	Because NLCs had better stability and entrapment efficiency, lower surfactant and lipid concentrations would be advantageous. NLCs have good ocular tolerability, according to toxicity testing conducted on human cornea cells.	71

Sl. No.	Drug	Excipient	Evaluation	Outcomes	References
7	Ranolazine	Glyceryl palmitostearate, oleic acid, precirol ATO, dextran sulphate, tween 80, steryl amine, Ranolazine.	The prepared NLCs had vesicle diameters in the range from 118.4 to 294.8 with PDI value of less than 0.5 i.e. 0.168. Zeta potential values that were extremely negative (-29.6 mV) were measured.	Enhancement of absorption rate and bioavailability and also increases the entrapment efficiency.	72
8	Luliconazole	Luliconazole, tween20, ethanol, capryol 90, oleic acid, acetone, Carbopol 934.	The prepared NLCs have optimum particle size with zeta potential ranging from -16.3 to -17.5.	The prepared NLCs gel has good penetration ability with hydrating effect.	73
9	Simvastatin	Simvastatin, Stearic acid, Oleic acid, Pluronic F-68, Lecithin.	Zeta potential with 35-40 mV that provides enough electrostatic physical stability, prolonged drug release pattern, particle size (< 200 nm) spherical morphologies with restricted size distribution and drug entrapment efficiency about (>75%).	Compare the bioavailability of SIM-NLC to the SIM suspension and you'll see a 4-fold increase after a single oral dose. To improve SIM oral bioavailability, NLCs may therefore offer effective nanodevices for the treatment of hyperlipidemia and prospective drug delivery systems.	59
10	Axitinib	Axitinib, Oleic Acid and Tween 80, ethanol.	The optimized formulation yielded good stability in the generated NLCs with 202.2 nm MPS, -21.5 mV zeta-potential, 0.44 PDI and 88% EE.	Improved bioavailability, dose reduction, frequency of administration, side effects related to dose and improved disease control are possible benefits of using Axitinib NLCs.	43
11	Artemisinin	Compritol, cholesterol, artemisinin, poloxamer 188, cephadex G-50, N ethylcarbodiimide hydrochloride, anhydride dimethyl sulfoxide, tween 80, 3- 2, 5-diphenyltetrazolium bromide (4,5-dimethylthiazol-2-yl), ethanol, potassium dihydrogen phosphate, sodium hydroxide, dichloromethane, transferrin, Fetal bovine serum, penicillin-streptomycin, phosphate-buffered saline and trypsin-EDTA.	NLC's with Mean particle size 145 nm, zeta potential 24.3 mV, polydisersity index 0.513, entrapment efficiency 82.3% and mean release time 24.0 hr was found.	Optimum for brain administration due to its excellent entrapment efficiency and regulated drug release profile.	59

Sl. No.	Drug	Excipient	Evaluation	Outcomes	References
12	Atorvastatin	Glyceryl monostearate, CompritolVR 888 ATO, CapryolPGMC (propylene glycol monocaprylate type I), Pluronic F68, Lecithin, Tween 80 and Gelucire43/01.	The NLCs with particle sizes ranging from 162.5 to 865.55 nm and their zeta potential are 34 to 23 mV.	NLCs to enhance AT's *in vivo* efficacy and oral bioavailability.	47
13	Nisoldipine	Nisoldipine, Trimyristin (dynasan-114; glyceryl trimyristate), Oleic acid, Egg lecithin E-80, Poloxamer-188, Methanol, acetonitrile and chloroform.	The optimized NLCs were measured for size, ZP and EE and the results were 110.4 nm, -29.4 mV and 97.07%, respectively.	To improve the oral bioavailability of ND, Nanostructured Lipid Carriers (NLCs) have been designed.	41
14	β sitosterol	Soxhlet apparatus was used to extract β sitosterol from Propolis sample, (mp 62-64ºC), with petroleum ether serving as the solvent, PSO, Lecithin (L-α-phosphatidylcholine) and Compritol 888 ATO US/NF.	Average particle sizes of NLC's ranging from 81 nm to 154 nm and zeta potential values ranging from -21.25 to -25.1 mV.	This process allows for the production of a large range of β sitosterol-containing nutritious foods that are very beneficial in reducing the risk of cardiovascular illnesses.	39
15	Donepezil	Donepezil hydrochloride, soy lecithin, oleic acid, stearic acid and sodium taurodeoxycholate hydrate, Commercial-grade Glycerol Monooleate (GMO) was utilized (Myverol, 18-99 K).	Average particle size, PDI, zeta potential, EE (%) and DL values of 233.90 (±4.16) 0.31 (±0.05)-40.60 (±1.95) 99.5 (±0.001) and 24.88 (±0.001), respectively, were used to characterize NLCs.	Enhancement of permeation rate, high entrapment efficacy. Enhanced treatment of Alzheimer's disease.	57
16	Diacerien	Diacerien, Capmul MCM, Carbopol 940, Pluronic F68, stearic acid, Tween 80.	The consistency of the NLC-based Diacerien gel was 3 months measured at 45ºC±2ºC/75% RH±5% RH.	Enhancement of absorption rate and bioavailability and also increases the entrapment efficiency.	52
17	Carvacrol	Beeswax (BW), acetic acid sodium heparin, Kolliphor188®, *p*-cresol (≥99.5%), carvacrol (≥99%), Stearic Acid (SA) and Acetonitrile (ACN).	NLCs formulation with the lowest particle size (98.42±0.80 nm), narrowest size distribution and greatest encapsulation efficiency.	Enhancement of absorption rate and bioavailability and also increases the entrapment efficiency.	56
18	Zolmitriptan (ZT)	Zolmitriptan (ZT), Low molecular weight Chitosan (CT), Guar gum, Pectin, Tween 80, Hard gelatin capsules, Acetic acid.	High percentage EE, PDI and ZP yield (78.14%, 343.87, -25.5 mV respectively) were observed with low particle size.	NLCs were incorporated into hard gelatin capsules that were gelling in situ to increase permeability and maintain the pharmacodynamic impact.	61

Sl. No.	Drug	Excipient	Evaluation	Outcomes	References
19	Cilexetil Candesartan	Hydroxymethyl cellulose, Cpryol90, Glyceryl monostearate, Cremophor RH 40, Sodium hydroxide (NaoH), potassium dihydrogen orthophosphate, potassium chloride, hydrochloric acid, methanol and acetonitrile.	High encapsulation efficiency (96.23%) with particle size 121.6 was observed.	Drug that is poorly soluble in water having increased oral bioavailability.	40
20	Paclitaxel	Cholesterol, oleic acid, tween80, ethanol, acetone Poloxamer 188, paclitaxel Avicel RC591, aerosol from mannitol, dextrose, sorbitol, PEG4000, HPLC grade acetonitrile and methanol, RPMI 1640 medium, sera and Human colorectal cancer cells (HT29), 3-(4, 5 Dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide.	Oleic acid concentration and surfactant % were shown to be the most influential influences on size. The number of drugs had a greater impact on zeta potential.	Enhancement of absorption rate and bioavailability and also increases the entrapment efficiency.	53
21	Bicalutamide	bicalutamide, Precirol ATO 5, Phosal 53MCT and Pluronic F-12, Captex 500P (triacetin), Sodium taurocholate.	Scanning Electron Microscopy (SEM) of the improved batch (NLC-2) indicated spherical morphology with a smooth surface. NLC-2 showed good stability for 6 months and a high drug encapsulation of 98.48±0.70%	Improve oral bioavailability of poorly soluble BCT.	54
22	5-FU	5-FU, Precirol ATO 5 (glyceryl palmitostearate), Labrasol, (caprylocaproyl polyoxylglycerides), Tween 80, Poloxamer 188, Solutol HS15.	The polydispersity index, zeta potential and average size of the 5-FU-NLC were found to be 0.352, -21.82 mV and 208.32 nm, respectively.	Significantly increase drug penetration through the stratum corneum, with significant retention and minimal skin irritation-a prerequisite for formulations to be used topically.	42
24	Vincristine sulfate (VCR)	VCR, Hyaluronic acid, Lecithin from eggs (purity>98%), tween-80, Sodium Dodecyl Sulfonate (SDS), Capric Triglyceride (CT), tris (hydroxymethyl) methyl aminomethane, Glycerin Monostearate (GMS), hexadecyl trimethyl ammonium bromide, Dichloromethane and acetone, 3-(4,5-dimethylthiaol-2-yl)-2,5-diphenyltetrazolium bromide.	The VCR-NLCs and HA-NLCs had particle sizes, zeta potentials and entrapment efficiencies of 187 nm, -8.61 mV, 33.12% and 192 nm, -32.82 mV, 34.41%, respectively.	HA-NLCs were a potential delivery system for VCR that might greatly increase oral bioavailability.	24

Sl. No.	Drug	Excipient	Evaluation	Outcomes	References
25	Nobiletin	Nobiletin, Labrafac lipophile WL 1349 and Geleol mono and biglycerides NF, lecithin, Poloxamer 188 (Pluronic F68), Methanol and acetonitrile, ultra-pure water.	NLC demonstrated a spherical form measuring 112.27±5.33 nm in diameter, -35.1±2.94 mV in zeta potential, 0.251±0.058 polydispersity index and 81.06%±6.02% EE.	Enhancement of absorption rate and bioavailability and also increases the entrapment efficiency.	44

Phase Inversion Method

The addition of formulation ingredients while magnetic stirring is occurring, dilution below cooling conditions and posterior heating and cooling cycles are all included. The next three steps involve heating and cooling the mixture three times, from room temperature to 85°C and back to 60°C, at a rate of 4°C per minute/min. It is this heating that causes the emulsion to reverse.[35]

Demerits

Very tedious method.

Membrane Contractor Technique

By using this method, small lipid droplets are formed by pushing molten lipid against a porous membrane. Particles are simultaneously released via the pore and distributed throughout the membrane module. NLCs form as the result of normal cooling.[36] Membrane contractor technique described in Figure 3.

Emulsification-Solvent Evaporation Technique

This approach involves dissolving the lipids and the active component in a solvent that is water-immiscible. The resultant solution is subsequently emulsified using an aqueous surfactant solution. NLCs are then created when the solvent evaporates while being constantly agitated. Since there is no heat involved, this approach works well with actives that are heat-sensitive. The principal limitations of this method are the diluted NLC particles resulting from the lipids' inadequate solubility in the solvents used and the toxicity of the solvent residue.[37]

Emulsification Solvent Diffusion Method

To ensure the initial thermodynamic stabilization of both phases, this approach creates an o/w emulsion from an organic phase partially saturated with water and partially water-miscible solvents (such as tetrahydrofuran and benzyl alcohol).

This method can produce particles with a mean diameter of 30-100 nm. The primary benefit of this approach is its rejection of heat throughout the preparation process.[38]

Characterization of NLCs

In order to determine the quality of the product created, it is crucial to characterize every nanocarrier system. The NLCs' small particle size and complicated lipid makeup make them difficult to describe.

Particle size, polydispersity index

The NLCs' average particle size is between 50 and 300 nm. The concentration and type of lipid, as well as the surfactant, are some of the formulation parameters that determine the NLCs' particle size and Poly Dispersity Index (PDI). The NLCs' size of particle can be measured using a variety of methods. Size of particle can be determined by dynamic light scattering. The method is non-invasive and relies on the Brownian motion of particles within a medium. Here, the scattered light intensity is measured. The size distribution of NLCs is called the PDI. Low PDI values (<0.3) indicate product homogeneity, while high values (0.5) imply considerable polydispersity, or heterogeneity.[62]

Zeta Potential

Surface charge is measured using zeta potential. The system's aggregation is determined by the potential difference across the particles.

The repulsion between particles, which results in the physical stability of the system, is caused by the net positive or negative charge. Physical stability is exhibited by NLCs with zeta potentials greater than +30 and less than -30.[63]

Morphological studies

Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM) can be used to analyze the morphology of the NLCs. TEM is typically used to examine NLC microscopy. Using this method, the carbon-coated copper grids are covered with a little drop of the NLC formulation diluted in water. Uranyl acetate or phosphotungstic acid are used to stain them. After letting the drop dry, it is examined. Liquid lipid that has adhered to the surface of NLCs is seen as black patches. Most of the particles that are seen have spherical or elliptical shapes.[62]

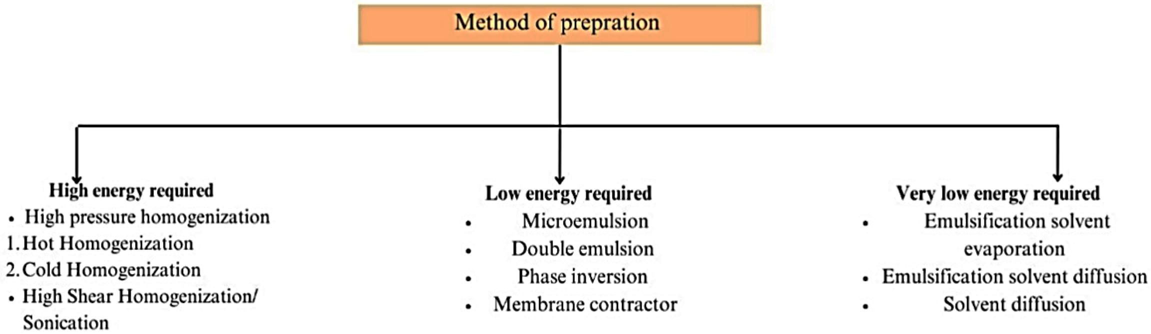

Figure 2: Types of methods of preparation of NLC's.

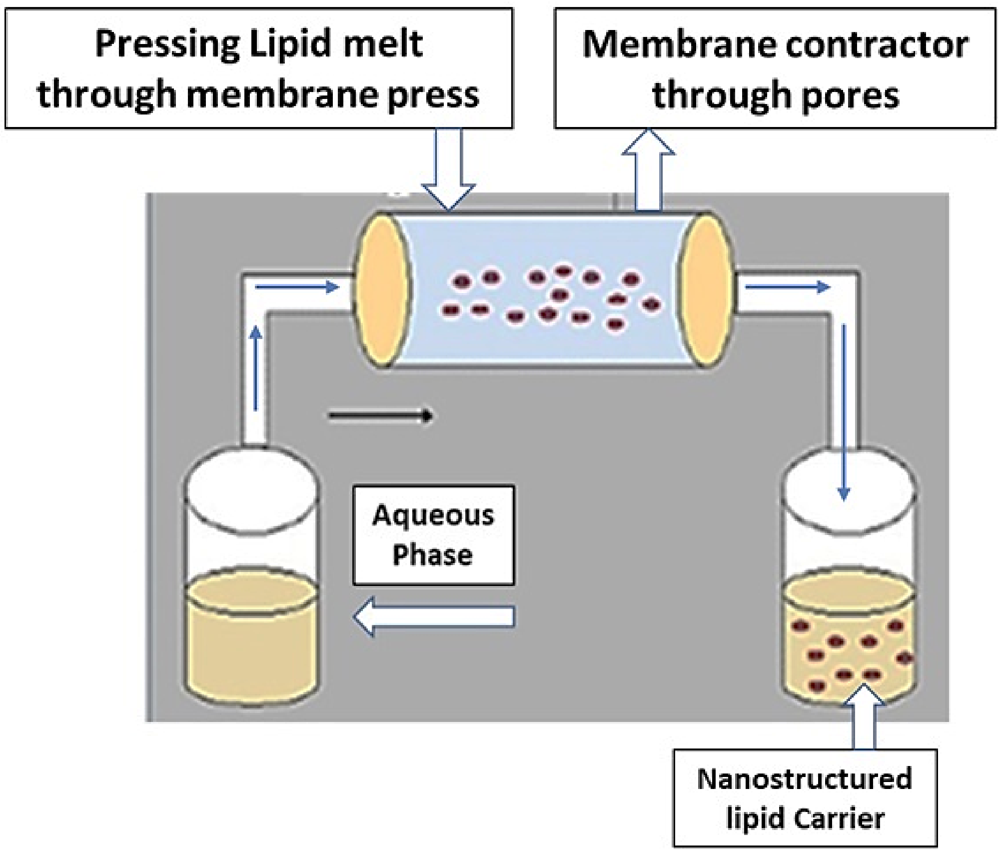

Figure 3: Membrane Contractor Technique.

Entrapment Efficiency

The proportion of the entire quantity of medication in the mixture to the amount of medication entrapped within the carrier is commonly referred as drug entrapment efficiency. The entrapment efficiency was evaluated using a variety of separation methods, including ultrafiltration, centrifugation and dialysis, as well as analytical methods, such as UV spectrophotometry or high-performance liquid chromatography, or HPLC. The active component can be measured using these techniques. There are two methods to assess the effectiveness of entrapment: directly and indirectly.

The formula for direct method is given below,

$$\%Entrapment\ Efficiency = \frac{amount\ of\ drug\ entrapped}{initial\ amount\ of\ drug\ present} \times 100$$

The formula for estimating entrapment efficiency by indirect method is given below,

$$\%Entrapment\ Efficiency = \frac{initial\ amount\ of\ drug\ added - unentrapped\ drug}{inital\ amount\ of\ drug\ added} \times 100$$

Crystallinity and polymorphism

Since the lipid matrix and the loaded drugs may change polymorphically during storage, it is important to characterize the crystallinity of the NLC components, potentially resulting in undesired drug leakage. Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) tests are carried to look into crystallinity and polymorphism status. Particle crystallinity has an impact on both release rates and encapsulation efficiency.[63]

Surface tension measurement

The emulsification process causes the system's interfacial tension to decrease as emulsifier concentration rises. It is common practice to measure the lipid nanoparticles' surface tension using the Wilhelmy plate method. A further method for determining the nanoparticulate systems' surface tension is the contact angle measurement. To measure the surface tension of NLC; one can use the highly precise and user-friendly Kibron instrument, which is a torsion balancing device. It makes use of a special ultrasensitive microbalance with a sensor that is exclusive to Kibron, along with the maximum draw force approach. When it comes to surface tension measurement, the device is on par with Du Noüy rings or platinum Wilhelmy plates.

In vitro Drug Release

Diffusion and biodegradation are the primary mechanisms regulating the drug release profile from NLCs. To estimate *in vitro* drug release from these nanocarriers, side-by-side diffusion cells with a biological or artificial membrane-like ultra-centrifugation, reverse dialysis sac, dialysis bag, centrifugal ultra-filtration and ultrafiltration are frequently used. The drug's release profile is evaluated using an HPLC or UV spectrophotometer.[64]

Stability of Nanostructured

Different colloidal structures, including liposomes, mixed micelles, nanoemulsions and micelles, can be present in NLC and have an effect on the formulation's stability. The pearl-like network of particles seen in highly concentrated NLC dispersions indicates that network development prevents collision and perikinetic flocculation. One of the main issues is that NLC is physically unstable when it comes to shell formation and aggregation during storage. To maintain a product's physical stability, especially if preparations consist of fluid or semisolid and dispersed in water then preservatives are used.

Techniques to overcome NLC Stability Issues

Polyethylene Glycol (PEG),

Spray Drying,

Lyophilization.

Polyethylene Glycol

Ensuring the colloids' physical stability and good dispersibility.

Enhances the blood circulation's colloidal presence for systemic application.

Reduce the thrombogenicity of drugs carriers and improve the stability of colloids in gastrointestinal fluid.

Improving greater biocompatibility

Spray Drying

Spray drying the NLCs dispersion can improve their stability.

Ideally, lipids should have a melting point of at least 70°C.

Lyophilization

Another efficient way to ensure the long-term stability of a product containing hydrolysable medications is lyophilization.

The end product of lyophilizing SLN/NLC without cryoprotectant frequently causes particle aggregation. Cryoprotectants include glucose, sucrose, maltose, mannose, sorbitol and trehalose as examples.[65]

Toxicity of Lipid Nanocarriers

Unfortunately, very limited information on the toxicity associated with nanoparticle-based drug formulations is available.[74] Nanocarriers are prepared for the delivery of bioactive molecules/ Active moieties in the human body. To launch the product in the market toxicity profile must be studied.[75] Literature survey revealed about sufficient data regarding the efficiency and quality of NLCs is available, as NLCs are prepared using GRAS excipients. Surfactants have potential to activate the immune system. Therefore, *in vitro* toxicity studies as cytotoxicity, genotoxicity and hemo compatibility need to be estimated/performed to get promising safety data.[76]

Cytotoxicity

The biocompatibility of lipid-based formulations need to be tested by the determination of cytotoxicity or cell viability. Normally, a cytotoxicity assay is conducted to check the potency of anticancer drugs and to prove its formulation efficiency. NLCs are used to increase the efficiency of through improving the cellular uptake of the drugs. The Lipid/ surfactants should need to remain inactive and cell viability remains unaffected. Lipids that are used to prepare NLCs are well tolerated at high doses by different cell lines.[77] However, most of the cell lines tolerate the lipid dose of 1 mg/mL when formulated as SLNs/NLCs.[78] Akanda *et al.*,[79] developed retinoic acid-loaded SLNs containing stearic acid and poloxamer 188, the cell line (androgen-sensitive human prostate adenocarcinoma) was well tolerated at a 3 mg/mL dose. Ghalaei *et al.*, reported that cetyl alcohol-containing hyaluronic acid-coated SLNs were tolerated at high doses by SK-OV-3 cells.[80] Cetyl alcohol-based SLNs are well tolerated by MCF-7 cells at doses reaching 2 mg/mL.[81]

Surfactant

Cetyltrimethylammonium bromide is the cationic surfactant which will be used at 1 mg/mL; it does not affect cell viability. Some reports suggests the cationic surfactants affect the integrity of the cell membrane.[82] Almeida *et al*., reported that SLNs are safe at 1 mg/mL without affecting cell viability.[83] Fangueiro *et al*., reported that the impact on cell viability can be controlled by limiting Cetyltrimethylammonium bromide content to 0.5% in SLNs.[84] Rahman *et al*., studied the toxicity of zerumbone-loaded NLCs after oral administration.[85] The histopathological data reported that NLCs did not exhibit any signs of toxicity on lungs, liver and kidney. Zhou *et al*., studied *in vitro* Caco-2 cells cytotoxicity studies revealed that that NLCs system did not show significant cytotoxicity[86] and cell viability (>90%).

CONCLUSION

Nanostructured Lipid Carrier (NLC's) is a novel drug delivery system, having a greater advantage over conventional dosage form. Nanostructured lipid carrier is possible carrier system with beneficial therapeutic effects and widely used in biomedical field. Aim of the present is study that for the effective oral administration of lipophilic drugs, NLCs is a new drug delivery technology, which improve the entrapment efficiency and oral bioavailability of drugs. Because of their quick absorption, bio acceptability and biodegradability, this carrier system (NLCs) has an ever-growing impact. Due to its site-specific and sustained release drug delivery capabilities, NLC's is attracting significant interest from researchers. Additionally, NLC's are appropriate for production in large quantities, as seen in the coming years in the pharmaceutical industry.

ACKNOWLEDGEMENT

We express our sincere thanks to Chairman, Business council of Progressive Education society, Pune, Maharashtra for providing necessary facilities to carry out the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NLC's: Nanostructured Lipid Carrier; **SLN:** Solid Lipid Nanoparticle; **PDI:** Polydispersity Index; **MCM:** Mono and Diglyceride of Medium Chain Fatty Acid; **HA:** Hyaluronic acid; **Mv:** Millivolt; **nm:** Nanometre; **°C:** Degree; **EE:** Entrapment Efficiency; **5-FU:** 5-Flurouracil.

SUMMARY

The objective of present study to develop Nanostructured Lipid Carrier system for enhancement of oral bioavailability. NLCs are a novel drug delivery system having greater advantages over conventional drug delivery system. To obtain a good NLC matrix the solid lipids and liquid lipids are mixed together into aqueous surfactant solution. NLC provides high drug loading capacity, high physical and chemical stability and good release controlling carriers.

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Cite this article: Haraka P, Kulkarni N, Gore S, Khade K, Dhole S. Nanostructured Lipid Carrier to Improve Oral Bioavailability. Indian J of Pharmaceutical Education and Research. 2025;59(3s):s788-s801.