IJPSR (2023), Volume 14, Issue 10 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 January 2023; received in revised form, 30 March 2023; accepted 31 May 2023; published 01 October 2023

NANOSTRUCTURED LIPID CARRIERS –A PROMISING CARRIER FOR IMPROVING ORAL BIOAVAILABILITY OF DRUGS

Dhinsha Murugan

Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai - 600003, Tamil Nadu, India.

Keywords:

Nanostructured lipid carriers (NLC), oral bioavailability, Lipid-based drug delivery system (LBDDS), Nanoparticle, Lipophilic drug, solubility

Correspondence to Author:
Dhinsha Murugan

Research Scholar,
Department of Pharmaceutics,
College of Pharmacy, Madras Medical College, Chennai - 600003, Tamil Nadu, India.

E-mail: dhinim1998@gmail.com

ABSTRACT: To deliver both conventional as well as novel drugs, the oral route was considered as the most preferable one because it reduces patient's non-compliance, well accepted by the patients, and can also eliminate the discomfort and pain accompanied by parenteral preparations. Even while oral formulations offer numerous advantages, several drawbacks substantially affect bioavailability. In recent years, lipid-based drug delivery techniques have gained more prominence over other nano-based techniques due to their high biocompatibility and increased bioavailability. Nanostructured lipid carriers (NLCs) are one of the lipid-based carriers developed to overcome some major limitations accompanied by solid lipid nanoparticles (SLNs) by replacing specific quantity of solid lipid with liquid lipid. Nanostructured lipid carrier based researches reveal that they can be the most propitious carrier to enhance oral bioavailability of lipophilic as well as hydrophilic drugs This review mainly focuses on some common barriers that affect the bioavailability of orally administered drugs and provide brief explanation of NLC types, components and fabrication method used in NLC formulations. The present review emphasizes the dominance of NLCs over solid lipid nanoparticles. This review further explains the mechanism of how NLCs improve the oral bioavailability of drugs.

INTRODUCTION: In commercially available drug products, around 60% of drugs are administered through oral route [1]. Around 70% of compounds under investigation are considered poorly soluble, and around 40% of currently marketed drugs are also considered poorly soluble [2]. The molecular weight and lipophilicity of newly synthesized chemical entities are greatly increased because of combinatorial chemistry and screening of molecules to improve its pharmacological effects by minimizing toxicities. It ultimately results in decreasing the aqueous solubility of drug molecules.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(10).4724-32

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(10).4724-32

The bioavailability of orally administered drugs mainly depends on the solubility of drugs at their site of absorption. Apart from that, permeability is the second criterion that affects the drugs' bioavailability. In 1995, Amidon *et al*. introduced Biopharmaceutical Classification System (BCS) based on drug solubility (Based on USP aperture) and permeability (Based on intravenous injection comparison).

In the scientific aspect, the oral bioavailability of drugs categorized in BCS class II is augmented by improving the aqueous solubility. BCS class III drugs are augmented by improving intestinal permeability [4]. For BCS class IV, solubility and permeability improvement are necessary for its oral bioavailability augmentation [1]. Researchers have endeavored a range of ways to improve oral bioavailability For example Polymeric micelles formation, development of nanoparticles, lipid-based formulations like liposomes, emulsions etc.

Researchers improve the bioavailability of lipophilic drugs (lipophilic drugs) and highly soluble carriers by creating a mixture of poorly water-soluble drugs (solid dispersion). Researchers have also studied using chelating agents and ionic polymers to enhance the absorption of drugs [5]. Nanotechnology-based approaches are gaining more popularity in recent times because surface area of the particles increases when their size decreases, resulting in accelerated disintegration by a small order of magnitude. This may be sufficient in certain circumstances to enhance bioavailability. Here, lipid-based carriers used to deliver drugs have given a glimpse of hope in recent decades due to their beneficial effects on the absorption of drugs [6].

Physiological Issues in Oral Delivery: Oral medication's effectiveness is largely determined by how drugs and drug delivery vehicles are processed by the gastrointestinal tract [7]. Extreme acidic conditions inside the stomach (pH 1-2.5) are the first biological barriers to any orally delivered medicine. Degradation of most of drugs substantially decreases their effectiveness. The Macrolid antibiotic erythromycin-A is rapidly inactivated in the stomach because of its high acid sensitivity. Gastric enzymes (pepsin) and pancreatic enzymes (amylase, lipase, peptidase *etc*.), which are found in abundance near the small intestine's major entry (duodenum) can destroy biopharmaceuticals [8].

Drug degradation in the intestine, generally caused by luminal fluids, bacteria or enzymes in gut wall has posed substantial problems in bioavailability [9]. CYP3A family of enzymes is the most common phase-1 drug-metabolizing species in humans. It is thought to metabolize 50–70% of commonly prescribed medications [10]. Researchers have found that CYP3A in the small intestine is typically 10–50% of those in the liver. Nevertheless, some people have had CYP3A equal to or above those seen in the liver [9, 10]. Sedatives such as triazolam and diazepam, antidepressants like imipramine, anti-arrhythmias like amiodarone, quinidine and disopyramide, antihistamines like terfenadine and loratidine, calcium channel antagonists like diltiazem, are metabolized by this enzyme [11]. P-gp is found in diverse of tissues, including kidney, liver, BBB cells, lungs, adrenals, pancrease, bladder and spleen as well as the stomach, jejunum and oesophagus which are essential for oral delivery of drugs. P-gp mRNA levels grow longitudinally in the gut, with the lowest level in the stomach and the greatest level in the colon, in direct contrast to the CYP3A observation [10]. Cyclosporine, digoxin, edoxaban, tacrolimus are some examples of drugs that are substracted of the P-gp efflux pump. The activity of the metabolic CYP3A4 enzymes and the P-gp system are linked because they perform together to prevent lipophilic drugs from entering the systemic circulation [10].

The stomach's alkaline microclimate and the small intestine's acid microclimate alters the drug's absorption. Intestinal mucus and UWL have a major role in limiting lipophilic drug absorption and maintaining an acidic microenvironment in small intestines [13]. The aqueous diffusion layer proximal to intestinal membrane, often known as unstirred water layer (UWL), has long been suggested as a significant obstacle to drug absorption through intestine [14]. Drug molecules in intestinal lumen must penetrate the UWL in order to reach brush border membrane. Because lipophilic compounds have low solubility in aqueous fluid, diffusion via this layer has been recognized as rate-limiting and it greatly affects the bioavailability [15]. **Fig. 1** depicts some of the physiological barriers encountered during the oral route.

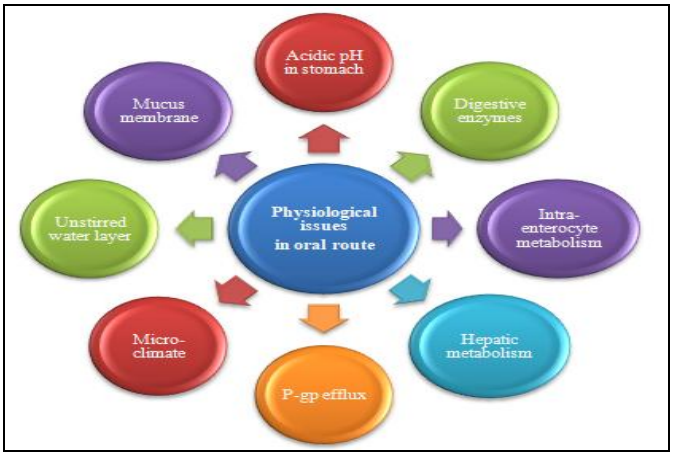

FIG. 1: PHYSIOLOGICAL ISSUES IN ORAL ROUTE

Lipid-Based Delivery of Drugs [16]: Lipid-based drug delivery systems are primarily made up of specific lipid combinations. LBDDS can imitate the natural digesting process of lipid-based food in GI tract. So, this LBDDS has recently acquired much

interest in improving oral bioavailability of drugs. They have better drug loading capacity and dissolution. LBDDS have a better future as a drug carrier because of their similar composition of biomembrane and enhanced biomembrane penetration. Different types of LBDDS is given in **Table 1.**

TABLE 1: CLASSIFICATION OF LBDDS [17, 18]

LBDDS (Lipid based drug delivery system)		
Emulsion	**Vesicular system**	**Lipid particulate system**
Microemulsion**,** Nanoemulsion**,** Self-emulsifying drug delivery system (SMEDDS)	Liposomes, Niosomes, Phytosomes, Transferosomes, Ethosomes, Phytosomes, Pharmacosomes, Colloidosomes	Solid lipid nanoparticles Nanostructured lipid carriers Lipid drug conjugates

Nanostructured Lipid Carrier: In 1990, M. R. Gasco from Italy and R.H. Muller/ Berlin and J. S. Lucks from Germany worked on lipid nanoparticles at the same time, but they used a different method for the formulation, namely the former used the microemulsion technique and latter using high-pressure homogenization technique. Solid lipid is the unique particulate carrier in this formulation; later, these formulations were considered the best alternative to liposomes, polymeric nanoparticles, and nanoemulsion. This formulation was known as solid lipid nanoparticles (first-generation nanoparticles). Followed by SLN, in 1999 Nanostructured lipid carriers were designed to overcome the shortcomings of Solid lipid nanoparticles. These are second-generation nanoparticles. At that time, researchers believed only lipophilic drugs could be loaded into NLC but not hydrophilic drugs. Muller and Orbrich created lipid-drug-conjugates (LDC) to address these issues in 2001. But several recent studies reveal that, apart from lipophilic drugs, NLCs act as the best carriers for hydrophilic drugs, too [19]. For example, Awadeen *et al.* developed Zolmitriptan/ chitosan nanostructured lipid carrier particles by the Double emulsion (W/O/W) technique. Zolmitriptan is a hydrophobic drug that comes under BCS class III (High soluble; low permeable); by formulating ZT-NLC, the researchers improved the permeability and thereby augmenting the bioavailability of ZT [20]. NLCs are nanoparticulate carrier systems having a particle size range of 10 nm to 1000 nm [24]. Solid lipid, liquid lipid, solubilizer/surfactant , and water are the main constituents in NLCs. The objective underlying NLC-based formulation is to create particles in which oil is incorporated into the solid lipid core, resulting in increased drug loading capacity and controlled release [21].

Comparison between NLC and SLN: Comparison between various properties of NLC and SLN are given in **Table 2.**

TABLE 2: NLC AND SLN COMPARISON

Solid lipid nanoparticles	Nanostructured lipid carriers
Developed in 1990	Developed in 1999
Particulate carrier: solid lipid	Particulate carriers: solid lipid, liquid lipid
Particle size: 120-200 nm	Particle size: 10-1000nm
Form perfect crystal structure	Highly imperfect arrangements
High drug expulsion, precipitation of drug crystal in aqueous phase	Strongly immobilize drugs
Water content: 70-90.9%	Less water content
Low drug loading capacity	High drug loading capacity than SLN
Low physical stability	High physical stability than SLN
Types: Homogenous matrix model, drug enriched shell model, Drug enriched core model	Types: Imperfect type, Amorphous type, Multiple types

Types of NLC [22]:

Type I: Imperfect Crystal: Highly disordered matrix, Having many gaps and spaces. Allow more drug particles to be accommodated in amorphous clusters.

Type II [21]: Multiple Types: High oil content. When oil is introduced more than its solubility phase separation occurs, resulting in a microscopic nano-compartment in which oil is encased in a solid matrix.

Type III: Amorphous type: Addition of hydroxyl stearate, octacosanyl (or) dibutyl adipate in solid lipid form structureless amorphous phase.

NLC Components [21]: All components employed in NLC have been GRAS (Generally Recognized as Safe) by regulatory authorities. The components used are generally biodegradable, biocompatible, non-toxic, and easy to get regulatory approval. Commonly used excipients in NLCs are solid lipids, liquid lipid, surfactants. Ideal solid lipid to oil ratio is from 70: 30 to 99.9: 0.1 and 0.5% to 5% of surfactants are used as stabilizers [23]. Lipid components used in NLC formulations are listed in **Table 3** and surfactants used in NLC formulations are listed in **Table 4.**

TABLE 3: EXCIPIENTS USED IN NANOSTRUCTURED LIPID CARRIERS [25, 27-38]

Lipid components	
Solid lipid	**Liquid lipid**
Glyceryl monostearate	Capryol® PGMC
Gelucire® 43/01	Medium chain triglycerides
Lauric acid	Capryol ™ 90
Glyceryl tripalmitate	Capmul PG-8
Cetyl palmitate	Labrafec CC
Stearic acid	Labrafil WL 2609 BL
Palmitic acid	Labrafil ILM 1944 CS
Compritol ATO 888	Labrafil M 1944 CS
Dynasan 114	Polyglyceryl-3- dioleate
Dynasan118	Castor oil
Imwitor 900K	Oleic acid
Softisan® 154	Capmul MCM C8
Trimyristin	Isopropyl myristate
Percifac ATO 5(Glyceryl palmitostearate)	Phosal 53 MCT, Captex 100
	Cremophore EL
	Solutol® HS-15
	Corn oil
	Ethyl oleate
	Soybean oil
	Miglyol- 812
	Cetyl recinoleate

TABLE 4: SURFACTANTS/ SOLUBILIZERS USED IN NANOSTRUCTURED LIPID CARRIERS

Surfactants/ Solubilizers	Reference
Pluronic® F- 68 (Poloxomer 188)**,** Pluronic® F-127, (Poloxomer 407)**,** Sodium taurocholate	27,28,32,35,38, 25, 25
Sodium dodecylsulfate, Tyloxapol, Soy phosphatidyl choline, Polyvinyl alcohol, Egg lecithin (PC-98T), Soy lecithin (S 75), Polysorbate 80 (Tween 80), Polysorbate 60 (Tween 60), Polysorbate 20 (Tween 20), DSPE-PEG (Distearoylphosphatidyl-ethanolamine PEG)	25, 25, 25, 25, 30, 30, 33, 34, 37, 25, 25

Techniques Used in the Fabrication of NLC [22, 23, 25]: Different techniques used to fabricate nanostructured lipid carrier (NLC) are short-listed in **Table 5.**

TABLE 5: TECHNIQUES USED IN THE FABRICATION OF NLC [25]

Technique with high energy level	Technique with low energy level	Technique with organic solvent
High pressure homogenization, High shear homogenization, ultrasonication	Microemulsion, Membrane contactor, Double emulsion	Emulsification-solvent evaporation Emulsification-solvent diffusion Solvent injection, Nanoprecipitation

Technique with High Energy Level:

High-Pressure Homogenization (HPH): In HPH-technique, liquid is squeezed through a confined area at high pressure(100-2000 bar). The high pressure combined with the small gap size results in extremely high acceleration and pressure drop. The mechanism involved: high shear stress and cavitation forces. The hot HPH technique is carried out at temperatures over the lipid's melting point. High-shear mixers are commonly used to create a pre-emulsion. Usually, up to 3 cycles at a bar pressure of 500 and increased temperature are employed.

Formed pre-emulsion (hot) is cooled and solidified. In Cold HPH-technique hot lipid blend and drug mixture are usually solidified with dry ice or with liquid nitrogen.

Cold surfactant solution is added in grinded and crushed lipid Microparticles, forming a cold pre-suspension. Homogenization is carried out in 5-10 cycles at bar pressure of 1500.

High Shear Homogenization: Rotor-stator homogenizer is used in this technique. High shear rate of 5000-25000 rpm is applied at a temperature higher than the lipid's melting point. High shear homogenization alone does not reduce the particle size. So in HPH-technique and ultrasonication, this approach is typically employed as a pre-homogenization step.

Ultrasonication: The cavitation in aqueous dispersions induced by intense ultrasound with a wave frequency generally around and above 20 kHz is the fundamental for ultrasonication. By applying ultrasound with the help of sonotrode in pre-emulsion, form NLC.

Technique with Low Energy Level:

Microemulsion Technique: This method utilise high amount of surfactants to form micro-emulsion. Molten lipid blend and hot surfactant solutions are mixed together until microemulsion is formed. Under gentle stirring, the heated micro-emulsion is disseminated in a large amount of cold water (2-3 °C). This harden/solidify liquid droplets.

Membrane Contactor: To produce NLC, the gaseous phase in the membrane contactor technique is replaced with molten lipid mixture. Small droplets are formed when the mixture is squeezed through the membrane.

A heated surfactant solution circulates on the other side of the membrane, switching the droplets. The surfactant molecules encase and stabilize the liquid lipid droplets.

Double Emulsion Technique: To formulate hydrophilic drug loaded NLC, this technique is most suitable. Initially primary emulsion (W/O) is formed, then this primary emulsion is further dispersed in aqueous solution to form secondary emulsion (W/O/W).

Technique with Organic Solvent:

Emulsification-Solvent Evaporation Technique: Lipid mixture/blend is dissolved in water immiscible organic solvent (chloroform) and emulsified with surfactant solution. Evaporation of organic solvent form NLC (particle size rages from 25 to 100 nm).

Emulsification-Solvent Diffusion Technique: Lipid mixture/blend is dissolved in partially water-soluble organic solvent (benzyl alcohol) and emulsified with surfactant solution.

When the emulsion is diluted with water, organic solvent diffuse into the aqueous phase and form NLC (particle size below 100 nm).

Solvent Injection Technique: Lipid mixture/blend is dissolved in water-soluble organic solvent (ethanol) and mixed with surfactant solution. Since the organic solvents used are highly aqueous soluble, emulsion is not formed. Lipid precipitate by rapid migration of organic solvent into the aqueous phase.

Stabilization of NLC Formulation: Physical instability of NLC during storage, such as aggregation or gelling, is a key problem. The nanoparticle features of all NLC formulations should be preserved. To assure the physical stability of the NLC during storage, two ways might be used:

- Lyophilizing the nanoparticle dispersion to remove water
- Introducing a preservative to the dispersion.

Lyophilization: Freeze drying the nanoparticle dispersion does not affect the particle size, but freeze-drying without cryoprotectant aggregate the formulation.

Water molecules from the nano-dispersion are completely removed. Some cryoprotectants which are commonly used: sucrose, lactose, mannitol, trehalose, Avicel® RC591.

Preservatives: To sustain the physical stability of dispersions, preservatives are used. The selection of suitable preservatives is crucial because some preservatives can also destabilize the NLC formulation. Khosa *et al.* classified the preservatives based on their effect in NLC formulation as given in **Table 6.**

TABLE 6: CATEGORIZATION OF PRESERVATIVES BASED ON THEIR EFFECT IN NLC

Categories	Preservatives
Stability not influenced	Propylene glycol, Caprylyl glycol, Ethanol, Propylene glycol and pentylene glycol combination
Minor stability challenges	
Major stability challenges	
Stabilizing effect	

Mechanism of NLC to Enhance Oral Bioavailability [10-12, 14, 26]:

Mixed Micelles [7, 9]: After ingesting NLC, it is exposed to different GIT environments. Enzyme lipase hydrolyze lipids in NLC into free fatty acids and monoglycerols. In the intestinal lumen, these digested products combine with bile salt and phospholipids to form mixed micelles. During the digestive process drug loaded in NLC are transferred to mixed micelles, considerably increasing the bioavailability. It was reported that smaller lipid particles create mixed micelles more effectively during lipid digestion than bigger particles, which can accelerate the transfer of drugs to mixed micelles. Thus the formed mixed micelles transport drug through aqueous mucus and/or UWL and make it accessible for enterocyte absorption. In enterocyte, the drug is entrapped in chylomicrons (endogenously formed lipid particles by enterocytes from lipid components fed by mixed micelles). Finally, through the chylomicron-mediated pathway, drugs reach lymphatic circulation. Similarly, it reaches systemic circulation through subclavian veins and bypass liver, thus avoiding first-pass metabolism. Also it promotes trans-enterocyte delivery. Studies report that drugs that are transported via paracellular are not susceptible to intracellular enterocyte enzyme metabolism.

Mucus Adhesion [26]: Mucus prevents foreign particles from passing through the GIT because of its hydrophilic nature and negative charge. Nevertheless, researchers have used mucus as a technique to improve plasma concentration and therapeutic effectiveness of pharmaceuticals by creating NLC with the capacity to attach to mucus. Mucus-binding nanoparticles have a longer residence time in the GI system, allowing for passive drug administration and improved bioavailability. To give NLC mucoadhesion properties, two alternative techniques are used. The first technique involves electrostatic interaction between negatively charged mucus and positively charged polymer-coated nanoparticles. Second, the creation of covalent bridges between mucus and thiomers bound on NLC surfaces.

Mucus Penetration: Literature demonstrates that the neutral charge eliminates electrostatic attraction between mucin and NLCs, overcomes mucus barrier characteristics, and aids NLC transit over the mucus membrane to the systemic circulation. Nanoparticles coated with PEG offer hydrophilicity while impeding RES acquisition by limiting opsonin adsorption on their surface, which is one of the primary challenges in delivering medicines to locations other than the liver and spleen. Furthermore, PEGylation results in improved nanoparticle transport via the paracellular pathway.

Increase Permeability [24, 26]: Intestinal permeability is highly influenced by the surfactants used in NLC formulation. Surfactants promote intestinal permeability by inhibiting P-gp efflux transport. The Poloxamer opens the epithelial cell junction and promotes paracellular transport by deforming the cell membrane.

Prevent Degradation of Drug: Since, the drug is encapsulated with lipid carriers, it protects compounds against chemical and enzymatic breakdown in the hostile GI environment.

Overall Benefits [7-14, 21]: Overall benefits of NLC formulations during oral administration are summarised in **Fig. 2.**

FIG. 2: OVERALL BENEFITS OF NLC

Formulation Enhanced Oral Delivery: Table 7 depicts some NLC formulations that enhance oral bioavailability.

TABLE 7: ORAL DELIVERY OF NLC FORMULATIONS

Drug	Solid lipid	Liquid lipid	Fabrication method	Highlights	Ref.
Atorvastatin	Gelucire®43/01 Glyceryl monostearate Compritol®888 ATO	Capryol® PGMC	High-shear homogenization followed by ultrasonication method	In comparison to Atorvastatin suspension and commercial product (Lipitor VR) Atorvastatin-NLC demonstrated 3.6 and 2.1 fold improvement of bioavailability respectively	27
Baicalin	Glyceryl monostearate	Medium chain triglycerides	Emulsion- evaporation and low temperature-solidification method	AUC and MRT of BA_NLC were approximately 1.9 fold and 1.7 fold greater than BA-suspension respectively	28
Candisartan cilexetil	Glyceryl monostearate	capryol™ 90	Hot homogenization-ultrasonication method	Oral bioavailability is increased	29
Docitaxel	Percifac ATO 5	Medium chain triglycerides	Emulsification-ultrasonication method	D-NLC's relative bioavailability is augmented 4.3 fold compared with docetaxel solution	30
Ezitimibe	Glyceryl monostearate	Capmul PG-8	Hot high-pressure homogenization	Improve solubilisation of drug, improve oral bioavailability and pharmaceutical bioactive	31
Felodipine	Compritol®888 ATO	Oleic acid	High-shear homogenization followed by ultrasonication method	Felodipine loaded NLC were capable of augmenting the bioavailability of drug by 2.0 folds when compared to marketed product	32
Fenfibrate	Compritol®888 ATO	Labrafil M 1944 CS	Hot homogenization-ultrasonication method	The greater C_{max} values as well as the four fold increase in AUC of NLC in plasma, clearly demonstrated a significant increase in bioavailability of drug	33
Glutathione	Stearic acid	Oleic acid	Emulsification-solvent evaporation technique followed by ultrasonication	Glutathione loaded NLC were successfully designed to eliminate the degradation of Glutathione by intestinal enzyme and structural changes in oral delivery	34
Nisoldipine	Dynasan 114	Oleic acid	Hot homogenization-ultrasonication method	ND-loaded NLCs shows 1.09 fold increased oral bioavailability compared to Nisoldipine suspension	35
Raloxifen	Glyceryl monostearate	Capmul MCM C8	Solvent diffusion method	RLX-NLC showed 3.75 fold improved bioavailability than Raloxifen suspension	36

CONCLUSIONS: Some drugs have high potency, but because of their low solubility, penetration problems, first-pass metabolism, and other GIT actions, the oral bioavailability of these drugs drastically decreases. In the past few decades, researchers have developed a number of new drug entities whose primary aim was to reduce the toxicity of the drug molecules and increase their potency, but to some extent, they still have not succeeded. The reason is the high lipophilicity of the drug and its larger molecular weight. On the other hand, instead of developing new molecules, some researchers developed carriers to deliver drugs. The nanostructured lipid carrier is the most promising nano-carrier because of its vast range of benefits. At first, researchers believed that it was the best carrier for lipophilic drugs, but later research emphasized that NLC also acts as the best carrier for hydrophilic drugs. Because of its smaller particle size and mimicking of the natural lipid-based digestion in the stomach, greater interest is shown in NLC-based formulations. Also, excipients used in these formulations are GRAS listed as non-toxic and biocompatible compared to other polymeric excipients. Several studies are being conducted on NLC. It is expected that in the near future, NLC will also be evaluated as a gene-targeting carrier.

ACKNOWLEDGEMENT: The author would like to express respectful gratitude for permitting to utilization of the College of Pharmacy, Madras

Medical College, Chennai, India to carry out the work.

CONFLICTS OF INTEREST: The author has no conflict of interest with any person or institute.

REFERENCES:

1. Alqahtani MS, Khazi M, Alsenaidy MA and Ahmad MZ: Advances in oral drug delivery. Frontiers in Pharmacology 2021; 12: 1-21.
2. Basavaraj S and Betageri GV: Can formulation and drug delivery reduce attrition during drug discovery and development- review of feasibility, benefits and challenges. Acta Pharmaceutica Sinica 2014; 4: 3-17.
3. Stegemann S, Leveiller F, Franchi D, Jong HD and Linden H: When poor solubility becomes an issue: From early stage to proof of concept. European Journal of Pharmaceutical Sciences 2007; 31: 249-261.
4. Wagh MP and Patel JS: Biopharmaceutical classification system: Scientific basis for biowaiver extensions. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2: 12-19.
5. Poonia N, Kharb R, Lather V and Pandita D: Nanostructured lipid carriers: Versatile oral Delivery vehicle. Future science OA 2016; 2(3).
6. Gupta H, Bhandari D and Sharma A: Recent trends in oral delivery: A review. Recent patents on drug delivery & formulation 2009; 3: 162-173.
7. Song NN, Zhang SY and Liu CX: Overview of factors affecting oral drug absorption. Asian Journal of Drug Metabolism and Pharmacokinetics 2004; 4: 167-176.
8. Homayun B, Lin X and Choi HJ: Challenges and recent progress in oral drug delivery systems for Biopharmaceuticals. Pharmaceutics 2019; 11: 1-29.
9. Wacher VJ, Salphati L and Benet LZ: Active secretion and enterocytic drug metabolism barriers to drug absorption. Advanced Drug Delivery Reviews 2001; 46: 89-102.
10. Wacher VJ, Silverman JA, Zang Y and Benet LZ: Role of P- Glycoprotein and cytochrome P450 3A in limiting oral absorption of Peptides and peptidomimetics. Journal of Pharmaceutical Sciences 1998; 87: 1323-1329.
11. Khan F, Pandey P and Upadhyay TK: Cytochrome P450 enzymes in the metabolism of drugs and chemical carcinogens: A perspective on the toxicity and carcinogenisis. Lamber Academic Publishing 2019; 1-51.
12. Desai PP, Date AA and Patravale VB: Overcoming poor oral bioavailability using nanoparticle formulations-opportunities and limitations. Drug Discovery Today: Technologies 2012; 9: 87-95.
13. Yeap YY, Trevaskis NL and Porter CJ: Lipid absorption triggers drug supersaturation at the intestinal unstirred water layer and promotes drug absorption from mixed micelles. Pharmaceutical Research 2013; 30: 3045-58.
14. Jonathan MM, Avital B, Brian JK, Robert AC, Thomas BB, Gregory EA, Gordon LA and Arik D: The solubility-permeability interplay: mechanistic modeling and predictive application of the impact of micellar solubilization on intestinal permeation 2011; 8: 1848-56.
15. Hetal T, Bindesh and Sneha T: A review on techniques for oral bioavailability enhancement of drugs. Int J of Pharma Sciences Review and Research 2010; 4: 205-223.
16. Jaiswal P, Gidwani B and Vyas A: Nanostructured lipid carrier and their current application in targeted drug delivery. Artificial cells, Nanomedicine and biotechnology 2014; 1-14.
17. Pouton CW: Lipid formulation for oral administration of drugs: non-emulsifying, self emulsifying and self-microemulsifying drug delivery systems. European Journal of Pharmaceutical Sciences 2000; 2: 93-98.
18. Shresha H, Bala R and Arora S: Lipid- based drug delivery systems. Journal of Pharmaceutics 2014; 1-10.
19. Garcês A, Amaral MH, Sousa JML and Silva AC: Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cutaneous use: A review. European Journal of Pharmaceutical Science 2018; 112: 159-167.
20. Awadeen RH, Boughdady MF and Meshali MM: Quality by design approach for preparation of Zolmitriptan/ chitosan Nanostructured lipid carrier particles- formulation and Pharmacodynamic Assessment. International Journal Of Nanomedicine 2020; 15: 8553-8556.
21. Kanojia N, Sharma N and Singh S: Applications of nanostructured lipid carriers: Recent advancements and patent review. Biointerface Research in Applied Chemistry 2022; 12: 638-652.
22. Chauhan I, Yasir M and Singh AP: Nanostructured lipid carriers: a groundbreaking approach for transdermal drug delivery. Advanced Pharmaceutical Bulletin 2020; 10: 150-165.
23. Khosa A, Reddi S and Saha NR: Nanostructured Lipid Carriers for Site – Specific Drug Delivery. Biomedicine and Pharmacotherapy 2018; 103: 598-613.
24. Rajalakshmi G, Dhanapal CK and Sundararajan R: An insight to nanostructured lipid carrier system. Journal of Drug Delivery and Therapeutics 2020; 10: 173-182.
25. Svilenov H and Tzachev C: Solid lipid nanoparticles- A promising Drug delivery system. Nanomedicine 187-236.
26. Natarajan J, Karri V and Anindita D: Nanostructured Lipid Carrier (NLC): A Promising Drug Delivery System. Glob J Nano 2017; 1.
27. Elmowafy M, Ibrahim HM, Ahmed MA, Shalaby K, Salama A and Hefesha H: Atorvastatin- loaded nanostructured lipid carriers (NLCs): Stratergies to overcome oral delivery barriers. Drug Delivery 2017; 24: 932-941.
28. Luan J, Zheng F, Yang X, Yu A and Zhai G: Nanostructured lipid carriers for oral delivery of baicalin: *in-vitro* and *in-vivo* evaluation. Colloids and Surfaces A Physicochemical and Engineering Aspects 2014; 1-27.
29. Anwar W Dawaba HM, Afouna MI, Samy AM, Rashed MH and Abdelaziz AE: Enhancing oral bioavailability of candisartan cilexetil loaded nanostructured lipid carriers: In vitro characterization and absorption in rats after oral administration. Pharmaceutics 2020; 12: 1-19.
30. Fang G, Tang B, Zhang Y and Tang X: Improved oral bioavailability of docetaxel by nanostructured lipid carriers: *in-vitro* characterizations, *in-vivo* evaluation and intestinal transport studies. Royal Society if Chemistry 2015; 5: 96437-96447.
31. Agrawal YO, Mahajan UB and Agnihotri VV: Ezitimibe-loaded nanostructured lipid carrier based formulation Ameliorates hyperlipidaemia in an experimental model of high fat diet. Molecules 2015; 26: 1-18.
32. Patil AS, Jaknoor V, Gadad AP and Bolmal U: Nanostructured lipid carrier: A potential system for enhanced oral bioavailability of felodipine. Indian Jof Pharmaceutical Education and Research 2022; 56:77-85.
33. Tran TH, Ramasamy T, Troung DH, Choi HG, Yong CS and Kim JO: Preparation and characterization of fenofibrate loaded nanostructured lipid carriers for oral bioavailability enhancement. American Association of Pharmaceutical Sciences 2014.

34. Ahmed AM, Mohammed HA, Faris TM, Hassan AS and Aboubakr EM: Nanostructured lipid carrier based oral glutathione formulation Mediates Renoprotection against Cyclophosphamide-Induced Nephrotoxicity, and Improves Oral Bioavailability of Glutathione Confirmed through RP-HPLC Micellar Liquid Chromatography. Molecules 2021; 261-21.
35. Dudhipala N, Janga KY and Gorre T: Comparative study of nisoldipine-loaded nanostructured lipid carriers and solid lipid nanoparticles for oral delivery: preparation, characterization, permeation and pharmacokinetic evaluation. Artificial Cells Nanomedicine and Biotechnology 2018; 1-10.
36. Shah NV, Seth AK, Balaraman R, Aundhia CJ, Maheswari RA and Parmar GR: Nanostructured lipid carriers for Oral bioavailability enhancement of Raloxifene: Design and *in-vivo* study. Journal of Advanced Research 2016; 7: 423-434.
37. Neves AR, Lucio M, Martins S, Lima JLC and Reis S: Novel resveratrol nanodelivery systems based on lipid nanoparticles to enhance its oral bioavailability. International Journal of Nanomedicine 2013; 8: 177–187.
38. Gadad AP, Tigadi SG, Dandagi PM, Mastiholimath VS and Bolmal UB: Rosuvastatin Loaded Nanostructured Lipid Carrier for Enhancement of Oral Bioavailability. Indian J of Pharma Education and Res 2016; 50: 605-611.

How to cite this article:
Murugan D: Nanostructured lipid carriers - a promising carrier for improving oral bioavailability of drugs. Int J Pharm Sci & Res 2023; 14(10): 4724-32. doi: 10.13040/IJPSR.0975-8232.14(10). 4724-32.