International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page:www.iscientific.org/Journal.html

Advancing oral drug bioavailability: A comprehensive review of Nanostructured Lipid Carriers

D. Pranitha[1], *Malarkodi Velraj*[2*]

[1]*Vels Institute of Science, Technology & Advanced Studies, Pallavaram, Chennai, Tamil Nadu, India.*

[2]*Vels Institute of Science, Technology & Advanced Studies, Pallavaram, Chennai, Tamil Nadu, India.*

Abstract

Orally administered drugs often encounter issues with bioavailability due to their poor solubility. In response to this challenge, Nanostructured Lipid Carriers (NLCs) have emerged as a highly promising solution. NLCs are engineered to mimic the natural lipid digestion processes that occur in the gastrointestinal tract, comprising a combination of solid and liquid lipids, surfactants, and water. They shield drugs from degradation in the gastrointestinal tract, facilitate the creation of mixed micelles, enhance drug permeation through barriers and allow efficient transit through mucus. Various techniques were employed to prepare NLC's are high-energy methods like high-pressure homogenization, high shear homogenization, and ultrasonication, as well as low-energy methods like microemulsions and membrane contact methods. Solvent-based techniques such as solvent evaporation, solvent diffusion, and solvent injection also play a role in NLC formulation. Nonetheless, continuous scrutiny and research are essential to assess their safety profile and long-term implications fully.

Keywords: Solid lipids, Liquid lipids, Stabilizers, Surfactants, Bioavailability.

Full length article **Corresponding Author*, e-mail:*malarkodiv.sps@velsuniv.ac.in*

1. Introduction

In the vast arena of formulations and medications, approximately 60% of active ingredients are intended for oral administration [1]. Surprisingly, nearly 70% of novel compounds under research face bioavailability challenges related to poor solubility, while approximately 40% of drugs in the current market encounter the same issue [2]. This decline in aqueous solubility is often a result of the complex chemistry and screening eventually resulting in the increased molecular weight and lipophilicity of those drugs. As bioavailability of oral drugs primarily hinges on the solubility of drugs at their absorption sites, alongside permeability representing another pivotal factor. According to the BCS classification of drugs the bioavailability depends on solubility and permeability of the administered drug and most of the drugs in the market belong in the BCS-II class. Simply it means bioavailability of a BCS-II drugs with low solubility and high permeability can be enhanced by improving the solubility and vice versa for BCS-III drugs with low permeability and high solubility [3].Researchers have explored various approaches to enhance oral bioavailability, such as forming micelles with polymers, nanoparticles, and employing lipid-polymer based systems like liposomes. Solid dispersions which disperses poorly water-soluble drugs with highly soluble carriers, has also been developed, along with the utilization of chelating agents and ionic polymers to achieve enhanced drug absorption [4]. Recent advances in nanotechnology had gained significant scientific attention, primarily because of the inversely proportional relationship between particle size and surface area which results in faster disintegration of the drug molecules leading to enhanced bioavailability [5].On the other hand alongside the dug related problems, there are various other issues that lead to low bioavailability of drugs with the oral drug delivery. Gastrointestinal pH is a foremost barrier that results in the degradation of many drugs like Erythromycin-A resulting in the hindered absorption and there by pharmacological activity. gastric enzymes in the stomach and intestine leads to the changes in the drug molecules [6]. Gut bacteria and fluids also cause a substantial degradation of most drugs there by significantly reducing their efficacy. Notably, researchers have observed that CYP3A activity in the small intestine metabolize about 50-70% of the drugs like diazepam, imipramine, loratadine, diltiazem etc [7] and prevent the absorption of lipophilic molecules into the systemic circulation [8]. The alkaline microclimate in the small intestine alters the absorption of the lipophilic agents and unstirred water layer is a hurdle for drug absorption from the intestine [9].Thus all the above factors stand as a rate limiting steps that affects the oral bioavailability of administered

drugs.One of the approaches to combat the above factors is delivery of drugs through a lipid based drug delivery system. Lipid-based drug delivery systems primarily consist of specific lipid combinations and polymers. These systems are designed to mimic the natural digestion process of lipid-based food in the gastrointestinal (GI) tract thereby protecting drugs. Consequently, lipid-based drug delivery systems have gained significant attention and recognition in recent times in improving the bioavailability of oral drugs.Lipid-based drug delivery systems are advantageous over other with superior capacity of drug loading and dissolution properties. These characteristics make them a promising choice as drug carriers due to their similarity in composition to cell membranes and their enhanced ability to penetrate into the cells [10]. In this review a detailed discussion was carried out on various mechanisms of enhancement of bioavailability through NLCs, their preparation methods and various drugs of which NLCs were produced and their advantages.

1.1 Nanostructured lipid carriers (NLC)

NLCs are nanoparticle based carriers with size between 10-100nm in diameter. Lipid in solid form and liquid forms, surfactants and water are primary ingredients which forms particles of oil incorporated into a solid lipid core [11]. NLCs utilise solid lipid as a distinctive particulate carrier and so considered as superior to the existing lipid drug delivery systems like liposomes, nanoparticles or the nano-emulsions. They are initially termed as solid lipid nanoparticles but later the limitations were addressed and called as NLCs. They are second generation lipid nano particulate systems which are initially believed to load only lipophilic drugs and pose a challenge to load water soluble drugs. Later conjugated of lipid and drug were introduced to address this problem and NLCs stand as best systems to load hydrophilic drugs tool [12]. Researchers produced chitosan based BCS-III drug-NLCs using double emulsion technique which delivered a significantly enhanced permeability and bioavailabilitywith better loading and control in the release of drug [13].The components in the NLCs (Solid and liquid lipids, surfactants) were well regulated and accepted as they are biocompatible, degradable and safe. Ideal amount of the lipid to oil in the NLC ranges from 70-30% to 99-1% and the stabilizers in a range of 5-0.5% were added to the final particles [14].

1.2 Mechanisms of NLCs to enhance Bioavailability

1.2.1 Protection from degradation of drug

The encapsulation of drugs within NLCs provides protection against pH related and enzymatic breakdown in the gastrointestinal (GI) tract. This protective effect helps maintain the stability and effectiveness of the drugs as they traverse the GI tract, enhancing their overall bioavailability.

1.2.2Formation of Mixed micelles

After administration orally, NLCs are prone to various gastric climates hosting enzymes like lipases that break down lipids into fatty acids by hydrolysis. In the intestine, they are converted into mixed micelles (MMs) and the drugs loaded in the NLCs are transferred into MMs which rapidly increase the bioavailability of the drugs. It has been observed that smaller lipid particles are more effective at creating mixed micelles during lipid digestion than larger particles, accelerating the transfer of drugs to mixed micelles. Subsequently, these formed mixed micelles transport the drug through the aqueous mucus and/or the unstirred water layer (UWL), making it accessible for absorption by enterocytes. This pathway allows drugs to reach the systemic circulation via the subclavian veins, bypassing the liver and thus avoiding first-pass metabolism [15].

1.2.3 Enhancement of permeation

The choice of surfactants in nanostructured lipid carriers (NLCs) has a significant impact on intestinal permeability. Surfactants play a crucial role in promoting gut permeability by inhibiting drug transport through P-glycoprotein (P-gp) efflux. Additionally, the use of surfactants like Poloxamer can enhance permeability by opening the junctions of epithelial cells and facilitating intercellular permeation through the deformation of the plasma membrane [16].

1.2.4 Mucoadhesion and transit through Mucus

The hydrophilicity and -ve charge of the mucus acts as a barrier for the drugs and foreign particles from permeation and absorption through the GIT. However, researchers have found innovative ways to leverage mucus to enhance the plasma concentration and therapeutic effectiveness of oral drugs through NLCs. The nanoparticles bind to the mucus and adhere to the lining of the gut thus providing extended time in the GIT. This prolonged contact allows for passive administration of drug and ultimately leading to enhanced bioavailability. To confer mucoadhesive properties to NLCs, involves establishing an electrostatic link between the mucus and polymer-coated nanoparticles via negative and positive charges. The second technique involves creating covalent bridge between thiomers present on the surface of the NLC and mucus [17]. Furthermore, the literature shows that nanoparticles with neutral charge diminish the interaction between the NLCs and mucus. Thus NLCs are easily transited across the mucus membrane and their entry into the systemic circulation is facilitated. Nanoparticles that are coated with polyethylene glycol (PEG) not only offer hydrophilicity but also hinder the reticuloendothelial system (RES) from acquiring them by limiting adsorption of opsonin on their surface. This is a significant benefit in delivering medications to locations other than the liver and spleen. Furthermore, PEGylation leads to an improved transport of nanoparticles via the intercellular pathway, enhancing their overall effectiveness in drug delivery [18].

1.3 Techniques for preparation of NLC

1.3.1 High Energy techniques

1.3.1.1 High Pressure homogenization

The High-Pressure Homogenization (HPH) technique allows the flow of liquid squeeze through a tiny area using high pressure ranging from 100bar to 2000bar. Hot-HPH involves elevated temperatures over the melting point of the lipid and high shear mixers are often used to emulsify under pressure of upto 500bar. The formed emulsion is subsequently cooled and solidified.On the other hand, in the cold HPH technique, the blend of hot lipid and drug are solidified using dry ice or liquid nitrogen to maintain lower temperatures during the process. A cold surfactant solution is added to lipid microparticles that have been ground and crushed, forming a cold pre-suspension. Homogenization is then conducted in approximately 5 to 10 cycles, with a bar

pressure of 1500. This process helps create stable lipid nanoparticles and ensures effective dispersion of the lipid particles within the solution.

1.3.1.2. High Shear Homogenization

High Shear Homogenization involves the use of a rotor-stator homogenizer. This technique applies a high shear rate ranging from 5000 rpm to 25000 rpm at a temperature above the melting point of the lipid. High shear homogenization is commonly used as a pre-homogenization step in combination with other techniques such as High-Pressure Homogenization (HPH) and ultrasonication to achieve the desired particle size reduction and homogenization.

1.3.1.3. Ultrasonication technique

Ultrasonication relies on the phenomenon of cavitation in the drug dispersions induced by intense ultrasound. Typically, ultrasonication employs ultrasound with a wave frequency generally around and >20kHz. This technique involves applying ultrasound, often with the use of a sonotrode, to a pre-emulsion. This ultrasonic treatment plays a crucial role in the formation of NLC, facilitating the reduction of particle size and the homogenization of the lipid carrier system.

1.3.2 Low energy techniques

1.3.2.1 Microemulsions

This technique requires a substantial amount of surfactants to generate a micro-emulsion. It entails blending a melted lipid mixture with a hot surfactant solution until the formation of microemulsion. Following this, with gentle stirring, the hot micro-emulsion is dispersed in a large volume of cold water, usually at a temperature of 2-3°C. This cooling phase results in the solidification of liquid droplets, achieving the desired properties for the lipid carrier system.

1.3.2.2. Membrane contact technique

In the production of nanostructured lipid carriers (NLCs), the membrane contact technique involves substituting the gaseous phase with a molten blend of lipids. As the mixture is tightly passed through the membrane, it enables the formation of small droplets. On the opposite side of the membrane, a hot surfactant mixes, enveloping and stabilizing these liquid lipid droplets with surfactant molecules. This process serves to create and maintain the desired particle size and stability of NLC.

1.3.2.3. Dual Emulsion technique

For the formulation of water soluble drug-loaded-NLCs, Dual emulsion technique is particularly well-suited. It begins by producing a primary (water-in-oil or W/O) emulsion, and then this emulsion is further dispersed in an aqueous solution to generate a secondary (water-in-oil-in-water or W/O/W) emulsion. This approach is ideal for encapsulating hydrophilic drugs within NLCs, allowing for effective drug delivery and enhanced bioavailability.

1.3.3 Solvent utilization techniques

1.3.3.1 Solvent evaporation

The lipids blend is first dissolved in a organic solvent, typically chloroform, and then emulsified by combining with a surfactant. Subsequent evaporation of the organic solvent leads to the formation of nanostructured lipid carriers (NLC) with very small particle sizes ranging from 25nm to 100 nm. This process allows for the creation of small-sized NLC particles, suitable for various drug delivery applications.

1.3.3.2. Solvent Diffusion

The lipids blend is dissolved in a water-semi soluble organic solvent, typically benzyl alcohol, and emulsified using surfactant. Upon dilution of the emulsion with aqueous solvent, the organic solvent diffuses into the aqueous phase, leading to the formation of nanostructured lipid carriers (NLC) with particle sizes below 100nm.

1.3.3. 3. Solvent injection

In this method, the lipids blend is dissolved in a water miscible organic solvent, such as ethanol/acetone, and a surfactant. However, as the organic solvents that are used are easily soluble in water formation of emulsion does not happen. Instead, the lipid precipitates due to the rapid migration of the organic solvent into the aqueous phase. This process prevents the formation of an emulsion but result in the desired nanostructured lipid carriers (NLC) formation.

1.4 Applications of NLCs

The table 1 provides an overview of various drugs that have been encapsulated in nanostructured lipid carriers (NLCs) to enhance their bioavailability. These drug-NLC formulations have shown significant improvements in bioavailability compared to traditional drug suspensions or commercial products. Notable achievements include a remarkable 252.78% increase in bioavailability for Amisulpride when formulated as NLCs [19]. Atorvastatin demonstrated a substantial 3.6-fold improvement in bioavailability compared to both suspension and the commercial product Lipitor VR. Baicalin exhibited approximately 1.9-fold increased values in AUC and a 1.7-fold greater MRT compared to its suspension. These results highlight the potential of NLCs as a promising drug delivery system to enhance the therapeutic effectiveness of various pharmaceutical compounds. Additionally, the table includes information on the solid and liquid lipids used in these formulations, demonstrating the versatility of NLCs in delivering a wide range of drugs with improved bioavailability.

1.5 Drawbacks of NLCs

A concern regarding the safety of nanostructured lipid carriers (NLCs) is the conflicting reports about their potential to trigger oxidative stress. There have been observations of indications of oxidative stress activation, such as the significant activation of cellular defense mechanisms, in HepG2 liver cancer cells following treatment with lipid-based nanoparticles prepared using CTAB.

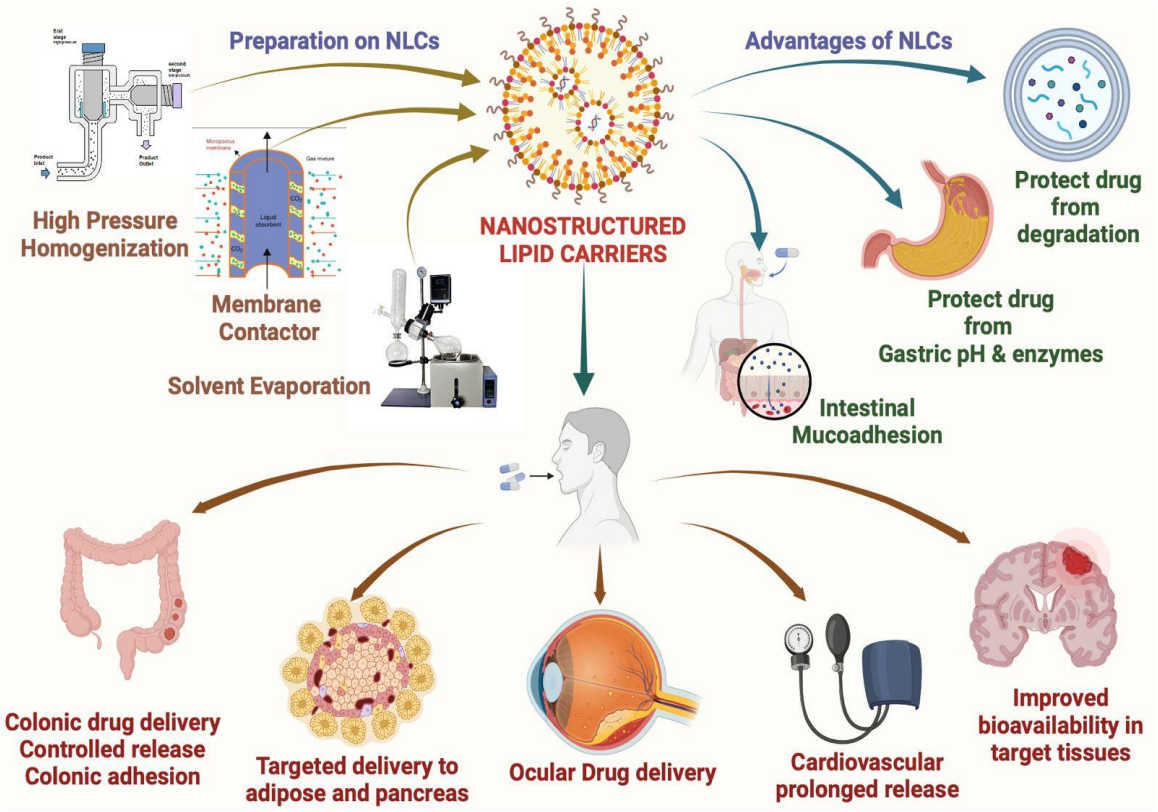

Figure 1: Applications of Nanostructured Lipid Carriers

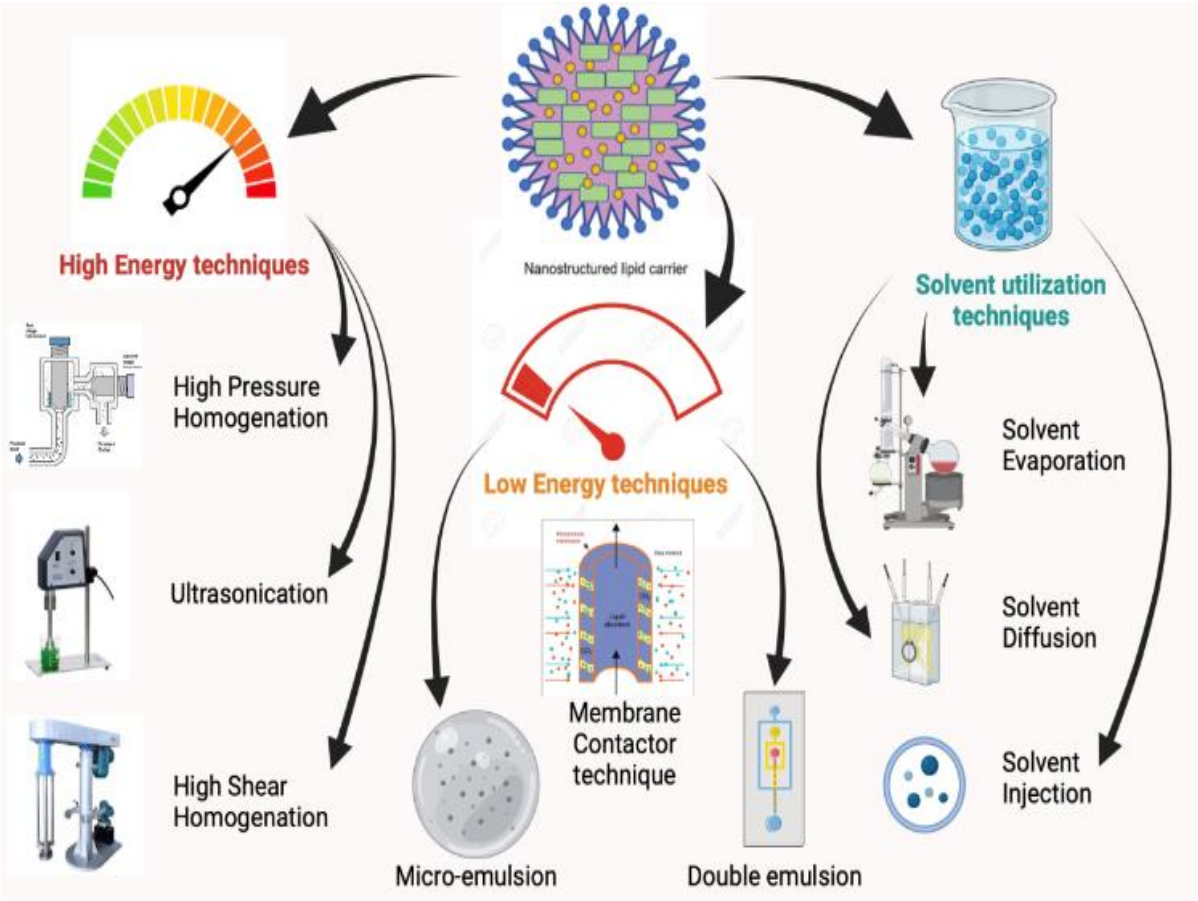

Figure 2: Various methods of preparation of NLCs

Table 1: Application of NLCs to various drugs

Drug	Liquid Lipid	Solid Lipid	Effect achieved	Ref.
Amisulpride	Capryol™-90	Gelucire®43/01	2.5 times increase inbioavailability	[19]
Atorvastatin	Capryol®-PGMC	Glyceryl MonostearateGelucire®43/01Compritol®888	3.6 times increase in bioavailability	[20]
Baicalin	Triglycerides-Medium Chain Length	Glyceryl Monostearate	1.9 times increase in AUC and 1.7 times increase in MRT	[21]
Budesonide	Miglyol-812 N/F	Precirol-ATO-5	2 times lowering of inflammation. Sustained action in colon for over 24 hrs	[22]
Candisartan Cilexetil	Capryol^{tm}-90	Glyceryl Monostearate	Increase in bioavailability	[23]
Docitaxel	Triglycerides-Medium Chain Length	Percifac-ATO-5	4.3 times increase in bioavailability	[24]
Etoposide	Soya Lecithin	Glycerylmonostearate	Extended Tmax and 3.5 times increase in bioavailability	[25]
Ezitimibe	Capmul-PG-8	Glyceryl Monostearate	Increase in solubility and bioavailability	[26]
Ezetimibe	Capryol™-90	Monosteol™	2.5 times increase in solubility and bioavailability	[27]
Felodipine	Oleic Acid	Compritol®888-ATO	2 times increase in bioavailability	[28]
Fenofibrate	Labrafil-M-1944-CS	Compritol®888-ATO	Increase in Cmax and 4 times increase in AUC	[29]
Fenofibrate	Capte-100	Precirol-ATO-5	3.6 times increase in bioavailability	[30]
Glutathione	Oleic Acid	Stearic Acid	Eliminated glutathione degradation by enzymes and prevention of drug structure changes	[31]
Lovastatin	Squalene	Precirol	Controlled drug release	[32]
Mangiferin	Miglyol-812	Glyceryl Monostearate	5.6 times increase in ocular bioavailability	[33]
Miconazole	Capryol™-90, Capryol™-Pgmc	Compritol®888-Ato,Precirol-Ato-5	Better activity at 17-fold lower dose of miconazole.	[34]
Nisoldipine	Oleic Acid	Dynasan-114	2 times increase in bioavailability	[35]
Olanzapine	Castor Oil	Glyceryl Tripalmitate	5.5 times increase in oral bioavailability	[36]
Olmesartan Medoxomil	Capmul-MCM-EP	Gelucire-44/14	5 times increase in bioavailability	[37]
Progesterone	Sesame Oil	Stearic Acid	High permeation through duodenum	[38]
Raloxifen	Glyceryl Caprylate	Glyceryl Monostearate	3.7 times improved bioavailability	[39]
Recombinant HumanEpidermal Growth Factor	Miglyol®182	Precirol®ATO-5	Increased wound healing expression	[40]
Resveratrol	Miglyol-812	Cetyl Palmitate	Release controlled over several hours	[41]
Rosuvastatin	Capryol^{tm}-90 OrOleic Acid	Lauric Acid Or Stearic Acid	1.5 times increase in bioavailability	[42]
Simvastatin	Oleic Acid	Stearic Acid	4 times increase in bioavailability	[43]

Telmisartan	Oleic Acid	Glyceryl Monostearate	3.46 times increase in bioavailability	[44]
Tretinoin	Oleic Acid, Castor Oil	Stearic Acid, Palmitic Acid,	Irritation of tretinoin is lowered, increase in drug loading, prolongation of drug release	[45]
Vinpocetine	Miglyol-812N	Compritol-888-ATO	Sustained release of the drug without bursts in the release	[46]

2. Conclusion

The utilization of nanostructured lipid carriers (NLCs) represents a significant advancement in the quest to enhance the oral bioavailability of pharmaceutical compounds. The success in the improvement of drugs like Amisulpride, Atorvastatin, Baicalin, and numerous others underscore the potential of NLCs in addressing the challenges posed by poor solubility and limited permeability. The versatility of NLCs, with their ability to protect drugs from degradation, create mixed micelles, enhance permeation, and transit through mucus, positions them as an appealing option for drug delivery. It is crucial to acknowledge the potential concerns surrounding NLCs, particularly their impact on oxidative stress. The observed activation of cellular defence mechanisms in response to certain NLC formulations raises questions about their safety and long-term effects. Further research is warranted to comprehensively understand the mechanisms behind these phenomena and to develop NLC formulations that minimize such risks. Future research should delve deeper into the safety profile of NLCs. Understanding the factors contributing to oxidative stress and devising strategies to mitigate them is essential. Long-term studies evaluating the impact of NLCs on cellular health and potential side effects must be conducted to ensure the safety of these drug delivery systems. However, continued research and development are required to address safety concerns, customize formulations, and navigate the path to clinical adoption. These endeavours will unlock the full potential of NLCs and revolutionize drug delivery in the pharmaceutical landscape.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] M.S. Alqahtani, M. Kazi, M.A. Alsenaidy, M.Z. Ahmad. (2021). Advances in oral drug delivery. Frontiers in pharmacology. 12:618411.

[2] S. Basavaraj, G. V. Betageri. (2014). Formulation and drug delivery reduce attrition during drug discovery and development—review of feasibility, benefits and challenges. Acta Pharmaceutica Sinica B, 4(1):3-17.

[3] H. Chavda, C. Patel, I. Anand. (2010). Biopharmaceutics classification system. Systematic reviews in pharmacy. 1(1):62.

[4] N. Poonia, R. Kharb, V. Lather, D. Pandita. (2016). Nanostructured lipid carriers: versatile oral delivery vehicle. Future science OA. 2(3):FSO135.

[5] H. Gupta, D. Bhandari, A. Sharma. (2009). Recent trends in oral drug delivery: a review. Recent patents on drug delivery & formulation. 3(2):162-73.

[6] B. Homayun, X. Lin, H. J. Choi. (2019). Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics. 11(3):129.

[7] V. J. Wacher, L. Salphati, L. Z. Benet. (2001). Active secretion and enterocytic drug metabolism barriers to drug absorption. Advanced drug delivery reviews.46(1-3):89-102.

[8] L. L. Furge, F. P. Guengerich. (2006). Cytochrome P450 enzymes in drug metabolism and chemical toxicology: An introduction. Biochemistry and Molecular Biology Education. 34(2): 66-74.

[9] J.M. Miller, A. Beig, B.J. Krieg, R.A. Carr, T.B. Borchardt, G.E. Amidon, G.L. Amidon, A. Dahan. (2011). The solubility–permeability interplay: mechanistic modelling and predictive application of the impact of micellar solubilization on intestinal permeation. Molecular pharmaceutics. 8(5): 1848-1856.

[10] P. Jaiswal, B. Gidwani, A. Vyas. (2016). Nanostructured lipid carriers and their current application in targeted drug delivery. Artificial cells, nanomedicine, and biotechnology. 44(1):27-40.

[11] N. Kanojia, N. Sharma, N. Gupta, S. Singh. (2022). Applications of nanostructured lipid carriers: recent advancements and patent review.Biointerface Research in Applied Chemistry. 12:638-52.

[12] A. Garces, M. H. Amaral, J. S. Lobo, A. C. Silva. (2018). Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cutaneous use: A review. European Journal of Pharmaceutical Sciences. 112:159-67.

[13] R. H. Awadeen, M. F. Boughdady, M.M. Meshali.(2020). Quality by Design Approach for Preparation of Zolmitriptan/Chitosan Nanostructured Lipid Carrier Particles–Formulation and Pharmacodynamic Assessment. International Journal of Nanomedicine. 9(1):8553-68.

[14] A. Khosa, S. Reddi, R. N. Saha. (2018). Nanostructured lipid carriers for site-specific drug delivery. Biomedicine & Pharmacotherapy. 103:598-613.

[15] N. N. Song, S. Y. Zhang, C. X. Liu. (2004). Overview of factors affecting oral drug absorption.Asian journal of drugmetabolism and pharmacokinetics. 4(3):167-76.

[16] G. Rajalakshmi, C.K. Dhanapal, R. Sundhararajan. (2020). An insight to nanostructured lipid carrier system. Journal of Drug Delivery and Therapeutics. (6-s):10173-82.

[17] J. Natarajan, V.V. Karri, D. Anindita. (2017). Nanostructured lipid carrier (NLC): a promising

drug delivery system. Global Journal of Nanomedicine.1(5):001-6.

[18] A. Beloqui, M.A. Solinís, A. Delgado, C. Évora, A. Isla, A. Rodríguez-Gascón. (2014). Fate of nanostructured lipid carriers (NLCs) following the oral route: design, pharmacokinetics and biodistribution. Journal of microencapsulation. 31(1):1-8.

[19] A.E. El Assasy, N.F. Younes, A.I. Makhlouf. (2019). Enhanced oral absorption of amisulpride via a nanostructured lipid carrier-based capsules: development, optimization applying the desirability function approach and in vivo pharmacokinetic study.American Association of Pharmaceutical Scientists. 20:1-4.

[20] M. Elmowafy, H.M. Ibrahim, M.A. Ahmed, K. Shalaby, A. Salama, H. Hefesha. (2017). Atorvastatin-loaded nanostructured lipid carriers (NLCs): strategy to overcome oral delivery drawbacks. Drug delivery. 24(1): 932-941.

[21] J. Luan, F. Zheng, X. Yang, A. Yu, G. Zhai. (2015). Nanostructured lipid carriers for oral delivery of baicalin: in vitro and in vivo evaluation. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 466:154-9.

[22] A. Beloqui, R. Coco, M. Alhouayek, M.Á. Solinís, A. Rodríguez-Gascón, G.G. Muccioli, V. Préat. (2013). Budesonide-loaded nanostructured lipid carriers reduce inflammation in murine DSS-induced colitis. International journal of pharmaceutics. 454(2): 775-783.

[23] W. Anwar, H.M. Dawaba, M.I. Afouna, A.M. Samy, M.H. Rashed, A.E. Abdelaziz. (2020). Enhancing the oral bioavailability of candesartan cilexetil loaded nanostructured lipid carriers: In vitro characterization and absorption in rats after oral administration. Pharmaceutics. 12(11): 1047.

[24] G. Fang, B. Tang, Y. Zhang, X. Tang. (2015). Improved oral bioavailability of docetaxel by nanostructured lipid carriers: *in-vitro* characterizations, *in-vivo* evaluation and intestinal transport studies. Royal Society if Chemistry. 5:96437-47.

[25] T. Zhang, J. Chen, Y. Zhang, Q. Shen, W. Pan. (2011). Characterization and evaluation of nanostructured lipid carrier as a vehicle for oral delivery of etoposide. European journal of pharmaceutical sciences. 43(3):174-9.

[26] Y.O. Agrawal, U.B. Mahajan, V.V. Agnihotri. (2015). Ezitimibe-loaded nanostructured lipid carrier based formulation Ameliorates hyperlipidaemia in an experimental model of high fat diet. Molecules. 26:1-18.

[27] G. Shevalkar, P. Vavia. (2019). Solidified nanostructured lipid carrier (S-NLC) for enhancing the oral bioavailability of ezetimibe. Journal of drug delivery science and technology. 53:101211.

[28] A.S. Patil, V. Jaknoor, A.P. Gadad, U. Bolmal. (2022). Nanostructured lipid carrier: A potential system for enhanced oral bioavailability of felodipine. Indian Journal of Pharmaceutical Education and Research. 56:77-85.

[29] T.H. Tran, T. Ramasamy, D.H. Truong, H.-G. Choi, C.S. Yong, J.O. Kim. (2014). Preparation and characterization of fenofibrate-loaded nanostructured lipid carriers for oral bioavailability enhancement. American Association of Pharmaceutical Sciences.15:1509-15.

[30] Z. Tian, Y. Yi, H. Yuan, J. Han, X. Zhang, Y. Xie, Y. Lu, J. Qi, W. Wu. (2013). Solidification of nanostructured lipid carriers (NLCs) onto pellets by fluid-bed coating: preparation, in vitro characterization and bioavailability in dogs. Powder technology. 247: 120-127.

[31] A.M. Ahmed, H.A. Mohammed, T.M. Faris, A.S. Hassan, E.M. Aboubakr. (2021). 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.26(24):261-21.

[32] C.C. Chen, T.H. Tsai, Z.R. Huang, J.Y. Fang. (2010). Effects of lipophilic emulsifiers on the oral administration of lovastatin from nanostructured lipid carriers: physicochemical characterization and pharmacokinetics. European journal of pharmaceutics and biopharmaceutics. 74(3):474-82.

[33] R. Liu, Z. Liu, C. Zhang, B. Zhang. (2012). Nanostructured lipid carriers as novel ophthalmic delivery system for mangiferin: improving in vivo ocular bioavailability. Journal of pharmaceutical sciences. 101(10):3833-44.

[34] A. Mendes, A.C. Silva, J.A.M. Catita, F. Cerqueira, C. Gabriel, C.M. Lopes. (2013). Miconazole-loaded nanostructured lipid carriers (NLC) for local delivery to the oral mucosa: improving antifungal activity. Colloids and Surfaces B: Biointerfaces. 111: 755-763.

[35] N. Dudhipala, K.Y. Janga, T. Gorre. (2018). 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. 46(2):1-10.

[36] N. Jawahar, P.K. Hingarh, R. Arun, J. Selvaraj, A. Anbarasan, S. Sathianarayanan, G. Nagaraju. (2018). Enhanced oral bioavailability of an antipsychotic drug through nanostructured lipid carriers. International Journal of Biological Macromolecules. 110: 269-275.

[37] V. Kaithwas, C.P. Dora, V. Kushwah, S. Jain. (2017). Nanostructured lipid carriers of olmesartanmedoxomil with enhanced oral bioavailability. Colloids and Surfaces B: Biointerfaces. 154:10-20.

[38] M. Elmowafy, K. Shalaby, M.M. Badran, et al. (2018). Fatty alcohol containing nanostructured lipid carrier (NLC) for progesterone oral delivery: in vitro and ex vivo studies. Journal of Drug Delivery Science and Technology. 45:230-9.

[39] N.V. Shah, A.K. Seth, R. Balaraman, C.J. Aundhia, R.A. Maheshwari, G.R. Parmar. (2016). Nanostructured lipid carriers for oral bioavailability

enhancement of raloxifene: Design and in vivo study. Journal of advanced research. 7(3): 423-434.

[40] G. Gainza, D.C. Bonafonte, B. Moreno, J.J. Aguirre, F.B. Gutierrez, S. Villullas, J.L. Pedraz, M. Igartua, R.M. Hernandez. (2015). The topical administration of rhEGF-loaded nanostructured lipid carriers (rhEGF-NLC) improves healing in a porcine full-thickness excisional wound model. Journal of Controlled Release. 197: 41-47.

[41] A.R. Neves, M. Lúcio, S. Martins, J.L. Lima, S. Reis. (2013). Novel resveratrol nanodelivery systems based on lipid nanoparticles to enhance its oral bioavailability. International Journal of Nanomedicine. 10(2):177-87.

[42] V. Pokharkar, A. Patil-Gadhe, G. Kaur. (2018). Physicochemical and pharmacokinetic evaluation of rosuvastatin loaded nanostructured lipid carriers: Influence of long-and medium-chain fatty acid mixture. Journal of Pharmaceutical Investigation. 48:465-76.

[43] H. A. Fathi, A. Allam, M. Elsabahy, G. Fetih, M. El-Badry. (2018). Nanostructured lipid carriers for improved oral delivery and prolonged antihyperlipidemic effect of simvastatin. Colloids and Surfaces B: Biointerfaces. 162:236-45.

[44] C. Thapa, A. Ahad, M. Aqil, S.S. Imam, Y. Sultana. (2018). Formulation and optimization of nanostructured lipid carriers to enhance oral bioavailability of telmisartan using Box–Behnken design. Journal of Drug Delivery Science and Technology. 44:431-9.

[45] V.M. Ghate, S.A. Lewis, P. Prabhu, A. Dubey, N. Patel. (2016). Nanostructured lipid carriers for the topical delivery of tretinoin. European Journal of Pharmaceutics and Biopharmaceutics. 108:253-61.

[46] C.-Y. Zhuang, N. Li, M. Wang, X.-N. Zhang, W.-S. Pan, J.-J. Peng, Y.-S. Pan, X. Tang. (2010). Preparation and characterization of vinpocetine loaded nanostructured lipid carriers (NLC) for improved oral bioavailability. International journal of pharmaceutics. 394(1-2): 179-185.