Nanostructured Lipid carrier: A Novel Approach to enhance Solubility, Bioavailability, Stability and Permeability of Drug.

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Abstract:-

The number of studies describing nanostructured lipid carrier (NLC) based formulation has been increased solubility, bioavailability, and stability of drug and formulation. Both solid lipids and Liquid lipids are used to compose the core matrix of Nanostructured lipid carriers. Nanostructured lipid carrier shows some advantages over traditional drug delivery systems, including increase the solubility and ability to enhance storage stability, improved permeability and bioavailability, reduced adverse effect, prolonged half-life, and tissue-targeted delivery.[61] NLCs have attracted increasing attention in recent years, finally, the Application of NLC and the approach of formulating NLC in a different form are discussed. This article will focus on Nanostructure lipid carriers and the development of NLC formulation, their safety, applications, and especially their ability to improve drug delivery. NLC entrapped drugs to facilitate solubility and stability, and because of its crystalline, amorphous nature. It shows to rapidly dissociate after parenteral drug administration and to result in the superior oral bioavailability of poorly water-soluble drugs. The enhancement in solubility, bioavailability, permeability, and stability of some drugs are reviewed.

Keywords: Nanostructured lipid carrier. Solubility, Bioavailability, Permeability, Parentral

Introduction:

NLC was introduced at the end of the 1990s [69] to overcome the potential limitations of SLN described above the formation of lipid crystals affects drug loading, and the ongoing crystallization process towards a perfect crystal causes drug expulsion. NLC has been proposed as the SLN of a new generation; they comprise particles with a solid lipid matrix with an average diameter in the nanometer range. This carrier system can be used to overcome the observed limitations of conventional SLN, thus increasing the payload and preventing drug expulsion. For the production of NLC, very different lipid molecules are often mixed, i. e., blending solid lipids with liquid lipids. The resulting matrix of lipid particles shows a melting point of depression

compared to the original solid lipid. Hence, an increase in drug loading capacity can avoid/minimize potential expulsion of the active compounds during storage and can prevent a reduction in the water content of the particle suspension has lower water content. The Nanostructured lipid carrier are the novel drug delivery system offers more drug loading, Alteration of drug release and improved performance in final dosage forms,Which include cosmetics, parentrals , solid, liquid dosage forms Many hydrophilic and lipophilic drugs are incorporated into NLC,used to improved solubility,bioavailability,permeability of dosage forms.[8]

Salient Features:

Formulation of lipid carrier is a useful solution to enhance Solubility, Bioavailability, better Physical stability and high entrapment of lipophilic and hydrophilic drugs.[65] The NLC improves the solubility of the drug without modifying the structure of a molecule. The GRAS status of lipid is approved and lipids are commercially available so that NLCs is one of the choices for the topically applied drug.[64] The small size of the lipid particles ensures close contact to the stratum corneum thus enhancing drug penetration into the mucosa or skin. Increase of skin hydration and elasticity and These carriers are highly efficient systems due to their solid lipid matrices, which are also generally recognized as safe or have a regulatory accepted status.

Advantages of Nanostructured lipid carrier :

- Regulate and target drug release.
- Enhance the stability of pharmaceuticals.
- Improve drug content.
- Beneficial for carrying lipophilic and hydrophilic drug.
- Avoid organic solvent.
- Simple and economical.
- Cleared GRAS status.

Disadvantages of Nanostructured lipid carrier

- Cause irritation action of some surfactant.
- Cause cytotoxic effects like concentration

Methods of Manufacturing of NLC

Different methods of SLN/NLC formulation are described here-

1. Homogenization techniques
   i. Hot high-pressure homogenization technique
   ii. Cold high-pressure homogenization technique
   iii. Melt emulsification ultrasound (ultrasonication) homogenization technique (High shear homogenization and/or ultrasound technique)
2. Microemulsion technique
3. Emulsification-solvent evaporation technique
4. Solvent displacement or injection technique
5. Emulsification-solvent diffusion technique
6. Phase inversion technique
7. Film ultrasonication dispersion technique
8. Multiple emulsion technique

Formulation application:

NLCs as nano lipid carriers find potential applications in various fields. The applications are divided into two broader aspects covering the therapeutic applications which include enhancement of solubility, Bioavailability, improved permeation through the skin as well as mucosa.and the second part describes the applications in other fields including parentals to reduce irritation and improve the availability of the drug in the systematic circulation. These are discussed below

i. Improved bioavailability:

Enhancement in oral bioavailability can be achieved by means of reducing the hepatic first metabolism.Such a problem with conventional dosage form can be minimized by any suitable novel drug delivery system such as a prodrug concept or by the use of a novel lipid-based systems like lipid nanoparticles, microemulsion, and Self emulsifying microemulsion Solid lipid nanoparticles, Nanostructured lipid carrier, drug delivery system.[66] Polymeric nanoparticles suffered from some drawbacks like toxicity and unavailability of some good techniques for the production of nanoparticles on a large scale. Compare to polymeric nanoparticles,

SLNs gaining some advantages in terms of less toxicological risk because of natural origin lipids. Despite SLNs being good carriers, less capacity of drug loading and expulsion of the drug during storage may require to think of some good technique to overcome such problems. As an effect, nanostructured lipid carriers (NLCs) have been developed, which to some extent can avoid the aforementioned limitations. NLCs can be defined as the second generation of SLNs having solid lipid and liquid lipid (oil) matrix that creates a less ordered or imperfect structure which helps in improving drug loading and decreases the drug expulsion from the matrix during the storage period and reduces the dose and also Improves bioavailability of a drug. [67,68] prepared Lurasidone hydrochloride loaded NLC by solvent evaporation method and improved bioavailability of LRD in the brain by 2 fold. In another work [5] prepared ezetimibe loaded nanostructured lipid carrier loaded NLC to enhanced bioavailability and pharmacodynamic activity of ezetimibe. [51] prepared Asenapine loaded nanostructured lipid carrier to enhanced brain bioavailability and show better safety and therapeutic profile. Some another example of enhancement of bioavailability by preparing NLCs are listed below:

Sr.No.	Drug	Mehod	Purpose	Author	Reference
1.	Lurasidone Hydrochloride	Solvent evaporation method	Improved bioavailability of LRD in brain by 2 fold Lurasidone hydrochloride	Jazuli et.al.	[46]
2.	Ezetimibe	Microemulsion Technique	Enhanced bioavailability of ezetimibe and its pharmacodynamic Potential	G.Shevalkaran d P.Vavia	[5]
3.	Asenapine	high shear homogenization and sonication method.2	NLC enhanced brain brain bioavailability and better therapeutic and safety profile of ANLC	Sanjay Kumar Singh et.al	[51]
4	Simvastatin	Hot melt homogenization	SVNLCs enhanced bioavailability of SV	Gamaleldin I. Harisa	[35]
5.	Nimodipine	High-pressure homogenization	Improved oral bioavailability of NMP	Teng et al	[14]
6.	Epigallocatechin-3-gallate	high shear homogenization and ultrasonication technique,	Increase oral bioavailability of polyphenols	A. Granja et al.	[13]
7.	Thymoquinone	high-speed homogenization followed by ultrasonication	Improve its poor oral bioavailability	Elmowafy et al.	[10]
8	Exemestane	ultrasonication technique	EXE-loaded NLCs improved 3.9-fold in bioavailability	A. Singh et al.	[20]
9	Rosuvastatin	high shear homogenization	Improve bioavailability with 2 folds	Anand Panchakshari Gadad	[55]
10	Apixaben	Ultra-sonication method	Improved oral bioavailability	Mowafaq M. Ghareeb	[28]
11	Lacidipine	Solvent injection technique	Improved relative bioavailability(4-fold) of Lacidipine loaded NLCs to Lacidipine	Senthil Kumar M et al.	[19]
12	Raloxifene	solvent diffusion method	improvement in bioavailability of poorly soluble RLX	Nirmal V. Shah	[16]

Table No.1: NLCs formulation for enhancement of bioavailability

ii. Improved solubility:

solubility enhancement of poorly water-soluble drugs is one of the key challenges in pharmaceutical research. Various techniques have been reported to increase the dissolution rate of poorly water-soluble drugs, such as cyclodextrin complexation approach, freeze-drying or lyophilization, solid dispersion strategy, liposomal formulations, and solid lipid nanoparticles approach. Kelidari et.al prepared spironolactone loaded NLC formulation and reported as one of the efficient ways to enhance the solubility of the poorly water-soluble drug.[50] Lipid nanoparticle can enhance the dissolution rate by oral bioavailability of water insoluble drug.The increase in the dissolution is mainly due to a significant reduction in the drug particle size down to the nano range leading to the higher surface area available for dissolution. (Musallam Almousallam) also prepared Dacarbazine loaded NLC to improve drug solubility and prolong drug release [15].

Sr.No.	Drug	Method	Purpose	Author	Reference
1	Spironolactone	Probe ultra-sonication method	Improved 5.1and 7.2-fold in the release of the drug loaded NLc	Kelidari et al.	[50]
2.	Dacarbazine	High shear dispersion	improve the drug solubility and prolong drug release	Musallam Almousallam	[15]
3.	Repaglinide	emulsification–ultrasonification Technique	NLC shows better solubility and sustained release	Swidan et al.	[54]
4	Isotretinoin	Hot homogenization technique.	Water solubility enhanced by 5.22 folds	Shailesh L. Patwekar	[36]
5	Valsartan	Melt emulsification technique	Improving solubility and bioavailability of valsartan	Ravish J.Patel	[40]
6.	Sylimarin	Emulsion evaporation method	Enhancing the solubility and intestinal permeability of lipophilic SLM.	Vieri Piazzini et.al	[43]

Table No.2: NLCs formulation for enhancement of Solubility

iii. Improved stability:

Nanostructured lipid carriers were developed as an alternative carrier system to emulsions, liposomes, and polymeric nanoparticles. NLC help to improve the stability of various cosmetic, Vitamins and other drugs nanoparticles.[62] The stabilities (chemical, photo, and storage) of drug nanoparticles like Vitamin D, Candesartan, Spironolactone, Mometasone Furoate, Efavirenz was improved when these drugs are converted into second-generation NLC (Nanostructured lipid carriers). lipid nanoparticles have a beneficial role in the improvement of stability of drug-loaded nanoparticles. (Thakkar.et.al) Prepared Candesartan cilexetil loaded NLC by Melt emulsification and ultrasonication method and improved stability of the drug [34] In another work (Norhayati Mohamed Noor) Prepared Dutasteroid NLC and improved stability of the drug [45]. (Kaur et.al) Prepared Mometasone furoate loaded NLC and improved stability of NLC form [58]. Some other examples are listed below:

Sr.No.	Drug	Method	Purpose	Author	Reference
1	candesartan cilexetil	Melt emulsification ultrasonication method	Improved stability of formulation	Thakkar, et al	[34]
2	Dutasteride	melt-dispersion ultrasonication method	Improved stability of DST-NLCs	Norhayati Mohamed Noor1	[45]
3	Mometasone Furoate	Microemulsion technique	Prepared formulation shows more stability in NLC form	Kaur et al.	[58]
4.	Efavirenz	Melt emulsification ultrasonication technique	High encapsulation efficiency and long term stability.	V. Pokharkar et al.	[53]
5.	Retinyl palmitate	ultrasonication method	NLC provide better stability than Microemulsion	Pamudji et al.	[60]
6.	Isotretinoin	Hot homogenization technique method	Improve spredability and stability of water insoluble drug.	Shailesh L. Patwekar	[34]
7.	Podophyllotoxine	emulsion-evaporation and low temperature-solidification methods	Prepared NLC formulation stable at 4℃ for more than 6 months.	GAO et al	[6]
8.	Loratadine	High pressure homogenization method	Prepared physically stable formulation	Uner et al	[18]
9.	Mefenamic acid	Emulsion and evaporation method	NLC matrix confers better storage stability and higher suitability for the controlled release.	S. Khurana et al.	[17]
10..	Hirsutenone	high pressure homogenization (HPH) method	The NLC formulation of HST show greatest stabilization of HST	S. G. Lee et al.	[25]
11.	Green Robusta Coffee Beans Extracts	high shear homogenization and ultrasonication technique	NLC improve the stability of the extract and increase skin	Nichcha Nitthikan et.al.	[26]
12.	Cholecalciferol	Emulsion evaporation method	NLC loaded emulsion improves stability of Vitamin	Tae-Rang Seo	[41]
13.	NLC loaded in Aliginate hydrogel	hot highpressure homogenization technique (HPH)	Enhance physical stability,	R. Sun and Q. Xia	[37]
14.	Coumarin	Probe sonication	NLCs showed good physical stability	J. Iemsam-Arng et al.	[27]
15.	Furosemide	Solvent diffusion method	Furosemide loaded NLC are stable	Anurughma and Neema	[42]

Table No.3: NLCs formulation for enhancement of stability

vi. Parenteral:

Solid lipid nanoparticles has been intensively studied as drug delivery systems for several routes of administration such as peroral, parenteral, dermal, and topical delivery. Parenteral administration of lipidic

material came to success when submicron emulsion based products, such as Diazemuls (Diazepam, Actavis, Zug, Switzerland) and Diprivan (Propofol, AstraZeneca, London, UK), were commercialized in the market of the pharmaceutical industry. Liposomes represent the first generation of the novel lipidic carriers, which revolutionized the scenario in parenteral drug delivery. The successful commercialization of various injectable liposomal products such as AmBisome® (Amphotericin B, Gilead Sciences, Foster City, US), Doxil® (Doxorubicin, Centocorortho biotech, Philadelphia, US) and DaunoXome® (Daunorubicin, Gilead Sciences, Foster city US) [70] indicates the potential advantages of liposomes as novel lipid carriers. The potentials of nanoparticles-based lipidic carriers such as SLN and NLC have thus been explored in the parenteral drug delivery. The administration of SLN or NLC via the parenteral route improved bioavailability, targeting and enhanced cytotoxicity against multidrug-resistant cancer cells have been observed. Liu and coworkers developed docetaxel loaded NLC (DTX-NLC) to reduce toxicity and improve therapeutic efficacy for parenteral delivery. The nanostructured lipid carriers possess the advantages of reducing the high dose-dependent toxicity of anticancer drugs and continuing research will facilitate the clinical application of the current study. In another study, Jia and coworkers developed silybin loaded NLC to see the effect of biodistribution and pharmacokinetics after parenteral administration. Silybin loaded NLC showed higher AUC values and circulated in the bloodstream for a longer time compared with silybin solution. The tissue distribution demonstrated high uptake of silybin-NLC in RES organs particularly in the liver [70]

Sr.No.	Drug	Method	Purpose	Author	Reference
1.	Trans retinoic acid	novo emulsification method	Prepared NLC loaded Intravenous injection to improve drug loading	Chinsriwongkul et al.	[8]
2.	Paclitaxel	solvent emulsification-diff usion method	Prepared NLC loaded intracellular carrier.	JaberEmami et.al	[28]
3.	β –Artemether	Microemulsion technique	Intravenous b-artemether formulation	Patil et al.	[51]
4.	Tamoxifen	high-pressure homogenization method.	Prepared Tamoxifen NLC laoded intravenous formulation.	Chaw Yee BehID	[2]

Table No.4: NLCs formulation for parentral application.

v. Improved permeation:

Poorly water-soluble drug candidates are becoming more prevalent. It has been estimated that approximately 60–70% of the drug molecules are insufficiently soluble in aqueous media and have very low permeability to allow for the inadequate and reproducible absorption from the gastrointestinal tract. Incorporation of the active poorly water-soluble component into inert lipid vehicles such as oils, surfactant dispersions, solid dispersions, solid lipid nanoparticles(SLN)
emulsions, microemulsions, nanoemulsions, micro/nano emulsifying formulations, and nanostructured lipid carrier(NLC), and improved the permeability of the drug through the mucosa and skin. Porkorn kraisit et.al prepared a nanostructured lipid carrier by using a hot homogenization method to improved permeability of Triamcinolone acetamide. In another work Jong-Suep Baek et.al prepared Tadafil loaded NLC to improved skin permeability of tadalafil. Brijesh Shah and dignesh hunt) prepared venlafaxine loaded NLC to enhance nasal permeation. Some other examples are listed below:

Sr.No.	Drug	Method	Purpose	Author	Reference
1.	Triamcinolone Acetonide	hot homogenization method	TA-loaded NLC formulations had a higher permeation	Pakorn Kraisit , Narong Sarisuta	[47]
2.	Tadalafil	hot-melted ultrasonic method	NLC improved the skin permeability of tadalafil.	Jong-Suep Baek Cuong Viet Pham Chang-Seon Myung Cheong-Weon Cho	[3]
3.	Venlafaxine	high shear homogenization method	Enhanced nasal permeation	Brijesh Shah, Dignesh Khunt	[57]
4.	Lidocain	solvent diffusion method.	Improved drug diffusion and permeation.	Zhao et al.	[12]
5.	Silymarin	solvent diffusion followed by ultrasonication method	Improved permeation of syllimarine via topical application.	Babar Iqbal et.al.	[29]
6.	All-trans-Retinoic Acids	de-novo emulsification method	Increased the skin permeability	Ponwanit Charoenputtakun	[9]
7.	Variconazole	high-pressure homogenization	higher skin permeation and retention .	Seh Hyon Songet.al	[44]
8.	Betamethasone dipropionate	high shear homogenization & sonication	increase the penetration of drug to deeper skin layers	Pierre A. Hanna	[21]
9.	Nepafenac	Melt-emulsification and ultra-sonication techniques.	enhanced penetration of nepafenac into HCECs	Shihui Yu et.al	[48]
10	Deacetylated	Melt emulsification method.	NLC Enhanced corneal penetration in ocular drug delivery system	Tian et al.	[59]
11.	Saquinavir	High pressure homogenization technique	NLCs enhanced 640 SQV permeability up to 3.5-fold.	A. Beloqui et al.	[56]
12.	Zingiber zerumbet	Ultrasonication technique	enhance the penetration to the deeper layer of skin	N. A. Rosli	[39]

Table No.5:NLCs formulation for enhancement of permeation of drug.

Conclusion:

Lipid formulations are promising approach for various categories of drug molecules having challenging drug properties. NLCs formulation has shown great potential to be given by the oral route, as it improves the oral bioavailability by bypassing the first-pass effect and also overcomes the disadvantage of SLN formulation. The NLCs formulation of various lipophilic, as well as hydrophilic drugs, are mentioned above. NLCs are biocompatible, biodegradable, non-irritating, non-sensitizing. Although, few works have been done on the

solubility, bioavailability, stability and permeability enhancement of drugs. Among the various lipid formulations, the Nanostructured lipid carrier offers additional advantages in the enhancement of solubility, bioavailability, permeability and stability ease of manufacture and scale-up. The Nanostructured lipid carrier is designed to overcome issues like poor solubility, bioavailability, stability, and permeability of hydrophilic as well as Lipophilic drug.

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