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Review Article

An Insight to Nanostructured Lipid Carrier System

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Abstract

In pharmaceutical field, many drugs are being invented to combat the existing new diseases. The winds of change in the drug scenario are blowing forcefully worldwide. The emergence of new technologies provides an unique opportunities to exploit novel approaches in drug delivery. A shift from conventional drug delivery to novel drug delivery is noticed as shift from conventional drug delivery suffers from various drawbacks, But these new mighty compounds in drug therapy solely are not sufficient to meet the today's need. There is an urgent need for the smart technology, as the drugs available suffer from serious problems like poor solubility and poor bioavailability. Most of the drugs that are available therapeutically comes under BCS class II ie, poorly soluble and high lipophilic. To assure progress in drug therapy, the development of new drugs merely is not sufficient. Issues arising in delivery of new drugs should also be addressed. Thus there is an emergent need to improve the bioavailability of these drugs, the only remedy or boon for such drugs is the discovery of some smart technologies which can improve the bioavailability of these drugs. Nano drug delivery systems are the one such universal approach which fulfills the lacuna, which exists in conventional drug delivery systems. These Nano drug delivery systems, improves the pharmacokinetic profiles of many drugs. In 1980 K. Eric Drexler developed and popularized the concept of nanotechnology. In this review a deep insight on Nano structured lipid carriers is discussed elaborating its birth, significant qualities compared to other colloidal systems, its structure, characteristics, preparation and application are spotted.

Key words: BCS class, Lipophilic, Nano technology, Nano structured lipid carrier.

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INTRODUCTION:

A pharmaceutical carrier scheme is needy with ideal characteristics like efficient drug loading capacity, free from toxicity, controlled release characteristics, drug targeting and good stability. Colloidal carriers like emulsions, liposomes, micro particles and niosomes suffered from certain flaws like stability issues, lack of production techniques, phagocytosis by reticulo endothelial system¹. Nano carriers refer to materials prepared by the dissolution or dispersion of drugs with a variety of nanoparticles, which may be classified as either nanospheres or nanocapsules. The materials for the preparation of nanoparticles may be divided into polymers and lipid materials. The former is referred to as PNP, which includes polymer nanocapsules and nanospheres as well as polymeric micelles. The latter is called the lipid nanoparticle, and includes Nanoliposomes solid lipid nanoparticles and Nano structured Lipid carriers.

BIRTH OF NLC

Nano drug delivery systems may be of nanoparticles, nano carriers, nano emulsion or suspensions, fullerenes, nanotubes, quantum dots, nanopores, dendrimers, liposomes, magnetic nanopores and radio controlled nanoparticles.

Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. Initially synthetic/natural polymers were ideally used to manufacture .It suited to optimize drug delivery and reduce toxicity. Speiser and co-workers in the mid-seventies introduces polymeric nanoparticles. This developed as a variable substitute to liposomes as drug carriers after few years. Any nano drug delivery's success is by its ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. In spite of overwhelming advantages of polymeric nano particles, not

many products made it to market because of certain stumbling blocks like presence of solvent residues left over from production, the cytotoxicity of the polymers, and the lack of low-cost, qualified large scale production units yielding a product of a quality acceptable by the regulatory authorities, the scarcity of safe polymers have limited the wide spread application of nanoparticles to clinical medicine²

To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals.³ These lipid nanoparticles are known as solid lipid nanoparticles (SLNs) developed in 1991. In 1999, the complete patent rights for production of SLN by high pressure homogenization have been acquired by SkyePharma⁴. Great progress was made in treating different diseases using SLN. SLNs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposomes and polymeric nanoparticles). They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLN has special qualities such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, nutraceuticals and other materials.

SLN are like nanoemulsions differing only in the nature of lipids. By replacing liquid lipid with solid lipid, the formulation achieved greater potential. This benefited with enormous combined advantages of polymeric nanoparticles, fat emulsions, liposomes while avoiding their disadvantages. Being solid at room temperature, ease of dosing and handling, high meltingpoint waxes like glycerides or waxes form major constituent.⁵⁻⁷ Being an attractive colloidal carrier it overcome number of hurdles associated with conventional colloidal carriers.

ADVANTAGES OF SLN:

1. The size of sln is very significant, being in Nano size of 120-200 nm, they bypass Reticulo endothelial system thus bypass liver and spleen.⁸
2. Analogy with colloidal carriers' solid lipid nanoparticles stay stable for even 3 years.⁹⁻¹⁰
3. Controlled release of drug can be accomplished for several weeks. Further by attaching or coating with ligands, drug targeting is also guaranteed.¹¹⁻¹⁵
4. Less toxic when compared with polymeric particles due to embodiment of physiological biocompatible lipids.¹⁶⁻¹⁸
5. Feasibility of incorporating both hydrophobic and hydrophilic drugs.¹⁸
6. Due to immobilization of drug molecules by solid lipids the labile and sensitive drugs can be protected from chemical, photochemical or oxidative degradation.¹⁸
7. Excellent reproducibility with a cost effective high-pressure homogenization method as the preparation procedure¹⁹
8. Improvement and reduction in the variability of GI absorption of poorly water-soluble, lipophilic drugs.²⁰
9. Progress of sln is widespread. It find its applications in oral, parenteral, topical, peroral, transdermal, gene carrier therapy, cosmeceuticals, anti tubercular therapy, cancer therapy, proved as efficient in delivering

antiretroviral drugs to brain, as a potential and new adjuvant for vaccines.^{21,22}

10. Ease of manufacturing and regulatory approval, low cost.²³

The trade name 'SLNTM' has been registered world-wide in the pharmaceutical area, as has 'LipopearlSTM' for cosmetics. These SLN were attracting number of formulators worldwide till they found out certain shortcomings or flaws in it.

Drawbacks of SLN:²⁴

1. Limited drug loading capacity
2. Gellation tendency
3. Drug leakage during storage.
4. High water content of sln dispersion
5. Reduced particle concentration
6. Polymorphic transition.
7. Low incorporation due to crystalline structure of solid lipids.
8. Particle growing

To overwhelm the hurdles, at the turn of millennium, nanostructured lipid carriers or NLC, were developed to resolve, in some cases, the problems raised by SLNs. NLCs are produced by controlling the mixing of solid lipids with liquid oil, leading to special nanostructures in the matrix. The matrix of NLCs is composed of mixture of spatially different lipid molecules, normally mixture of solid and liquid lipid, which makes more imperfection in the matrix to accommodate more drug molecules than SLN.

NLC's are made up of a binary mixture of solid-lipid and a liquidlipid (oil) as a hybrid carrier having an average size of 10-500 nm. The mixture NLC's is consist of long chain of liquid and lipid (oil) of ratio 99.9: 0.1 and having a short chain of solid and lipid having a ratio of 70:30²⁵⁻²⁷.

These NLC appeared in late 1990's. This involves modification of SLNs by mixing solid and lipid nanoparticles followed by heating and cooling to form a stable system.

Qualities of NLC:

1. Despite of containing liquid lipid NLC behave as solids at room/ body temperatures. This is achieved by controlling the content of liquid lipid.
2. NLC strongly immobilize the drugs and prevent it from coalescing.
3. Particle size of NLC range from 10-1000nm.
4. The presence of liquid lipids with different fatty acid C-chains produces NLC with less organized crystalline structure and therefore provides better loading capacity for drug accommodation²⁴
5. By high-pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30-80%.
6. Liquid carrier materials in NLC have a higher solvent capacity. This increased solvent capacity is due to additional active incorporation space created through the generation of crystal imperfections due to the presence of liquid lipid, in the highly ordered crystal structure of the solid lipid material²⁸

7. A biphasic drug-release pattern is observed in NLC, which results from a rapid release of active from the liquid phase of the NLC, with a comparatively slower release of the API from the solid lipid portion of the NLC. This release pattern can be modulated by adjusting the proportions of the liquid and solid lipid carriers within the NLC.²⁹
8. The reason for good drug loading is, increased solubility of drug in liquid lipid than in solid lipid.
9. It has stable physical and chemical properties.
10. There is new and modified type of NLC's are available which is having a meticulous nanostructure. These meticulous nanostructures are responsible and also help to improve the stability of the formulations as well as increase the bioavailability, drug loading.³⁰

ADVANTAGES OF NLC ³¹⁻³⁵

1. A disordered crystal structure which prevents drug leakage.
2. A high drug pay load due to its microstructure.
3. The carrier material used is biodegradable and low in vivo toxicity.
4. The surface of NLC can be modified with surfactants for prolong release pattern
5. NLC's exhibits organizational targeting pattern
6. Better physical stability
7. Ease of preparation and scale-up,
8. Increased dispersability in an aqueous medium
9. High entrapment of lipophilic drugs and hydrophilic drugs
10. Controlled particle size
11. Furthermore, lipid nanoparticles are able to enhance the chemical stability of compounds sensitive to light, oxidation, and hydrolysis ³²
12. BCS class II/IV drugs bioavailability is significantly increased by using this novel lipid transport system.
13. Extended release of the drug,
14. Small size of the lipid particles ensures close contact to the stratum corneum thus enhancing drug penetration into the mucosa or skin.
15. Nlc has slower polymorphic transition and low crystallinity index, membrane permeability and drug release, creaming, gelling, and particle aggregation during storage compared with sln.³³
16. Improve benefit/risk ratio, easy approval by regulatory agencies, easier to validate.
17. In case of topical preparations, give local action when applied. It also acts as local reservoir, controlled release of drug, as penetration enhancer. Due to small size increase penetration into gaps between stratum corneum cells.³⁴
18. Studies have proven that this new Nano platform improved oral bioavailability drugs promoting their intestinal absorption.³⁵

19. This nano system has shed light of hope to treat many chronic diseases by modulating drug efficacy and sustained release of drug.
20. These lipid-drug conjugate (LDC) nanoparticles providing high loading capacities for hydrophilic drugs. Many researchers have proved these nlc are particularly useful for targeting water-soluble drugs to the brain.

Limitations of NLC ³⁶⁻³⁷

NLC being so successful in targeted drug delivery compared to SLN and other colloidal drug delivery systems, it also suffers from certain drawbacks like:

1. Cytotoxic effects related to the nature of matrix and concentration.
2. Certain surfactants used in formulation may have irritating and sensitizing action.
3. Still efficient methods are not there in NLC for delivering Protein, peptide and gene delivery.
4. NLC is still nascent, there is lack of sufficient clinical and preclinical trials in many areas particularly bone repair.

MICRO STRUCTURE OF NLC: ³⁸⁻⁴¹

In comparison with SLN, which is composed of perfect brick wall by using highly purified lipids the micro structure of NLC (shown in figure 1) is different disorganized structure. However, a high degree of spatial organization may lead to low drug loading. A more disorganized structure may be more advantageous. This microstructure disorganization leads to the presence of voids which can accommodate higher amount of drugs/bio active molecules. Such microstructural disorganization can be seen in Nano structured lipid carrier system (NLC) which is achieved by mixing solid lipid with liquid lipids or by using non purified raw materials instead of using highly purified lipids with relatively similar molecules.

Three types of NLC have been described: (I) imperfect type, (II) amorphous type and (III) multiple type

I) Imperfect type NLC (imperfectly structured solid matrix):

It is created when different types of lipid molecules are used to build the core of the particle. It is crystalline but presence of voids help to accommodate bioactive molecules or drugs. Mixing small amounts of chemically very different liquid lipids (oils) with solid lipids in order to achieve highest incompatibility leads the highest drug payload.

(II) Amorphous type (structureless solid amorphous matrix):

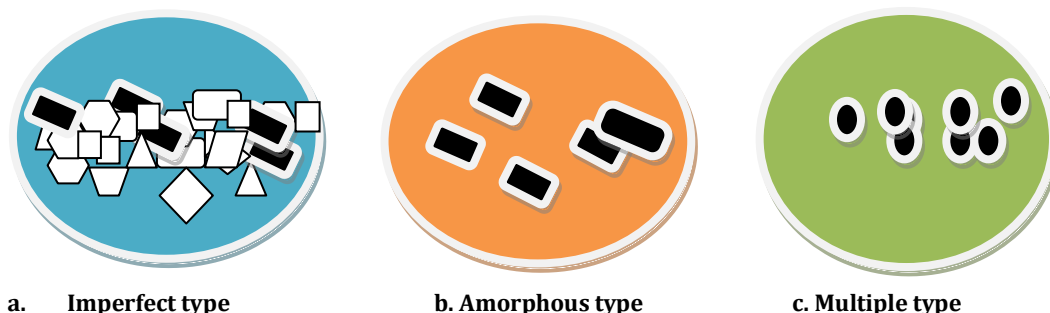
These are formed when particles are cooled they are not crystallize remaining in amorphous state. Therefore drug expulsion is minimized, as the transformation from polymorphic form to another does not occur. This kind of NLC can be achieved by mixing solid lipids with special lipids, e.g. hydroxyl octacosanyl hydroxystearate, isopropylmyristate or medium chain triglycerides such as Miglyol 812. ³⁸

(III) Multiple types (multiple oil in fat in water (O/F/W) carrier):

This resembles multiple emulsion type in which solid lipid core contains liquid oil compartments. This type is observed when liquid lipid is more than solid lipid. At high temperature complete miscibility occurs but during cooling

process precipitation occurs in the form of tiny droplets due to exceeding solubility of oil in solid lipid compound. Solubility of many drugs in a liquid lipid is higher than in a solid lipid. It has been reported that in case of lipids which lack appropriate drug solubilities, addition of a higher

amount of liquid lipid to the lipophilic phase combined the advantages of the solid matrix which prevented drug leakage, and of the liquid regions (oily nanocompartments) which showed comparatively high solubility for lipophilic drugs³⁹⁻⁴¹



a. Imperfect type

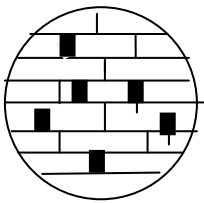
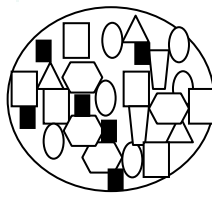
b. Amorphous type

c. Multiple type

Figure 1 Different types of NLC

Comparison between SLN and NLC⁴²⁻⁴⁴

Table 1: Comparison between SLN and NLC

SLN	NLC
Composed of solid lipid dispersed in aqueous medium, stabilized by surfactant	Composed of blend solid lipid and Liquid lipid (oils)
Ratio of solid lipid 1-30%w/w; Surfactant 0.5-5%w/w	Weight ratio of solid lipid and Liquid lipid 70:30 upto 90:10
Micro structure is highly ordered lipid matrix.	Microstructure is less ordered lipid matrix
Types of SLN a. Type I or homogeneous matrix model, b. Type II or drug-enriched shell model and c. Type III or drug-enriched core model.	Types of NLC Imperfect type Amorphous type Multiple type
Structure of SLN 	Structure of NLC 
Drug loading is less due to its high degree of order, the number of imperfections in the crystal lattice is reduced leading to drug expulsion	Drug loading is high as lipid matrix is less ordered. Having disordered structure provides higher space for drug loading Also due to high solubility of drug in liquid lipids.
Drug expulsion due to polymeric transition occur during storage	No drug expulsion
High water content (70-90.9%)	Less water content
During storage loss of drug due to lipid crystallization	No loss of drug
β modification of lipid to metastable polymorph occur	No modification
Slower release of drug as mobility of drug in crystalline form is less.	Faster release of drug as mobility of drug in crystalline form is less.

INFLUENCE OF EXCIPIENTS IN NLC:

The essential ingredients for the formulation of NLC are solid lipid, Liquid Lipid, Water and Emulsifier.

1. Lipids:

Lipids form the major constituents of NLC.

a. Solid lipid: They should be biodegradable, biocompatible, chemically stable without any toxic effects. The solid lipids used are solid at room temperature but melt at temperatures above 80°C. The lipids used are given in Table no: The selection of lipids for formulating is done by testing the solubility of drug in lipid. Since it has direct impact on drug entrapment and loading efficiency.⁴² Moreover the stability of drug and lipid is also a key feature. Compatibility studies must be done between drug and lipid. There should not be any phase separation till 24 hours of mixing drug and lipid for acquiring stable NLC.⁴³

b. Liquid lipid: The Liquid lipids used are either digestible oils from natural sources or oily components. These should be biocompatible, cost effective, non irritating. All the lipids used should be approved by regulatory agencies as GRAS (generally recognized as safe). The solid lipid to liquid lipid typical weight ratio as per literature ranges from 70:30 to 90:10. A melting point depression occurs when liquid lipid mixes with and solid lipids compared to the pure solid lipid. A decrease in particle size was observed with increment in liquid lipid due to decrease in viscosity and high molecular mobility. The resulting structure remains solid at room temperature with API-loaded liquid pocket.⁴⁴⁻⁴⁶

Quantity of Liquid lipid play a significant role in tailoring particle size and release rate of NLC since it may lead to reduction in viscosity and surface tension thereby producing NLC with smaller size, high surface area and promoting high percent cumulative drug release⁴⁷.

The liquid lipids used most commonly are listed in Table 2. Moreover vegetable oils, oils from plant sources, fish oils are gaining interest recently.

In short the role of lipids is salient frame work in NLC. With increase in lipid matrix, the particle size, entrapment efficiency are enhanced it may cause increase in viscosity, leading to reduction in drug escaping tendency and higher entrapment of drug. Thus selection of lipid contents is very pivotal in developing NLC with desired characteristics.

2. Emulsifiers:

In order to stabilize the system emulsifiers are used. Either lipophilic or hydrophilic emulsifiers are used. Combination of both can be used to prevent particle aggregation efficiently. They coat the surface of NLC there by providing long term stability. Emulsifiers are the fundamentals because they help in dispersing one immiscible phase with other. They tend to reduce the interfacial tension between two phases and increase the surface area of liquid droplets thereby yielding small particles.⁴⁸ The quantity of emulsifier added has influence on release kinetic profiles and entrapment efficiency. Reduction in interfacial tension by emulsifier occurs only up to a specified concentration after than increase in amount of emulsifier added leads to agglomeration may occur due to excess coating of particles and decrease in zeta potential.⁴⁹⁻⁵¹ Emulsifiers with HLB value ≥ 18 hydrophilic surfactants yields faster release pattern. A blend of surfactant is also used to enhance stability and viscosity of NLC.⁵² In a nut shell selection of emulsifier, its concentration is significant in fabrication of NLC with effective drug delivery, reduced particles size, narrow size distribution assuring predictable drug release.

PEG is added in NLC to prevent uptake by reticuloendothelial system and to prolong the circulation time of drugs.

Table 2 Excipients used in NLC

Excipients	Examples
Solid lipid	Tristearin, stearic acid, cetyl palmitate, cholesterol, Precirol® ATO 5, Compritol® 888 ATO, Dynasan® 116, Dynasan® 118, Softisan® 154, Cutina® CP, Imwitor® 900 P, Geleol®, Gelot® 64, Emulcire® 61
Liquid lipid	Medium chain triglycerides, paraffin oil, 2-octyl dodecanol, oleic acid, squalene, isopropyl myristate, vitamin E, Miglyol® 812, Transcutol® HP, Labrafil Lipofile® WL 1349, Labrafac® PG, Lauroglycol® FCC, Capryol® 90
Lipophilic Emulsifier	Myverol® 18-04K, Span 20, Span 40, Span 60,
Hydrophilic Emulsifier	Pluronic® F68 (poloxamer 188), Pluronic® F127 (poloxamer 407), Tween 20, Tween 40, Tween 80, polyvinyl alcohol, Solutol® HS15, trehalose, sodium deoxycholate, sodium glycocholate, sodium oleate, polyglycerol methyl glucose distearate
Amphiphilic Emulsifiers	Egg lecithin, soya lecithin, phosphatidylcholines, phosphatidylethanolamines, Gelucire® 50/13

MECHANISM OF DRUG RELEASE FROM NLC:

Partition coefficient of drug, particle size, dispersion of drug in lipid matrix influences the drug release. The drug release behavior from NLCs is dependent upon the production temperature, emulsifier composition, and oil percentage incorporated in the lipid matrix. Drug release is inversely

proportional to the partition coefficient of the drug. Decrease in particle size to nanometer scale causes increase in surface area, thus higher drug release. Drug should be dispersed equally in any lipid matrix for prolonged release of drug.

Drug release from lipid particles occurs by diffusion and simultaneously by lipid particle degradation in the body. Apart diffusion and degradation, in some cases, it might be desirable to have a controlled fast release. The release can be triggered by an impulse also. Since NLCs are in highly unordered lipid structures, to initiate a burst drug release, there is a need to convert highly unordered lipid structure to more ordered structure. This can be accomplished by trigger impulse. By converting into a more ordered structure with the help of triggering impulse, a burst drug release occurs.⁵³

This impulse can be of any thing such as increase in temperature, water evaporation in case of topical preparations. The drug amount in the outer shell of the

nanoparticles and on the particulate surface is released in a burst manner, while the drug incorporated into the particulate core is released in a prolonged way. Sustained release of the drugs can be explained considering both drug partitioning between the lipid matrix and water, as well as the barrier function of the interfacial membrane. The dialysis method and the utilization of the Franz cell are the modes for measuring *in vitro* drug release from nanoparticles. The interpretation of *in vitro* drug release profiles should consider the specific environment in the *in vivo* status. Enzymatic degradation of lipid nanoparticles may be influenced to a relevant extent by the composition of the particles.^{54-55.}

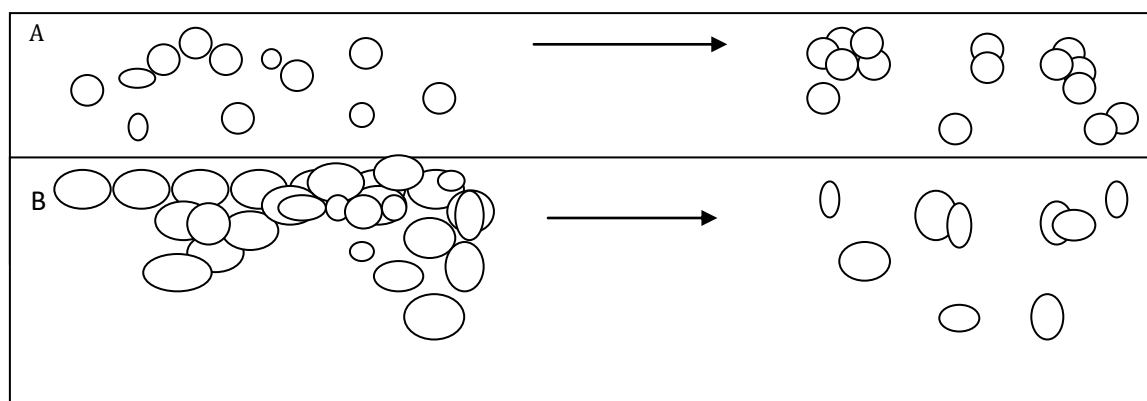


Figure 2: Modulation of drug release.

A. SLN - Drug release as aggregates

B. NLC - Drug release in disperse manner

DRUG DELIVERY 56-63

The lymphatic system is part of the circulatory system, which is composed of an intricate network of conduits that carry lymph. The primary function of the system is to carry interstitial fluid accumulation back to the circulatory system and to transport immune cells to the lymph nodes. Drug incorporated in NLCs reach the systemic blood circulation through the intestinal lymphatic system, as opposed to entering the systemic blood circulation through the portal blood. By this two major benefits are reduction in first-pass metabolism and an increased overall bioavailability for the active drug. In addition to intestinal lymphatic uptake, NLCs can be delivered by means of other lymphatic pathways, including subcutaneous and pulmonary lymphatic uptake. Subcutaneous and pulmonary delivery of NLC have enormous advantages such as active accumulation at the site of administration, avoidance of first pass metabolism, prolonged release, low clearance, reduced dosing frequency, less systemic toxicity etc.,

Darunavir is effective against wild type and PI-resistant HIV, and has a very low oral bioavailability of 37%. It is formulated with ritonavir to increase its bioavailability to 82%. This low bioavailability is common for oral anti-retrovirals, which typically have low-aqueous solubility, high CYP-mediated metabolism, and are often a substrate for P-glycoprotein efflux.⁶⁴

In case of Topical delivery Nanoparticles with size more than 100 nm are difficult to penetrate into stratum corneum but uptake of these particles can occur. As the outer layer of skin is rich in lipids, exchange of lipids between stratum corneum and nano carriers may occur. The presence of follicles along

with sebaceous glands promotes an environment rich in lipids. This helps in trapping lipid nano particles. Moreover sebum is a mixture of triglycerides, squalene and waxes. Some triglycerides present in NLC may accelerate entrance into follicles or sebaceous glands.

In case of oral delivery, drug loaded NLC pass through digestive system and lipid digestion occurs gradually. Initially triglycerides are broken into monoglycerides and free fatty acids by enzymatic action. The released bioactives are transported either actively or passively through enterocytes or they may enter lacteals through chylomicron-mediated pathway. In case of chylomicrons pathway micelles are formed with amphipathic bile salts surrounding drug and monoglycerides. These micelles reach brush border of the intestine and can be absorbed. In the

Monoglycerides, fatty acids and bioactives diffuse out from micelles in the enterocytes leaving micelles behind and further reforming triglycerides inside intestinal cells. These lipid constituents in aggregation with cholesterol and phospholipids form chylomicrons encapsulating bioactives inside them, which finally undergo exocytosis.

Large size of chylomicrons (approximately 80 nm) prevents their entry through blood capillaries and thus they enter via lacteals circumventing first pass metabolism of the bioactives associated with them. Particle size of NLCs also plays significant role in intestinal transport. The size below 300 nm is desirable for their transport across the intestine and should be suitably controlled.

Discrete techniques of NLC for its improved bioavailability:

1. Increased Permeability:⁶⁴⁻⁶⁵

The surfactant employed in the preparation of NLC alters the permeability by various mechanisms. It inhibits P-gp efflux transport and may increase intestinal permeability. Polaxmer used deforms the cell membrane and open epithelial cell junction and promote paracellular transport.

2. Inhibits Drug degradation:⁶⁶

NLC offer protection to drugs from chemical and enzymatic degradation dealing in harsh GI environment.

3. Mixed Micelle formation

The lipids used in NLC are similar to dietary lipids and thus include in bile secretion in small intestine. The lipids which undergo degradation upon action of enzymes to form lipid digestion products and are mixed with bile to form micelle. Thus facilitating ease transportation.⁶⁷

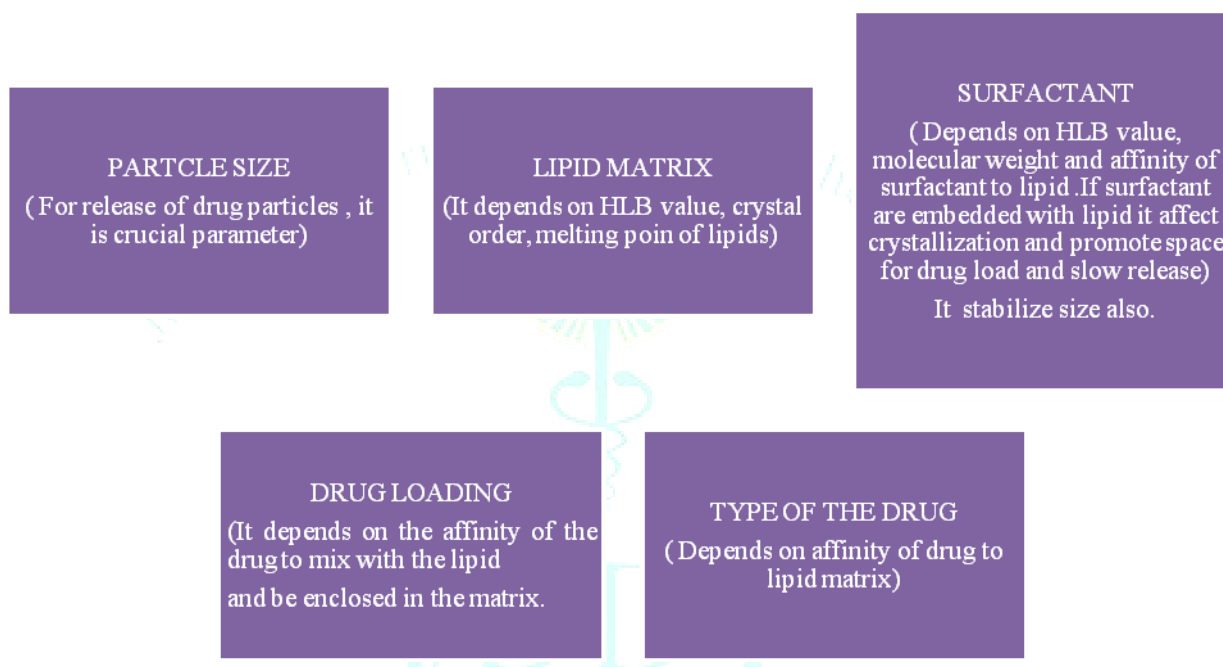
4. Muco adhesion characteristics:⁶⁸

Increased adhesion of carrier to mucus causes increased retention of drug release.

5. Direct uptake:⁶⁹⁻⁷⁰.

It is by intestinal lymphatic transport. NLC may stimulate chylomicron formation because of lipophilic transport this follows transcellular route of absorption. High lipophilicity promotes lymphatic intestinal absorption thereby avoiding first pass metabolism.

PARAMETERS THAT INFLUENCE THE RELEASE PROFILES ²⁷



PREPARATION ^{27,71}

There many methods for the preparation of lipid nanoparticulate drug delivery systems. The method used is dictated by the type of drug especially its solubility and stability, the lipid matrix, route of administration, etc.

1. Homogenization (Hot/cold)
2. Solvent Evaporation
3. Solvent emulsification and diffusion
4. Ultra sonication
5. Solvent injection
6. Phase inversion
7. Double emulsification
8. Melt dispersion
9. Supercritical fluid.

10. Film ultra sound dispersion method

CHARACTERIZATION OF NLC:⁷²

The formulated NLC's are characterized for physicochemical characterization as it is very essential to judge the feasibility of NLC's as ideal drug delivery system. The frequently used parameters are:

1. Particle size analysis: By Photon correlation spectroscopy and laser diffraction methods. The type and ratio of lipids have direct influence on particle size. The usage of emulsifier causes complete emulsification and thus reduces the particle size.
2. Zeta potential: Important parameter as it determines the aggregation and dispersion process affecting the stability. Presence of electric charge on surface prevents aggregation. For brain delivery positive charges are essential for efficient entry into blood brain barrier and to attach to anionic sites present in paracellular area over

there. In certain cases negative charge NLC is essential for stabilization.

3. Morphology of particles: Particle size radius, size distribution, size and morphology of particles can be analysed by Scanning Electron Microscopy (SEM) and Transmission electron microscopy. Atomic force microscopy (AFM) is also used for measuring morphological and surface features that are extremely small. A three dimensional view can be obtained by AFM.
4. Surface tension
5. Crystallization and melting behaviour: Differential Scanning Calorimetry (DSC) is used to study the melting behavior a drecrystallization of lipids. The more liquid lipid the less ordered the crystalline structure. X-ray diffraction technique is also used to know the status of lipids used.
6. Mobility and interactions : Mobility and interactions of solid lipid and liquid lipid is done by proton Nuclear Magnetic Resonance (NMR)
7. Molecular vibrations: Raman spectroscopy serves as tool in identification of molecular vibrations to detect high degree conformational order in NLC.

8. Molecular environment: Using the dye Nile red in fluorescent spectroscopy molecular environment or polarity of NLC is elucidated.
9. Drug loading efficiency/ encapsulation efficiency: This is determined by ultrafiltration, ultracentrifugation, gel filtration by sephadex, dialysis method. It is an important tool as it affects the release characteristics.
10. Drug release: The drug release behavior from NLCs is dependent upon the production temperature, emulsifier composition, and oil percentage incorporated in the lipid matrix. The drug amount in the outer shell of the nanoparticles and on the particulate surface is released in a burst manner, while the drug incorporated into the particulate core is released in a prolonged way. Dialysis method and utilization of franz cell are important methods to calculate drug release.

APPLICATIONS: 27, 71,72.

In the arena of drug delivery systems, the nlc has occupied unique place spreading its wings in wide areas to mitigate number of diseases. By delivering the drug through various routes NLC is finding its way to treat diseases.



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