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A REVIEW ARTICLE ON NANOSTRUCTURED LIPID CARRIERS (NLCS) FOR DRUG DELIVERY AND TARGETING SYSTEM.

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Abstract:
During the past decade, the number of studies describing nanostructured lipid carriers (NLC)-based formulations has been dramatically increased. The raise in NLC exploitation is essentially due to defeated barriers within the technological process of lipid-based nanoparticles' formulation and increased knowledge of the underlying mechanisms of transport of NLC via different routes of administration. This review article aims to give an overview on the current state of the art of nanostructured lipid carriers as controlled drug delivery systems for future clinics through novel NLC applications providing examples of successful outcomes. The reported data clearly illustrate the promise of these nanoparticles for novel treatments in the near future. Nanostructured lipid carrier (NLC), have been studied for their capability as biodegradable, biocompatible, and physiological lipids are generally used to prepare these nanoparticles. Hence, toxicity problems related with the polymeric nanoparticles can be minimized. Furthermore, stability of the formulations might increase than other liquid nano-carriers due to the solid matrix of these lipid nanoparticles. These nanoparticles can be produced by different formulation techniques. Scaling up of the production process from lab scale to industrial scale can be easily achieved. Reasonably high drug encapsulation efficiency of the nanoparticles was documented.

Keywords: *Nanostructured Lipid Carriers, NLC, SLN, lipid nanoparticles.*

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INTRODUCTION:

Over the last 20 years, nanotechnology has almost made its influence in all technical fields, including pharmaceutics. Industry estimations are propose that around 40% of lipophilic drug candidates are fail, because of their solubility and stability issues of formulations, which has been resolved by various advanced and novel lipophilic drug delivery technologies. The lipids employed to formulate lipid nanoparticle are generally physiological lipids i.e. (biocompatible and biodegradable) along with low acute and chronic toxicity-

The first generation of SLNs was established in initial of 1990. The merits of SLNs there physiological lipids are use in SLNs, not use of organic solvents, and the ability of large-scale production. As a drug delivery system, SLNs can develop bioavailability, creates shield on sensitive drugs from a rigorous environment, and control drug-release features. However, SLNs show some demerits as drug carriers containing a random gelation tendency, polymorphic change, and low incorporation due to the crystalline structure of solid lipids in formulations. At the turn of the era, **nanostructured lipid carriers** (NLCs) are present there to resolve, in certain cases, the problems raised by SLNs. NLCs are designed by controlling the mixing of both solid lipids with liquid lipids, projecting to special nanostructures in to the matrix. The new generations i.e. NLCs can be avoid the apparent drawbacks of SLNs, such as limited drug-loading capability and drug exclusion during storage of formulation, -

Fang, A Al-Suwayeh et al. (2013)Types of NLCs

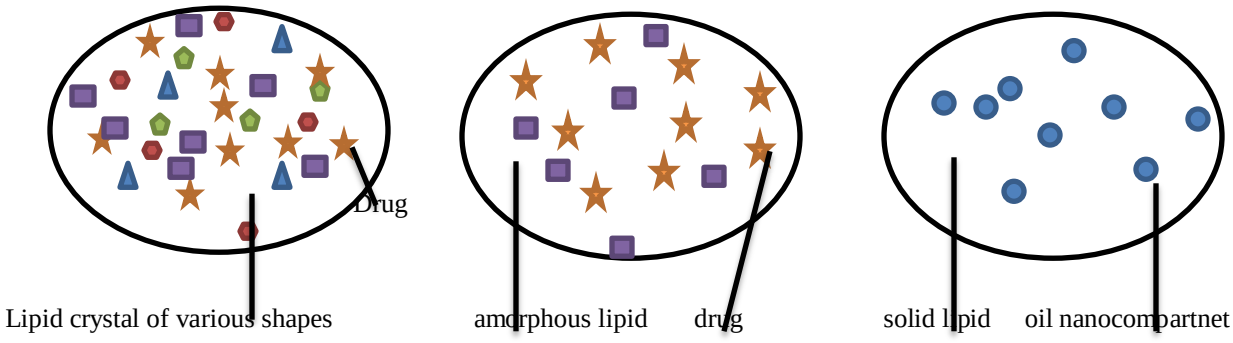
On the basis of using various methods of production and the composition of the lipid mixtures, different types of NLCs are achieved. The basic idea is to deliver a certain NLCs for the lipid matrix which is able increase the pay-load for active moiety and reduce the expulsion of compound during the time of storage.

There are three types of NLCs:-

1. The imperfect type,
2. The amorphous type, and
3. The multiple types.

The SLNs have limited drug loading capacity because of the formation of the lipid crystal. Towards a perfect concentration drug expulsion has been observed due to an ongoing crystallization development; therefore by avoiding crystallization, one can avoid these obstacles which is realised in the NLC type 2. The lipid matrix is solid but not crystalline, rather it is in an amorphous state (as shown in Table I). This can be achieved by mixing special lipids, for example, hydroxyoctacosanyl hydroxystearate with iso-propylmyristate. Th e form of fi ne droplets incorporated into the third type of NLC is a multiple system; comparable to w/o/w emulsions, that is oil-in-solid lipid-in-water dispersion. The solid lipid matrix contains tiny liquid oil nano-compartment particles. This type of NLC uses the fact that for a vast category of drugs, the solubility in oils is higher than their solubility in solid lipids (Uner and Yener 2007).

Fig No. 1 Schematic diagram illustrating structures of NLCs (1, 2, and 3 are disorder structure, amorphous structure and multiple structure, respectively)



Formulation Ingredients	Examples
Solid lipids	Stearic acid, Glyceryl Monostearate (GMS), Carnauba wax [138] Cetyl palmitate, Glyceryl Palmitostearate (Precirol® ATO 5), Glyceryl Behenate (Compritol® 888 ATO), Grades of Witepsol®, Grades of Softisan®,Gelucire®
Liquid lipid	Soybean oil, Medium chain triglycerides (MCT)/caprylic and capric triglycerides, Oleic Acid (OA), Isopropyl Myristate, α-tocopherol/ Vitamin E, Corn oil, Squalene
Surfactants	Poloxamer 188, Tween® 20, Tween® 80, Sodium dodecyl sulfate (SDS), Sodium deoxy cholate (SDC) Myverol™ 18-04K, Polyvinyl alcohol (PVA), Solutol® HS 15, Polyoxyl castor oil, Lecithin.

Table 1 Formulation ingredients for NLC.

PREPARATION METHODS FOR NLCs:-

A. High Pressure Homogenization Technique-

The HPH technique is well known for its large scale production of lipid NLCs as well as for good yield. In this process liquid forcing under high pressure of about 100-200 bars through a narrow orifice. The high pressure is creates shear stress due to this cavity made to break-down particles into nano-size range. HPH method is categorized into two types as follow: - hot homogenization and cold homogenization. In both the techniques, the lipids are kept at approximately 5-10º C above to melting point and then drug is added to the melted lipid.

B. Hot Homogenization Technique

Here the drug-molten lipid solution is homogenously dispersed in the aqueous surfactant solution which is also having the same temperature as like the drug-lipid solution. The assembly is interfuse to produce a high shear device to permit continuous stirring. The obtained pre-emulsion is forced to words the piston of homogenizer for making uniform particles and then nanoemulsion can recrystallize by cooling by lyophilization forming nanostructured lipid carrier.

C. Cold homogenization technique

The hot homogenization technique have certain complications with respect to partitioning of the API into aqueous surfactant phase leading to drug loss & drug degradation at high temperature. These problems are avoided by using of cold homogenization technique. The first step in this process is similar to hot homogenization, followed by rapid cooling of mixture solution which distributes the active moiety uniformly in the lipid matrix. This technique is suitable for thermos-labile drugs.-

D. Solvent Diffusion

Organic solvents are saturated in water to confirm the early thermodynamic equilibrium. The transitory oil/water emulsion is passed in to water under the constant stirring, which further goes in to solidification of dispersed phase forming NLCs because diffusion of the organic solvent. For dissolving a lipid aqueous immiscible solvents are used. Lyophilisation or ultra-filtration is required. Organic solvents filtrate may remain in the preparation.

E. Solvent emulsification-evaporation

In aqueous-immiscible organic solvent lipid are dissolve, and then emulsified in an aqueous phase having surfactants under constant stirring. The organic solvent will evaporate in the course of emulsification, causing the lipid precipitation. This method is suitable for thermolabile drugs. In this very dilute NP's are created. But organic solvent may possibly remain in the preparation. So the ultrafiltration or evaporation process is required.

F. Melting dispersion method

In melting technique, solid lipid and API are melted in an organic solvent held as oil phase, and concurrently water phase is also heated to the similar temperature as oil phase is having. Afterward, the lipid phase is added to a small amount of aqueous phase and the obtained emulsion is goes under the high speed stirring for few hours. To end with, product is cooled down to room temperature to obtain good yield NLCs.

G. High shear homogenisation and/or ultrasonication technique

This method is very less frequently used for the production of lipid nanoparticles. Initialy, the essential drug material is melted by the addition of phospholipids along with an aqueous phase, and lastly

diffusing the melted material at high temperature by automated stirring or ultrasonication technique.

H. Solvent injection (or solvent displacement) technique

Liquid is dissolved in a solvent like ethanol or DMSO, which help to diffuse very quickly in water. Then mixture is injected into an aqueous-surfactant solution. The solvent, because of diffusion in water, migrates rapidly in to the aqueous phase; lipid particles in the precipitate are leaved. Although this technique serves low shear, disadvantage is usage of organic solvents and it is remains in product.

I. Double emulsion technique

This technique is appropriate for encapsulating the hydrophilic drugs and usages w/o/w double emulsion technique. In double emulsion the drug and surfactant are encapsulated in the inner phase. Favorable stabilizer is dispersed in the aqueous phase having hydrophilic emulsifier which is help for stabilizing the primary emulsion.

J. Phase inversion

In this lipid, drug, water and surfactant are mixed well together and give magnetic stirring to solution, three heating and cooling cycles are performed, and then diluted by using cold water it causing phase inversion of the prepared emulsion and breaking resulting in formation of NLC. The advantages of this method is Thermolabile drugs can be incorporated in procedure. Avoidance of organic solvent can be possible. But it is unwieldy used technique.

CHARECTERIZATION:

Characterization techniques:

Characterization of NLC is a critical requirement similar to all other colloidal carriers system for evaluating quality, stability, efficacy and release kinetics of the delivery system. For SLN and NLC, it is pretty a challenging job as a being of an extremely small size. These characterization techniques are the measurement of morphology of the particles, particle size and its distribution, structural properties, surface charge and changes in crystallinity of particles, polymorphism and thermal behavior of the lipids, significant characterization methods for NLCs are given below:

I. Particle size and distribution

Particle size and its distribution is a most important characteristic which is shows effect on the solubility, stability, release rate pattern and biological action of the NLC. The diameter of NLC is ranging from 10 to 1000nm. Nevertheless, for site-specific delivery of drug, a 50–300nm range is desired particularly for CNS disorders and chemotherapeutics. This size range offers an easier crossing of barriers, increased uptake in cells and rapid action while, the size above 300nm make available to give sustained drug delivery. Sizes which are above than 300nm are desirable for intestinal delivery. Increase in particle size during storage shows agglomeration and therefore physical instability observed. A number of factors including composition of the formulation, the manufacturing process such as choice of process, equipment used, processing temperature, pressure and number of successions during HPH technique, sterilization, lyophilization these all are affect particle size. In general, a high surfactant/lipid ratio results in smaller particles size and particle size increase is with low surfactant concentrations. Higher drug concentrations give larger particle sizes in compare to low concentrations of drug. The methods like dynamic light scattering (DLS), quasi-light scattering (QLS), Photon correlation spectroscopy (PCS), multi-angle light scattering (MALS), quasi-elastic light scattering (QELS), are generally used, which are give information about size based on the corresponding hydrodynamic diameter in liquid dispersions.

II. Polydispersity Index

As we know SLNs/NLCs are generally having polydisperse nature, so the measurement of polydispersity index (PI) is very important to ensure the size distribution of the nanoparticle system. There must be lower PI value is required for more monodispered nanoparticle dispersion. Most of the researchers admit PI value less than 0.3 as optimum value. PI can be measured by using the PCS technique.

III. Zeta Potential

The zeta potential (ZP) specifies the overall charge a particle gets in a specific medium. The ZP is shows the amount of repulsion among the close and similarly charged particles in the prepared dispersion. High ZP shows highly charged particles medium. The stability during storage can be predicted form the ZP value. Generally, higher the ZP (negative or positive) can be prevent accumulation of the particles caused by electric repulsion and it was electrically stabilizes the dispersion. But, if in case of low ZP, attraction goes above to the repulsion and the dispersion coagulate so flocculation produsued. However, this assumption is not valid for all colloidal dispersion; particularly the dispersion which is contains tericstabilizers. The ZP value of −30 mV is adequate for good stabilization. The Zeta Potential can be determined with the help of PCS technique.

IV. Crystallinity and lipid modification

To achieve the stable NLCs the characterization of crystallinity and the degree of lipid modification is necessary. Further, these can be influence the entrapment efficiency (EE) and release kinetics. Generally used techniques such as "Differential scanning calorimetry" (DSC) and "X-ray diffraction" (XRD) for determining the structural characterization of particles and provide valuable data with respect to crystallinity and polymorphism of sample. DSC is very sensitive instrument that's way it is helps to understand the structural properties of a sample by determining heat exchanges i.e. under controlled temperature conditions the uptake or emission of thermal energy is carried out during period of melting or crystallization of sample. In DSC, firstly sample is heated and then cool down at a controlled rate and the flow of heat either uptake or emission is quantitatively checked. Although DSC instruments of high sensitive it can measure the minutest thermal changes, but it does not provide any information about the cause of these thermal events. The reason of these thermal changes such as melting, polymorphic transformations, dehydration, decomposition or degradation of the sample, these all can determined by using other complementary methods such as microscopy, XRD, thermo gravimetry or other spectroscopic techniques and these are helping to overcome the above problems.

V. Electron Microscopy

With the help of scanning electron microscopy (SEM) and transmission electron microscopy (TEM) the particulate radius and size distribution of NLCs can be measured, in case of observing the shape and morphology of the particles the electron microscopy is useful. TEM method consumes electrons transmitted through the specimen and SEM employs electrons transmitted from the surface of the sample. SEM holds high resolution and easy preparation of the samples. And after freeze-drying or freeze-thawing TEM permits visualization of nanoparticles.

VI. Atomic Force Microscopy (AFM)

For measuring the morphological and surface structures of extremely small particles the AFM is supreme technique. It doesn't uses photons or electrons but there is a very small sharp-tipped probe is situated at the free end of a beam which is passes by attractive forces among the tip and specimen surface. Even though electron microscopy is still repeatedly used, the AFM method offers considerable benefits: flexibility in ambient working situations, actual quantitative data gaining in three dimensions, nominal sample preparation times, and effective magnifications at the nano levels.

VII. Surface Tension

The surface tension of water at 20°C is about 72.8 dynes/cm. The addition of emulsifiers and lipid can knowingly decrease the surface tension to a lower value. The surface tension is decreases subsequently with increase of emulsifier concentration. Surface tension of the nanoparticles system is regularly measured by the Wilhemy plate method.

VIII. Nuclear Magnetic Resonance (NMR)

To examine the mobility of the sample materials in the inner core of NLC, proton NMR spectroscopy is done. Movement of the solid lipids and liquid lipids is linked with width at half amplitude of the signals. Wide-ranging signals and small amplitudes are features of molecules to the limited movement and strong interactions between molecules. The greater contour width of NLCs linked to the physical mixture of the materials added in NLCs leads to interaction of liquid lipid with solid lipid. Immobilization of the NLC particles is the stronger in compare to SLNs with totally crystallized cores.

IX. Raman Spectroscopy

Raman spectroscopy based on inelastic scattering of monochromatic light, it is detects vibrations and rotation of molecules afterward excitation due to strong laser beam. Expressing wavenumber in RS is inverse centimeter (cm-1). The water causes only broad peaks at 3500 cm-1. With respect to the aspect of oil incorporation in to crystalline lattice, the bands signifying order of lipid chains are to be concern.

X. Determination entrapment efficiency

The drug-loaded sample was ultracentrifuge at 12,500 rpm about 45min to separate the aqueous phase and lipid phase. The supernatant phase was then diluted by methanol, then it filtered through 40lm filter paper and the drug content was determined by UV-Visible spectrophotometer at 396nm.

The EE% of NLCs was determined by using the equation as follow:

$$\text{Entrapment efficiency \%} = \left(\frac{Wa - Ws}{Wa}\right) \times 100$$

Where, Wa means mass of drug added in to the NLCs formulation and Ws means analyzed weight of the drug in supernatant liquid.

XI. Drug release kinetics

The in vitro drug release model show highest value of the R2 was measured as best model for release from NLC design. The controlled or sustained release manner of drugs from NLCs formulation can be end result is prolonged half-life of formulation and retarded enzymatic action in systematic circulation. The drug release manners from NLCs are reliant on the production temperature, on emulsifier composition, and oil % incorporated in the lipid matrix. The dialysis technique and the use of Franz cell are the methods for determining in vitro drug release by NLCs. The interpretation of in vitro drug release profiles should consider the specific environment in the in vivo status. And the enzymatic degradation of lipoidal nanostructures may be influenced to a relevant amount by their composition of the particles.

Mathematical models of drug release as follow: Zero order, First order, Higuchi, Hixson-Crowell, Ritger-Peppas-Kormeyers, Brazel-Peppas, Hoffenberg, Baker-Lonsdale Weibull and Peppas-Sahlin.

XII. Stability study

The optimized NLC dispersion was subjected to stability study to assess evaluation of any physical or chemical changes during storage. For stability study the formulation was held in reserve at refrigerated condition (4±2° C) and at 25±2C/60±5% RH for 60 days in Borosil amber-colored glass container. The sample testing was done at intervals of 15, 30, 45 and 60 days after storage. Test samples from each formula at each temperature were analyzed for drug retaining efficiency. Also the NLC dispersion is visually examined for checking any physical instability (separation, aggregations, and so forth).

DRUG DELLIVERY BY NLCs-

NLCs as drug carriers for oral administration

The oral drug administration route is regarded as most common, because it offers a valuable option for treating numerous deadly diseases for the reason that of its having several advantages like patient compliance, cost–effectiveness and ease of administration. It is also highly chosen for chronically administered agents, such as antidiabetic, anti-tumor and antihypertensive agents. Charman and his colleagues are performed serious studies about the correlation between absorption enhancement and types of lipid used in formulation. A number of drugs were used in NLCs preparation for oral delivery. In most of the cases, aim was to increase oral bioavailability by means of increasing GI absorption or by bypassing the first-pass metabolism of the drug. Oral drug delivery systems occupy major share of the drug delivery in market, but oral drug delivery is constantly interested in newer option due to clumsy factors like low drug solubility, poor absorption window, rapid metabolism, high variability in the drug plasma level, and variability due to food effects. These factors may cause unacceptable in vivo results leading to failure of the oral delivery systems. From the past few years' colloidal drug carriers, such as, micelles, liposomes, neosomes, nanoemulsions, nanosuspensions and polymeric nanoparticles have overcome numerous above mentioned problems. But, these systems are also allied with several downsides as such as limited physical stability, accumulation, low yield, drug leakage on storing, presence of organic solvent residues, cytotoxicity, etc. Lipophilic compounds are being manufactured in lipid NPs for drugs to be given by oral route. Used for in vivo concert of poorly water soluble drugs are given orally, the limiting aspect is their resistance to being wetted and dissolution into the fluid in the GIT taking into consideration of potential degradation in the GIT and hence the rise in the dissolution rate of lipophilic drugs is related for optimizing BA. Lipid NLCs for oral route are related with their adhesive properties, as, once they are adhered to the GIT wall, they will be able to release the drug exactly wherever it should be absorbed.

Topical delivery:

Topical delivery is the desired way for skin diseases because of reduced systemic side effects as compared to oral and parenteral routes. It also avoids the first pass effect and keep maintain the concentration of drug at the site of action for longer duration particularly for drugs which have faster elimination. The major challenge is the low uptake of the drug because of the stratum corneum layer, which acts as an obstacle to toxic molecules along with therapeutics. In the recent years, lipid nanoparticles have extended consideration as novel colloidal carrier system for topical use. NLCs possess many benefits over conventional creams and emulsions by provides the controlled release action, protection of active moiety, improved permeability into the skin and minimum skin irritation. Greater drug release was observed with NLC. Examples - anti-inflammatory drugs such as flurbiprofen, indomethacin, celecoxib, various NLC formulations for topical delivery. eg-Lutein was also loaded in NLCs produced by highpressure homogenization to protect skin from photodamage. Eg:- If NLCs showed diameter range 150–350 nm, a zeta potential range - 40 to - 63 mV, and the encapsulated lutein remained in the skin, protecting the skin against UV.The important parameters for multiple-type topical formulations are their emolliency, which is affected by lubricity and spreading properties. Lubricity and spreadibility are

related to the formulation's ability to cover a surface and reduce the attrition, and these properties can be determined quantitatively. Although being independent on the properties of the applied surface, lubricity is expressed as a friction factor described by Stocke's law of friction: F6r ph n= where h stands for viscosity, r is the film thickness and v is the speed of moving film. In contrast, spreadibility is highly dependent on the applied surface, being described by the contact angle : S R r =/ where R is the radius of the wetted area and r is the radius of the initial droplet. Young's law describes the force balance at interfaces between solid substrate, liquid and gas phase.

NLCs for parenteral administration

The parenterals of lipidic substances came to success while submicron emulsion based products, for example Diazemuls and Diprivan were commercialized in the marketplace of pharmaceutical industry. Liposomes are signifying the 1st generation of the novel lipidic carrier system, which is modernized the scenario in parenteral drug delivery system. But they having the certain disadvantages like instability, high cost etc. Then potentials of SLN and NLC have been discovered in the parenteral drug delivery. The administration of SLN or NLC via the parenteral route improved bioavailability (BA), targeting and improved cytotoxicity beside multidrug resistant cancer cells have been observed. In study done by Jia and colleagues established silybin loaded NLC to see the outcome of bio distribution and pharmacokinetics afterward to the parenteral administration. Silybin loaded NLC exhibited greater AUC values and circulated in blood stream for an extended time in compare to the silybin solution. The tissue distribution is confirmed a high uptake value of silybin-NLC in RES organs mainly in liver.

Therapeutic challenges

The LNPs have been offered for delivery of several drugs and activities for numerous purposes. The analysis of all the uses of LNPs overcomes the purpose of this review. However, amongst the most fascinating and recent everyday jobs for LNPs, there are several challenges that are becoming the hot topic of drug therapy these days. Anticancer therapy, the overcoming of the blood--brain barrier (BBB), protein and gene delivery are research fields where the necessity of a safe and versatile drug carrier is vital, and LNPs have been proposed and verified to these goals.

Cancer therapy

The underlying principle of using Lipidic Nanoparticles for anticancer therapy is based on several physiological mechanisms. A tumor is often related with a defective, leaky vascularization as an outcome of the poorly regulated nature of tumor angiogenesis. To rise in cancer cell-selective cytotoxicity, a methodology that is gaining attention to surface-engineer NPs for active targeting is done. This strategy heroically acts the differences among cancer cells and healthy cells, in specific surface antigen (Ag) differences. Few primary examples are present in LNPs: in particular targeting through folate, transferrin and lectin receptors have been projected. Nanotechnology-based drug delivery systems are leading to cancer therapeutic modalities that are not only less toxic to the patient but also significantly more efficacious, carrying a significant promise toward new ways of treating cancer.

Carriers for Antitumor Drugs

The PNP drug delivery system is a highly valuable application for antitumor therapy. PNPs can regulate the drug release, prolong drug retention time in the body, and increase drug targeting at tumor site (and so efficacy) while reducing adverse side effects of drug. Also, the enlarged permeability of PNP improves the penetration of the drug in tumor cells. The mechanism of PNP transport across the cell membrane is differs from the free drug. PNPs are incorporated through endocytosis and therefore their uptake is not affected by the drug transporters in the cell membrane. Thus a combination of PNPs and antitumor drugs can avoid the multi-drug resistance of tumor cells facilitated by drug transporters. a tumor is often allied with a defective, leaky vascular construction as a outcome of the badly regulated environment of tumor angiogenesis. In interstitial fluid inside a tumor is usually inadequately drained by the badly formed lymphatic system. Hence, outcome submicron sized particulate issue may specially extravasate into the tumor and be retained there. This is said as the "enhanced permeability and keeping" (EPR) effect. This EPR effect can be taken benefit of by a properly considered nanoparticle scheme such as NLC to attain passive tumor targeting. By doing so, the above-mentioned poor tissue specificity difficulty can be around partly solved.

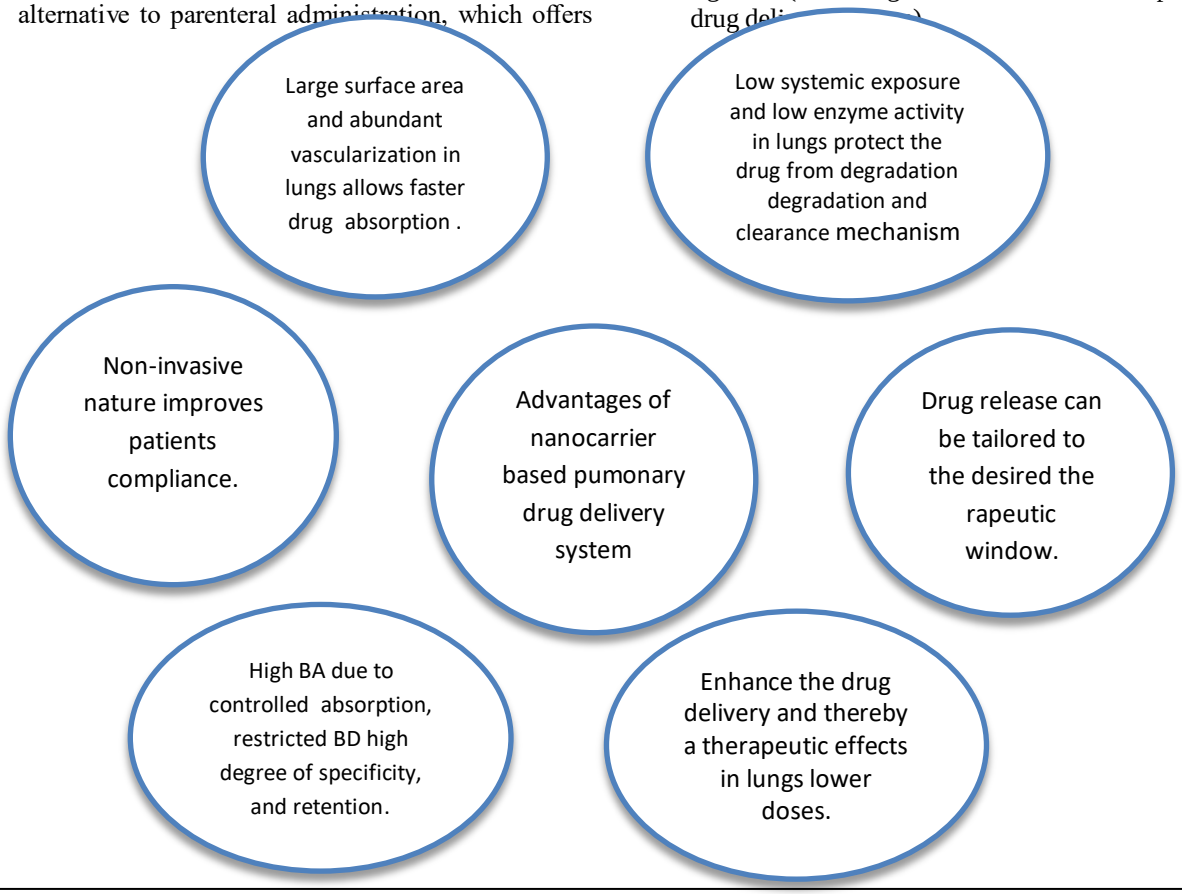
GENE DELIVERY

For the treatment of human diseases the development of gene therapy has boosted the usage of new crowds of gene delivery system. Nonviral vectors are widely investigated because of their adequate safety. Lipid nanocarriers, including liposomes and SLNs, can increase the Gene Delivery PLNs are used to delivery

genes that can be conveyed by non-viral vectors, such as cationic liposomes (DOTAP) and cationic polymers (PEI). Although liposomes and polymers have been shown to be effective both in vitro and in vivo, their action is limited by instability after administration. Moreover, the cationic surface of some polymers easily combines with serum proteins, leading to rapid removal from the systemic circulation and non-specific uptake by non-target tissues. Therefore, liposomes and polymers are not optimal gene delivery vehicles. Li et al. initiate that PLNs show greater stability and good biocompatibility compared with liposomes and PNPs. In one preparation of LPNs containing DNA, unmodified LPNs were composed of a PEI core and a polycarbonate three OA glycerin ester two stearic acylphosphatidylcholine lipid shell. Modified LPNs were delivered to HEK293 cells and MB MDA 231 breast cancer cells. The transfection efficiency was higher than when using liposomes; the colloid was more stable, and the toxicity to the HEK293 and MB MDA 231 breast cancer cells by the PLNs was low.

Intranasal delivery

Intranasal drug delivery is a reliable, safe and noninvasive for the delivery of CNS drugs and safe alternative to parenteral administration, which offers advantages of rapid absorption due to the high surface area, rich blood supply and porous endothelium of the nasal mucosa, avoiding the gastrointestinal and hepatic metabolism, fewer side effects and possibility of dose reduction and better patient compliance. NLC formulations by the intranasal route have been explored thoroughly for enriched delivery to the brain. Various pathways have been offered for intranasal delivery to the brain via. a) the systemic pathway, where the active drug compound is absorbed into the blood and by crossing the BBB it goes into to the targeted brain tissues; b) the olfactory pathway, where the drug is infuses the olfactory epithelium and through the olfactory bulb goes into the brain tissue or CSF; and c) the trigeminal pathway, where the drug is conveyed into the brain via the trigeminal nerve system. The olfactory bulb pathway and trigeminal nerve system pathways bypass the BBB and have gained importance in targeted delivery of a variety of therapeutics ranging from small molecules, proteins and peptides, stem cells and even plasmids to the brain. Several therapeutics such as artemether, tarenflurbil , valproic acid, lamotrigine , curcumin , proteins have been successfully shown to have achieved enhanced brain targeting, indicating superiority of intranasal delivery of NLC to the brain fig No.2 (Advantages of nanocarrier based pumonary drug del[illegible])



Ocular route:
The eye is a predominantly challenging organ for drug delivery systems. The drug bioavailability is limited by physical barriers that hinder drug access into the eye: (i) muco-aqueous barrier, (ii) corneal epithelium, (iii) iris blood vessels lacking on fenestrations, (iv) non-pigmented layer of the ciliary epithelium and (v) the retinal pigment epithelium (RPE) along with the retinal vessels epitheliu. Furthermore, physiological processes like blinking and tear drainage reduce the residence time of ocular drug delivery systems. Depending on the ocular site of administration (topical, intravitreal, intravenous, transscleral, suprochoroidal or subretinal), differences on the clearance and the toxicity of the nanocarrier are expected. Among from numerous nanotechnological approaches, lipidic nanocarriers have appeared as efficient ophthalmic drug delivery systems, particulartly NLC, which have been modified to prolong drug retention on the corneal surface encapsulating different drugs.

Encapsulated drug	Lipid nanocarriers. Composition	Production Method	Application
Ibuprofen	NLC Compritol 888 ATO, Gelucire44/14 Miglyol812, Stearylamine TranscutolP, CremphorEL	Melted-ultrasonic	Inflammation
Flurbiprofen	NLC Stearic acid/Miglyol812/Castor oil Compritol888 ATOTween80	HPH	Inflammation
Mangiferin	NLC Glyceryl monostearate, Gelucire 44/14, Miglyol812 Tween 80, Labrasol	Ultrasonication	Cataracts

Table 2 Drug loaded lipid nanoparticles (SLN, NLS) for ocular disorders applications.

CONCLUSIONS:

NLC is a potential approach for improving the bioavailability of highly lipophilic drugs with poor aqueous solubility, extensive first pass metabolism, affinity for P-gp efflux transporters, and susceptibility to intra-enterocyte metabolism. In a way, the high caliber of NLC system shadows the petition of other lipid-based dosage form. Disrupted matrices of NLC consequently lead to higher drug loading, higher drug entrapment, modulated drug release and ultimately enhanced drug absorption as compared with other lipid-based formulations having uniform matrices of lipids. These special features of NLC are exclusively attributed to their unique composition, which is constituted of a blend of incompatible solid and liquid lipids.

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