WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 15, 919-932. Research Article ISSN 2277– 7105

NANOSTRUCTURED LIPID CARRIERS: A POTENTIAL DRUG CARRIER FOR CANCER CHEMOTHERAPY

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Article Received on
14 Sept. 2022,

Revised on 05 October 2022,
Accepted on 26 October 2022

DOI: 10.20959/wjpr202215-26047

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ABSTRACT

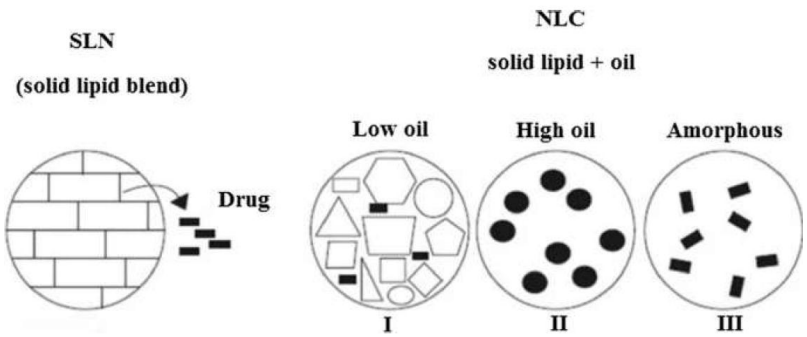
With the exponential growth of nanotechnology, the focus has been on medicinal endeavours, particularly for chemotherapy for cancer. As alternative carriers for pharmaceutical consignments, notably anticancer medicines, nanostructured lipid carriers have gained growing scientific and commercial attention in recent years. Anticancer mixtures frequently have drawbacks such as poor solubility, normal tissue toxicity, poor specificity, and instability, as well as a high incidence rate of drug resistance and rapid degradation, the requirement for large-scale output procedures, a rapid release of the drug from its carrier scheme, stability issues, the presence of leftover organic solvents from the output method, and the toxicity of the polymer with respect to the car. The advantages, varieties, drug release modulations, steadiness, and output approaches of NLCs are covered in this review. Additionally, the role of NLC in cancer treatment is discussed, and research hotspots are highlighted.

INTRODUCTION

The modern pharmaceutical advances have led to the discovery of a large number of powerful novel molecules. The only creation of new medications is insufficient to verify progress in pharmacological therapy. The novel medication compounds' poor water solubility and low bioavailability are two extremely common problems. Consequently, there is a growing need to create a pharmaceutical carrier system that resolves these issues. This carrier strategy should not be poisonous, have a sufficient capacity for pharmacological loading, and be capable of pharmaceutical targeting and controlled release properties. The system must

ensure the included pharmaceutical's personal and chemical stability. The production method's viability and price should both be readily available. The investigated colloidal systems each have drawbacks of their own. The rapid degradation by the pH of the stomach or by the intestinal enzymes and the bile salts if taken orally, the restricted physical and chemical steadiness throughout storage, the requirement for large-scale output methods, the rapid release of the drug from its carrier system, stability issues, and the residues of the organigrams are common drawbacks with colloidal schemes. These factors collectively render these colloidal carriers unsuitable as a mechanism for delivering pharmaceuticals. As an alternative to emulsions, liposomes, and polymeric nanoparticles, SLN have been proposed. SLN are made exclusively from solid lipids. As a result, after foundation, at least some of the particles undergo a higher energy change, or 'crystallisation. These adjustments can change into the low power, better organised version during storage. The crystal lattice's defects are few as a result of this modification's high degree of alignment, which leads to drug expulsion.

Nanostructured lipid carrier's classification:- Highly ordered crystalline lipid matrices are known to cause medication ejection from the study of suppositories. This can happen with lipid nanoparticles and microparticles formed from mixtures of solid lipids, particularly when the nanoparticles are ordered from highly pure lipids, such tristearin. Little room is left for pharmaceutical molecules due to the creation of highly ordered I or" alterations, especially during storage, and the expulsion of pharmaceuticals results in drug crystals in liquids and solid dosage forms. The particles should have a regulated nanostructure with enough room for the drug to fit in order to avoid this problem. For an NLCs nanostructure that was optimised, four different strategies were used. Solid and liquid lipids (oils) are combined to form type I. A very disordered, defective lipid matrix structure is created as a result of the different lipid organisational structures and the unusual crystallisation requirements, providing space for medicinal ingredients and amorphous clusters of medicines(Figure 1, I).



SLN with high crystallinity and Different types of NLC. I – Highly imperfect matrix, II – Multiple O/F/W type, III – non-crystalline amorphous NLC.

Drug solubility is typically greater in liquid lipids than in solid lipids. Based on this, particles with a high concentration of liquid lipids were formed (oils). The liquid lipid particles (nanoemulsions) are chilled during the production process from a molten state to room temperature in order to crystallise and pattern solid particles. A miscibility gap between the two lipids (solid lipid plus oil) occurs at high oil concentrations during the chilling phase, causing stage separation and the precipitation of tiny oily nanocompartments (Figure 1, II). Kind II drugs can be accommodated in the solid in this multiple oil/fat/water environment, although they are more soluble in the oily parts of the lipid matrix.

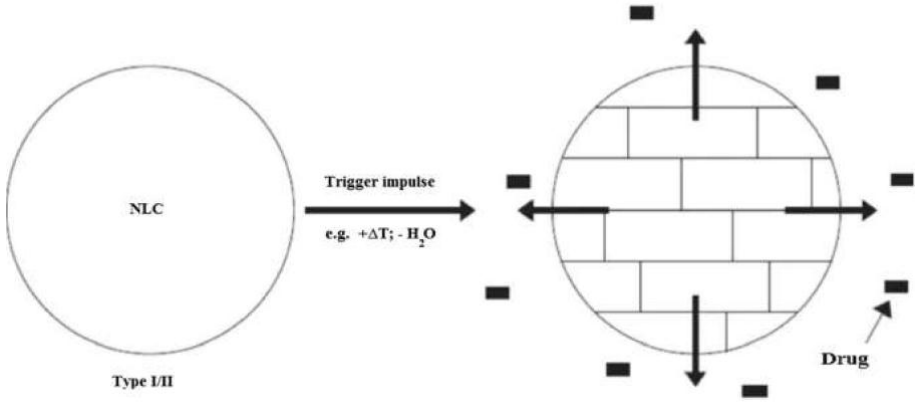
Lipids are mixed together in type III in a way that prevents crystallisation. Although it is amorphous, the lipid matrix is solid (Figure 1, III). Pharmaceutical ejection by crystallisation is prevented by crystallisation not occurring. Pharmaceuticals that are lipophilic are preferentially incorporated into lipid particles; hydrophilic medicines can only be integrated at low concentrations (however, this is still sufficient for highly powerful peptides and proteins). Pharmaceuticals that are soluble in water were coupled with lipids to create a water-insoluble lipidic conjugate in another version of the lipid matrix. The lipid drug conjugate (LDC) nanoparticle was produced by dissolving and processing the lipid conjugate dust in the same manner as the other varieties. Depending on the conjugation, this lipidic conjugate has a pharmacological loading of up to 30–50% for water-soluble drugs. Salt formation or covalent bonding are two methods of conjugation.

Modulation of Pharmaceutical Release

Pharmaceutical problems resulting from lipid particles are caused by diffusion and concurrent lipid element breakdown in the body. In some circumstances, having a regulated, rapid release following diffusion and degradation may be preferable. Perfectly, when the particles are delivered, an impulse should start this problem. Because of their highly disordered lipid

structures, NLCs support the pharmaceutical industry. Such a desired blew pharmacological release can be initiated by applying the initiate impulse to the matrix to change in a more ordered form. This is one method that some organisations' NLCs can be activated, such as when applying cream-containing particles to the skin. An increase in the temperature and water evaporation causes the issue rate of pharmaceuticals to rise (Figure 2). To treat psoriasis, treatments based on these cyclosporine-lipid particles are being developed. Both the cream itself and an NLC that is loaded with cyclosporine are present in the cream. A supersaturated structure (similar to micro emulsions but without strong surfactant engrossment) should develop after the cyclosporine has been applied to the skin, leading to enhanced cyclosporine penetration into the skin.

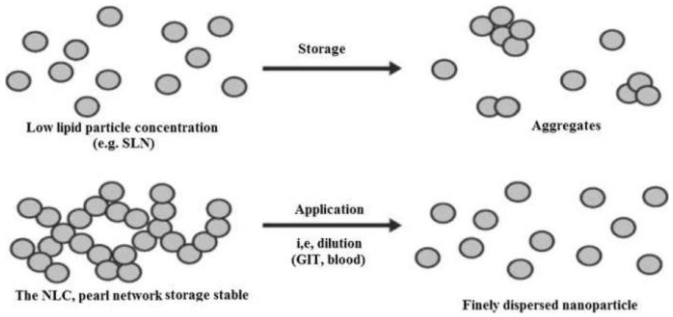
Figure 2: Triggered pharmaceutical releases from NLC by starting the alteration from a highly disorganized lipid structure to more organized stable modifications.



Long-Term Stability

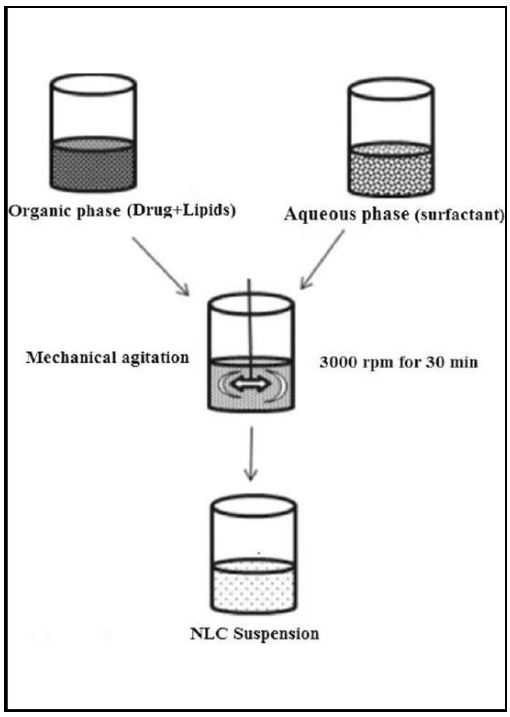
Element aggregation may occur when dispersions are stored for a long time. For SLNs, case creation and aggregation were described. In the dispersion media, lone particles spread; particle collisions can cause perikinetic flocculation (Figure 3a). Because the particles form a "pearl-like network" in the greatly intensified NLC dispersions, they are in a repaired location and won't collide or suffer perikinetic flocculation. The mesh is decimated, releasing single, non-aggregated particles following the management of the particles and dilution with fluids (gastrointestinal fluids, for example) (Figure 3b).Lipid particle dispersions with reduced lipid content (be reduced 30%, outside of patent coverage) and with 35% lipid were created at the same surfactant concentration. The gel-like NLC dispersion remained constant throughout storage, the low element dispersion consolidated during storage time, and following dilution, single particles were obtained with no size boost (Figure 4).

Figure 3



Aggregation method in reduced intensified dispersions (upper) and pearl-like network in NLC dispersions with stabilizing effect.

Figure 4



Output of NLC Nanosuspension.

Output of NLCs

Various conventional dispersion techniques can be used to create NLCs. The solvent diffusion approach is the preferred output technique, and it has even been argued that it is the best way for creating nanoparticles. Other techniques include the homogenization method, double emulsion, and supercritical fluid technology, among others. Here, the high pressure homogenization method is highlighted. The lipid phase is melted first. The medicine is then

dissolved in the liquid lipid, creating a drug-lipid melt. This melt is then thoroughly mixed with an aqueous surfactant solution that has also been heated to the same temperature. After that, the pre-emulsion is homogenised. In order to solidify the hot o/w emulsion, it must cool to room temperature. Nanostructured lipid carriers were created as a result of the nano emulsions' solidification. The extremely concentrated NLC dispersions are thick, pasty, or gel-like. There is no flowability in these systems. The goal of a multistep production procedure is to create an 80% NLC dispersion. First, high-pressure homogenization is used to create a 50% SLN dispersion. Such a dispersion weighs 100 grammes and contains 50 grammes of fat and 50 grammes of water. The additional 10 g of fat is added in the following step and mixed quickly with the remaining 50 g of water. This resulted in 110 g of dispersion that contained 50 g of new water and 60 g of lipid (55%) in total. Another 10 g of lipid are distributed in this 50 g of water stage in the following phase, and so on until a lipid concentration of 80% is reached. It is simple to produce NLC on a large scale. One tonne per hour and more high-pressure homogenizers are available. Furthermore, since these devices are accepted in parenteral output lines, there are no regulatory barriers.

Drawbacks encountered in cancer chemotherapy and the use of NLC

Many types of cancer, especially solid tumours, have historically posed significant hurdles to conventional treatment. Despite improvements in therapeutic combinations, chemotherapy still has a poor outcome. As examples, it should be noted that less than 20% of patients with ovarian, pancreatic, and esophageal cancers respond to chemotherapy.[26] Even in patients with cancers that respond well to chemotherapeutic agents, such as breast cancer, the clinical outcomes are typically below expectations. Cytotoxic anticancer medications have distinct challenges compared to other pharmaceutical classes, including low selectivity, high toxicity, and propensity to cause drug resistance. Conventionally administered cytotoxic agents frequently interact extensively and indiscriminately with serum protein and bodily tissues. Only a small portion of the medications reach the tumour site. This could increase systemic medication toxicity while also decreasing therapeutic efficacy. Furthermore, despite the fact that cytotoxic medications are solely intended to kill cancerous illness cells, they are actually hazardous to non-cancerous cells as well, especially those that divide quickly, such as gastrointestinal tract and skeletal bone marrow cells. Even when benchmark therapeutic amounts of anticancer medications are delivered, the typical tissue toxicities frequently take place. A major obstacle to developing an effective anticancer treatment is the lack of specificity of cytotoxic medications in terms of both pharmacological biodistribution and

pharmacology at the cellular level. The therapeutic value of cytotoxic drugs has been significantly reduced by their unfavourable side effect profile. The non-specific activity of the cytotoxic agencies might irritate or impair various organs or tissues depending on the use of medications. While practically all cytotoxic drugs typically cause side effects such nausea, vomiting, exhaustion, and hair loss, other side effects are drug-specific. An example of this is that anthracyclines can cause cardiotoxicity. Some of these negative effects can build up and be fatal. To confirm therapeutic efficacy, cytotoxic medicines typically have a steep dose-response bend and require high dosage intensities. This creates a difficult choice for clinicians between high pharmacological doses with a high risk of common tissue toxicities and low pharmaceutical dosages with low therapeutic response probabilities. The most effective presentation of conventional chemotherapy also faces other challenges. In addition to cellular mechanisms, different pharmaceutical permeation barriers present in solid tumours make it difficult to achieve high intratumoral pharmaceutical concentrations. As a result, cancerous disease units in solid tumours tend to be more resistant to chemotherapy than non-aggregating cancerous disease cells. Even though an anticancer medication has potent in vitro efficacy, this sort of drug resistance, also referred to as "non-cellular" drug resistance, may further result in impaired clinical outcomes. We think the NLC makes a commitment to go over at least some of these challenges.

Rationale of utilizing NLC for anticancer pharmaceutical delivery

Nanostructured lipid carriers could be exploited as an alternative drug carrier in the administration of anticancer drugs because the clinical outcomes of malignant disease are frequently below expectations.

In comparison to other drug classes, a tumour is frequently associated with a flawed, leaky vascular architecture because of the improperly controlled tumour angiogenesis environment. Additionally, a poorly developed lymphatic system frequently insufficiently drains the interstitial fluid within a tumour. Submicron-sized particles may thus preferentially extravasate and remain in the tumour. The "increased permeability and keeping" (EPR) effect is a common name for this. A properly designed nanoparticle technique, such as NLC, can take use of this EPR effect to achieve passive tumour targeting. The previously noted issue with inadequate tissue specificity can be partially resolved in this way. The external physico-chemical properties of NLC can also be changed to target them to the tissue of interest, further manipulating the bio distribution of NLC with advances in surface engineering. By

doing this, systemic drug toxicity is reduced and the amount of pharmaceuticals that can reach the targeted tumour locations is increased.

The advantages of NLC for cytotoxic drug delivery are personal stability, protection of labile medicines against degradation, controlled release, and ease of production. Other types of drug carriers utilised for cytotoxic drug delivery include polymeric systems and liposomes. At the same time, NLC avoids various issues that earlier pharmaceutical consignment systems encountered. The fairly high expense necessary for producing liposomal formulations on a big scale is not carried by NLC. Compared to methods like liposomes, they have less storage and drug leakage issues. Additionally, NLC does not reveal the considerable toxicity and acidity associated with a variety of biodegradable polymeric compounds. Pharmaceuticals that are cytotoxic and anticancer are renowned for their heterogeneity. They belong to a group of substances with a very diverse molecular structure and set of physicochemical characteristics.

Function of NLC for cytotoxic pharmaceutical consignment- advancement and strategies

Numerous cytotoxic medications, such cyclosporin-A, verapamil, and N 4 [2 (1,2,3,4tetrahydro6,7dimethoxy-2-isoquinolinyl)-ethyl]phenyl9,10dihydro5methoxy 9-oxo-4-acridine carboxamide (GG918), that have the ability to combat the multidrug resistance phenotype in units resistant In order to address the major trials in anticancer pharmaceutical delivery, a number of strategies have been developed, including I encapsulation of anticancer compounds that are water-soluble, ii) advanced control of the rate and duration of drug release, and iii) avoiding systemic clearance of NLC by the reticuloendothelial scheme (RES).

Encapsulation of water-soluble anticancer compounds

The lipid must dissolve and distribute into lipid droplets of submicron dimensions in aqueous medium, whether by mechanical or thermodynamic techniques, to allow creation of nanoparticles, regardless of the alternative NLC foundation procedure. To accomplish good pharmaceutical stacking, the medicine that will be encapsulated needs to be abundantly partitioned into the dissolved lipid droplets. Thus, since lipophilic anticancer combinations are predicted to partition efficiently in lipids, it is possible that they can be successfully incorporated into NLC. Additionally, because salts can be delivered with commonly available water-based vehicles (such as 0.9% saline), some lipophilic medicines are more frequently used in salt forms. On the other hand, a number of hydrophilic, water-soluble compounds

must also be included. It seems essential to find a method that will allow for the considerable incorporation of these water-soluble anticancer medications into NLC. Ionic salts of cytotoxic drugs have been encapsulated using a number of different strategies.

One uses the addition of organic opposing ions to create ionic patterns in pairs with the charged pharmacological compounds mentioned by Gasco and colleagues. To improve the loading of the saline forms of doxorubicin and idarubicin into SLN composed of stearic unpleasant, the group used decyl phosphate or hexadecyl. Significant advancements in the medicines' ability to partition into lipid were demonstrated. All the ascribe neutralization-based approaches outlined above may not be relevant to certain very water-soluble cytotoxic agents that do not bear any ascribe.

Advanced command of the rate and span of drug release

Early 90s saw the development of lipid-based carrier schemes, which frequently release medications in a non-uniform, biphasic fashion today. The rapid release of a big dose of medication is typically first noticed, followed by the drug's delayed and partial release. Upon submission, the brief initial pharmacological problem is frequently described as a "burst effect" or "burst release". The strong potency of cytotoxic chemicals creates a possibility for major difficulty in the delivery of anticancer drugs. If an anticancer treatment is delivered locally or systemically, a big dose that is rapidly released next to the injection site or into the systemic circulation could potentially pose a serious health risk. By combining solid lipids that are spatially incompatible with one another or solid lipids with trace amounts of oils, NLC reduces the crystallinity of the lipid. The ability of NLC to have a reduced blow effect and a higher payload of some medications that are oil-soluble makes them a reasonably alluring vehicle for the shipment of anticancer drugs. After the initial burst, drug issue from SLN can be delayed and partial. For instance, in several schemes delivering anticancer drugs including doxorubicin, idarubicin, and paclitaxel, the release was less than 0.1%.

Expanded drug issue is typically seen as a positive trait in the majority of treatments. Although it can be challenging to predict its impact during chemotherapy for cancer, Continuous exposure to suboptimal amounts of cytotoxic agents has been demonstrated to increase the expression of membrane-associated drug transporters, such as P-glycoprotein (P-gp), making malignant disease units more drug-resistant. This hypothetical risk may be avoided by an NLC system that releases anticancer medications considerably more quickly and without a powerful initial release.

Development of NLC schemes able to avoid clearance by reticuloendothelial system

Following intravenous administration, the RES, also known as the mononuclear phagocyte system, quickly releases pharmaceutical delivery systems such polymeric nanoparticles and liposomes from the systemic circulation. RES is a component of the immune system made composed of phagocytic cells, which often exist in the spleen, lymph nodes, and liver in a pattern resembling Kupffer units. These phagocytic cells can quickly remove pharmaceutical carriers that have been detected as foreign items. Only if the target tumour location was the liver, spleen, lymph nodes, or other organs would RES clearance of drug carriers be beneficial. However, for other malignancies, RES clearance is anticipated to be the main barrier to systemic cytotoxic drug delivery via NLC. A pharmaceutical particle carrier is made more resistant to RES clearance when it is covered in hydrophilic polymers. This is partially due to the fact that these polymers encourage the external adsorption of proteins that inhibit in vivo opsonization. This kind of polymer-coated drug delivery system is frequently referred to as "stealth" due to its ability to clearly avoid immune system surveillance, or more accurately, "long-circulating" drug carriers. This type of scheme can remain in the bloodstream for a very long time, with a half-life that ranges from a few hours in rat forms to up to 55 hours in human patients. By applying a polymer covering to the nanoparticles, long-circulating NLC formulations were created. Polymer molecules were pre-conjugated to lipophilic moieties to generate amphiphilic stealth outer layer agents, which facilitated a more secure attachment of the hydrophilic polymer up on the surfaces of the lipid cores.

It was demonstrated that the zeta potentials of nanoparticles were decreased and their mean diameters were enhanced by increasing the engrossment of the outer layer agency. The hydrodynamic volumes of the nanoparticles were enhanced due to the hydrophilic polymer materials that were present and that had been adsorbed up on the particle exterior employing conjugated lipophilic moieties. The polydispersity catalogue was also slightly increased by the use of larger lipid and polymer concentrations. Therefore, one should accept the possibility that outer layer NLC with a stealth agency may have an impact beyond only RES clearing rates. In addition, several element system physicochemical properties are altered, which may significantly affect NLC appearance, security, or formulation stability.

CONCLUSION

Pharmaceutical delivery systems using nanoparticulates have a significant impact on overcoming some of the barriers to effectively targeting a variety of different cell types.

Despite recent treatment advancements, the field of cell malignant disease still faces formidable obstacles. Chemotherapy that is frequently used has had unsatisfactory results because it harms the patient's health by increasing their susceptibility to various illnesses and frequently results in death by lowering their immune system. Thus, recent years have seen a surprising amount of developments in nanotechnology with a focus on improving cancer treatment.

By structuring the nanodrug carrier, anticancer medications can be delivered to tumour tissues in nanoparticulate form. The use of nanotechnology is projected to become more and more significant in the diagnosis, prognosis, and delivery of malignant illness treatments. Innovative, sophisticated applications that identify skin cancer units, deliver drugs to target tissue, describe treatment completion, and monitor intracellular changes to prevent precancerous cells from becoming malignant are anticipated to result from the rapidly expanding field of study known as nanotechnology. Since ongoing efforts by scientists, researchers, and medical professionals can actually ensure to do huge things with very little, the future is still exciting and wide open. The ideal consignment plan would be precise in its targeting. Various techniques been developed to direct nanoparticles to the desired tissues. These physical methods involve regulating the size, shape, and hydrophobicity of the particles. Additionally, to specifically target particular cell types, targeting agents such as antibodies and peptides that recognise the precise cell exterior proteins and receptors can be attached to the nanoparticle exterior.

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