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Review Article

Nanostructured Lipid Carriers in Chemotherapeutics: An Overview

Vidya Sabale, Manasi Jiwankar*

Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur, Maharashtra, INDIA.

ABSTRACT

Cancer is a life-threatening disease that is associated with persistent tissue injury and uncontrolled cell growth. The treatments available to treat cancer are chemotherapy, surgery and radiation therapy. These treatments are used in combinations, while the most preferred treatment is chemotherapy. Because of the Non-specificity of anticancer drugs, they kill normal healthy cells along with cancer cells which lead to severe side effects. To minimize such limitations associated with conventional chemotherapy, nanostructured lipids carriers can be developed. These are nanocarriers consisting of a mixture of solid and liquid lipids along with surfactants. Lipids used in the formulation of NLCs are biocompatible and biodegradable. NLCs ensure high drug payload, less drug expulsion and more stability on storage. NLCs enhance the aqueous solubility of lipophilic anticancer drugs. Their surface modification can help to overcome drug resistance in cancer therapy. Controlled and targeted drug delivery of anticancer drugs can be possible by formulating them as NLCs. NLCs can play an important role in targeting anticancer drugs by different mechanisms. This review highlights types, formulation methods, characterization of nanostructured lipid carriers and strategies to achieve targeted release of anticancer drugs loaded in NLCs.

Keywords: Cancer, Nanostructured lipid carriers, Drug targeting, Lipids, Anticancer drugs.

Correspondence:
Mrs. Manasi Jiwankar
Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur-440037, Maharashtra, INDIA.
Email: mmdnikam@gmail.com

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INTRODUCTION

Worldwide cancer is considered a deadly, life-threatening disease which is associated with many complications. The concern regarding this disease is its treatment, as the conventional treatment options are associated with severe side effects.[1] In cancer, there is a fast abnormal growth of cells with persistent tissue injury. Also, cancer can be spread from one part to another part of the body; hence better options for cancer treatment are essential.[2,3] Chemotherapy, surgery, radiation therapy, immunotherapy and hormone therapy are the currently available treatments for cancer that are used in combination.[4] In conventional chemotherapy, anticancer drugs show non-specific action on tumor cells which further affect normal non-cancerous cells and lead to multiple drug resistance.[5,6] Non-specificity of anticancer drugs makes significantly less amount of drug available at the cancer cells and the most of drug gets distributed throughout the body. This distribution of anticancer drugs throughout the body leads the killing of healthy cells along with cancer cells and also depression of the immune system which further affects the dose of anticancer drugs that should be given for the treatment of cancer.[7] These side effects of conventional chemotherapy can be minimized by developing a novel drug delivery system that will give site specificity and which in turn will increase the efficacy of anticancer drugs.

The nanoscale of nanocarriers has made possible delivery of various drugs, namely anticancer drugs, effectively at the targeted site. Also, the nanocarrier based drug delivery minimized the challenges related to the delivery of anticancer drugs and the side effects associated with conventional chemotherapy.[8,9] Nanocarriers containing lipids like liposomes, solid lipid nanoparticles, nanostructured lipid carriers have gained importance in cancer treatment. These lipid based nanocarriers can incorporate both hydrophilic and lipophilic drugs. In addition, they have good drug entrapment capacity and less toxicity.[10]

Two generations of lipid nanoparticles: SLNs vs NLCs

Solid lipid nanoparticles (SLNs) have gained importance in pharmacy. They are made of a lipid matrix which is solid at body temperature. SLNs are stabilized by the use of appropriate surfactants. The size of SLNs is generally less than one micrometer.[11,12] On other hand Nanostructured Lipid Carriers (NLCs) are considered second generation solid lipid nanoparticles which are made up of a blend of solid and liquid lipids and this lipid matrix is stable at body temperature.[13] There are some limitations associated with solid lipid nanoparticles

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that include crystalline nature of solid lipids, less entrapment efficiency, stability on storage and drug expulsion. In addition, the proportion of water used in preparation is high. To reduce these limitations associated with solid lipid nanoparticles, there is a need for nanoparticles that can form imperfect crystalline structures to increase drug payload and to minimize the drug expulsion. The presence of liquid lipid in nanostructured lipid carriers distorts the highly ordered crystalline structure of solid lipids which leads to the creation of imperfections in the lipid matrix. These imperfections further allow entrapping more drugs than solid lipid nanoparticles. The lipid matrix of NLCs maintained solid at room and body temperature by using the proper proportions of solid and liquid lipids. Compared to SLNs, NLCs show less toxicity, more entrapment efficiency, and no drug expulsion because of the immobility of the drug from the lipid matrix.[14,15]

Nanostructured lipid carriers

Nanostructured lipid carriers are considered second generation nanoparticles that came into existence in 1999.[13,16] Nanostructured lipid carriers are nanocarriers that are made up of a blend of solid and liquid lipid along with surfactants. Compared to solid lipid nanoparticles, nearly 5-40 percent of solid lipid proportion is replaced with liquid lipids in the case of nanostructured lipid carriers. Nanostructured lipid carriers can facilitate drug entrapment capacity and controlled the release of drugs.[17,18] Liquid lipid present in nanostructured lipid carriers distorts the highly ordered crystalline structure of solid lipids and forms the imperfect structure permitting higher drug payload and no drug expulsion. The drug cannot escape from the lipid matrix because of their amorphous nature.[13] The proportion of solid lipid and liquid lipid used for the preparation of nanostructured lipid carriers is generally 99:9:0.1 or 70:30. The system is stabilized by using surfactants of 1-5% concentration.[19-21]

Benefits of NLCs

High physical and Chemical stability.[22]

Ease of preparation.[23]

Biocompatible.[12]

Higher drug loading and entrapment potential.[13,24]

Improved drug release.[25]

Types of NLCs

NLCs can be classified as imperfect type, amorphous type and multiple type based on lipids used, surfactant concentration, nature of the drug, solubility characteristics and method of preparation.

Type I NLCs (Imperfect Type)

In the case of imperfect type, solid lipid and liquid lipid are mixed in such proportion to form a highly disordered imperfect lipid matrix. This formed imperfect lipid matrix further ensures high drug entrapment in it.[26-28]

Type II NLCs (Amorphous Type)

In the amorphous type there is no formation of crystalline structure and the lipid matrix is amorphous which ensures no drug escape from NLCs on storage.[28-30] Formation of this type of NLCs takes place by using lipids that do not recrystallize on cooling.[31]

Type III NLCs (Multiple Type)

In this type, NLCs are formulated by the double emulsion technique which is nothing but oil in fats in water. The formulation is done by using the phase separation technique. This method is used if the drug has more solubility in liquid lipid which further helps to increase drug payload.[9]

Composition of NLCs

The main ingredients required for the formulation of nanostructured lipid carriers include solid lipids, liquid lipids and water. The system is stabilized by using a surfactant or a mixture of surfactants.[23] The lipid matrix is imperfect and is made up of a blend of solid lipid and liquid lipid.[32]

Lipids

For the formulation of nanostructured lipid carriers, lipid selection plays an important role as this can further provide stability and desired physicochemical properties.[33] For selecting lipids many factors have to be considered that include:

Lipids should have biocompatibility, biodegradability. They should form nanoparticles that should be in the nano range.[34]

As NLCs consist of solid lipid and liquid lipid. Both lipids should be miscible with each other as well as they should be compatible with each other.[35]

The lipids should not show any toxicity. They should not form any toxic by-products while the formulation of NLCs.[36]

Lipids are more prone for degradation by oxidation or lipolysis. Therefore lipid used for the preparation of NLCs should show good chemical stability.[35]

Solid lipids used for the preparation of NLCs are glycerylpalmitostearate, cetyl palmitate, stearic acid, glycerylmonostearate and glycerylbehenate.[37-40] Most frequently used liquid lipids in the formulation of NLCs include oleic acid, natural edible oils, and medium chain triglycerides.[41-45]

Emulsifiers

In the formulation of nanostructured lipid carriers, emulsifiers are used for the dispersion of two immiscible phases into each other. Also, emulsifiers stabilize the system effectively by preventing the formation of aggregates.[46] They reduce the interfacial tension between lipid phase and water which further leads to the formation of small particles with more surface area.[47] Emulsifiers can be hydrophilic or lipophilic. A combination of hydrophilic and lipophilic emulsifiers prevents the formation of aggregates more effectively.[48-50] The most commonly used hydrophilic emulsifiers are pluronic F68, polysorbates, and poloxamer 188. Span 80, lecithins, and phospholipids are lipophilic emulsifiers used for the formulation of NLCs.[51-53]

Method of preparation

Fabrication methods for NLCs include High pressure homogenization (HPH), Microemulsion technique, Ultrasonication, Solvent diffusion technique, Solvent injection method, Solvent emulsification technique etc. Description of these methods used for preparation of NLCs is given in Table 1.

Characterization of NLCs

Zeta potential

Zeta potential is defined as the net charge present on the dispersed particles present in the dispersion medium. Zeta potential determination gives an idea about the stability of the system and also the presence of aggregates which can hamper the stability of the formulation.[70] Particles are more stable when they have a surface charge on them as they repel each other electrostatistically which further prevents particle aggregation.[71] The stability of colloidal dispersions can be evaluated by measurement of zeta potential as it gives an idea about electrostatic repulsion between the particles and also the presence of aggregation. 30 mv of zeta potential value is considered for physically stable preparations.[72]

Particle morphology

The shape and morphology of nanoparticles can be determined by Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). These techniques are also used for determining particle size distribution.[73] In the case of SEM and TEM, original morphology cannot be obtained because of many reasons that may include shrinkage of nanocarriers due to dehydration which leads to change in the structure of nanocarriers.[74] To eliminate the limitations associated with SEM

Table 1: Formulation Methods of NLCs.

Method	Procedure	References
Hot HPH	This method involves heating lipid phase containing drugs and lipids to form lipid melt. The aqueous phase containing surfactant solution is also kept at the same temperature as that of the lipid phase. Then aqueous phase is added to the lipid phase with stirring and resulting pre emulsion subjected to HPH which on recrystallization give NLCs.	54-57
Cold HPH	This method involves the dissolution of a drug in lipid melt which is further solidified with the help of liquid nitrogen. After milling it generates nanoparticles which are then dispersed in a cold surfactant solution. It is then subjected to HPH to generate NLCs.	
Microemulsion	This method involves heating lipid phase containing drugs and lipids to form lipid melt. The aqueous phase containing surfactant solution is also kept at the same temperature as that of the lipid phase. Then aqueous phase is added to the lipid phase with stirring. Lipid nanoparticles are then solidified by dispersing hot o/w microemulsion in ice cold water.	58,59
Ultrasonication	Dissolve lipid phase in organic solvent methylene chloride. Heat the mixture at 50°C. The aqueous phase consisting of surfactant solution is heated at the same temperature. Evaporate half of methylene chloride and then add the aqueous phase to the lipid phase with stirring. The resulted emulsion is then subjected to sonication and solidified by keeping in it ice bath.	15,60
Solvent diffusion method	This method comprises 2 stages in which the organic phase contains drug and lipophilic surfactant which then are added to organic solvent with increasing temperature. Then resulted organic mixture is added to the aqueous phase containing surfactant at room temperature with stirring until the formation of NLCs. To remove residue of solvent it is then kept in vacuum desiccators for 24 hr.	34,61-64
Solvent injection method	Dissolve lipid in ethanol or DMSO. This mixture is then added rapidly to the aqueous phase containing surfactant with the help of an injection needle which leads to the precipitation of lipid particles. The precipitate is then filtered to get nanoparticles.	65,66
Phase inversion temperature method	This method is based on the change in the phases in the emulsion that is from o/w to w/o. Change in the dispersion temperature has resulted in alteration in the interfacial structure of droplets which further gives phase inversion.	67-69

and TEM, a new technique that is atomic force morphology which gives three dimensional structures of nanocarriers is used.[75]

Particle size

Size of particle and particle size distribution plays an important role in the determination of the physical stability of the formulation. Measurement of particle size is done by using photon correlation spectroscopy and laser diffraction.[76] Particle size in nanoscale can be measured by using zetasizer.[77] In the case of NLCs particle size can be affected by the type and proportion of lipids and emulsifiers used. Also in the case of NLCs as emulsifier concentration increases, particle size decreases.[61]

Drug encapsulation efficiency

The entrapment efficiency can be defined as the ratio of the drug into particles by total weight of particles. Entrapment efficiency is also called encapsulation efficiency or drug payload capacity. Determination of drug encapsulation efficiency is very useful as it gives an idea about the efficiency of NLCs as a carrier.[78] The drug should have good solubility in lipids to get high entrapment efficiency.

Crystallinity and polymorphism

Both crystallinity and polymorphism can be determined by differential scanning calorimetry and X-ray diffractometry. These techniques give an idea about the melting and recrystallization pattern of solid lipids present in NLCs. The polymorphic transition of lipids also can be determined by using these methods. The crystal lattice structure of special crystalline compounds can be identified using wide angle X-ray diffractometry.[79]

Surface tension

Torsion balance, Kibron instrument, Wilhelmy plates can be used for the determination of surface tension. The mostly used instrument for measuring the surface tension of NLCs is torsion balance. Surface tension can also be determined by calculating contact angle.[80]

In vitro drug release

Release of drug from nanostructured lipid carriers is based on some factors like composition of lipid matrix, the concentration of surfactant and lipids, temperature used for formulation. Enzyme attacks in systemic circulation are prevented by developing controlled release formulation.[79] Firstly drug release will take place in a burst manner from the outer layer of nanoparticles and after that drug will get release from the inner core for prolong time period. Distribution of drug between water and lipid matrix can give an idea about the sustained release of drug.[81,82]

Cancer

Cancer is the second most disease in the world for death after cardiovascular disease.[83] In cancer there is persistent tissue damage is there which is associated with several other severe disorders and also leads to death. The uncontrolled cell growth as well as disturbed cell cycle results in the formation of tumors. Cancer metastasis is another reason for death a spread of disease can be there from one to another organ.[84,85]

Currently available treatments available for cancer are surgery, radiation, and chemotherapy. These treatments are used in combination. Among these treatments chemotherapy is the most commonly used treatment.[86] For metastatic cancer radiotherapy and surgery are the preferred treatments but these treatments are not sufficient if the spread of cancer is there throughout the body. As anticancer drugs can reach each organ through systemic circulation therefore anticancer drug therapy i.e., chemotherapy is the choice of treatment in case of metastatic cancers. These anticancer drugs act by inhibiting the growth of cancer cells but also they retard the growth of normal cells of GIT, bone marrow and hair follicles therefore these drugs are associated with unwanted severe side effects.[87]

Limitations of conventional cancer therapy

The intravenous route is preferred for administration of anticancer drugs as its makes drug available in systemic circulation immediately. IV route is effective for killing cancer cells but along with cancer cells, it also kills normal healthy which is thereby associated with many severe side effects.[2,3] Cardiotoxicity, nephrotoxicity, vomiting, nausea, diarrhea, loss of hair, neurotoxicity, myelosuppression are some of the side effects associated with IV administration of these anticancer drugs.[88-91] The non specificity of these chemotherapeutic agents towards tumor cells is because of their high volume of distribution which is also the reason for the availability of drug concentration in healthy tissue.[92]

Because of non-specificity of anticancer drugs conventional chemotherapy is unable to deliver the required concentration of drug to the tumor cells and also affects the functioning of the normal healthy cells which further leads to multiple drug resistance (MDR).[5,6] Most of the Anti-cancer drugs have restricted delivery at the targeted site because of their lipophilic nature.[93] One of the reasons behind the failure of chemotherapy is the drug efflux mechanism which makes very less amount of drug to be available at the site of action. Most lipophilic anticancer drugs are thrown out of the cell because of efflux transporters.[94] Therefore conventional chemotherapy is associated with many limitations like non-selectivity and non specificity of chemotherapeutic agents, toxic effects, and severe side effects and restricted targeting.[95]

Barriers in drug delivery to tumors

After the administration of the drug it gets entre into the systemic circulation and thereby gets distributed to various tissues and organs. There are different factors like physical and chemical

properties of anticancer drugs, physiological barriers, drug carriers that can limit the delivery of anticancer drugs to tumor cells.

In the case of malignant cancers as the cells show uncontrolled growth therefore these tumors do not have a specific structure and composition. This abnormal composition and non- specificity of tumors is the major barrier for penetration of anticancer drugs.[96] The main barrier which plays the main role in the delivery of Anti-cancer drugs is the uneven distribution of vasculature of tumors.[97] Another barrier is the structural characteristics of tumor vessels. These tumor vessels vary from the normal ones. Tumor vessels are leaky, defective, dilated and irregular. The endothelial cells have large fenestrations and there are no basement membranes. Impaired lymphatic networks are observed.[98] The third barrier that can affect the drug transport across the tumor is extracellular matrix composition of the tumor.[99] A very small amount of anticancer drugs is available at the site of absorption because of the extensive tendency of these drugs to bind with blood proteins and tissues which are very unpredictable.[100] This binding tendency of anticancer drugs results in less therapeutic action and more toxic effects. In addition, non-specificity of these anticancer drugs not only kills tumor cells but also the normal cells which leads to severe side effects.[101,102] Because of this non -specificity in terms of biodistribution and pharmacology of anticancer drugs even on normal therapeutic doses, these drugs can affect the normal healthy tissues and this is the main challenge in the treatment of cancer.

Drugs efflux pumps are considered as the special mechanism by which anticancer drugs are thrown out of the tumor cells which leads to insufficient action of anticancer drugs on tumor cells because of the availability of less amount of administered drug at the site of action. P glycoproteins are an example of this efflux transporter. Most anticancer drugs are P-gp substrates and overexpression of this transporter may decrease the therapeutic effectiveness of anticancer drugs.[103]

Another physiological barrier to the delivery of anticancer drugs is the tight junctions of epithelial cells present in some tumors. These tight junctions formed because of interconnections of proteins. These tight junctions are considered as one of the physiological barriers which do not allow the drug to enter inside the tumor. As drug entry is restricted inside the tumor because of tight junctions it leads to less availability of drugs inside the tumor and low therapeutic efficacy.[104]

In multiple drug resistance, cancer cells are resistant to structurally and functionally different drugs which are not related to each other after the treatment with an anticancer drug. Multiple drug resistance is considered as one of the limitations of chemotherapy.[105] Mechanism of multiple drug resistance involves overexpression of efflux transports like P-gp or MDR associated proteins.[106] These efflux transporters belong to ATP- binding cassette family. These efflux transporters are responsible for low concentration of anticancer drugs inside the tumor as these transporters throw out the drug outside the cancer cells which further leads to the development of resistance.[107] Non-selectivity and Non-specificity of anticancer drugs is another problem associated with effective chemotherapy. These drugs kill normal non cancerous cells alone with cancer cells because of their non-specific action. This non- specificity further also results in severe side effects which also affect the drug dosing. High drug doses cannot be given as they will harm normal cells and low doses will not give the required therapeutic action.

Nanocarriers in cancer therapy

Because of non-specificity of anticancer drugs, there is the destruction of cancer cells along with non-cancerous cells which is also the main reason for less availability of the drug at the target site and toxic effects associated with conventional chemotherapy.[5] To avoid all these problems there is a need to develop such drug delivery systems that can give targeted drug release and will minimize the toxic effects. Nanocarrier based drug delivery systems like nanostructured lipid carriers can have the potential to reduce the limitations associated with conventional chemotherapy which can give selectively targeted drug release with minimum toxicity and avoid multiple drug resistance.

Nanostructured lipid carriers can be developed for therapeutic and cosmetics purposes. As the lipids used in the formulation of NLCs show good biocompatibility and biodegradability therefore they are safe and very suitable to use as a potential drug delivery system. They can entrap both hydrophilic and lipophilic drugs. NLCs offer many advantages as they have more drug payload capacity, biocompatibility, biodegradability. They can also increase the bioavailability of drugs and facilitate the controlled and sustained release of drugs. They have the potential to prevent enzymatic degradation of drugs as well as the first pass metabolism of the drugs.[108,109] Nanostructured lipid carriers can be the budding drug delivery system for delivering anticancer drugs because of their ability to enhance and stabilize the anticancer drugs physically and chemically. In addition these carriers are responsible to improve the therapeutic efficacy of anticancer drugs.[13,110,111]

Nanostructured lipid carriers are preferred to deliver anticancer drugs for many reasons. Firstly, NLCs have the size in the nano range which offers a high surface area. Further this increases affinity of these nanoparticles with anticancer drugs which helps to attain controlled and targeted drug delivery. Interaction of NLCs with biomolecules improves drug uptake across the cell membrane and the ability to bind ligands which further reduce the dose and minimize side effects.[112,113] Secondly a selective drug delivery across leaky endothelium of tumor is possible because of Enhanced Permeation Retention (EPR) effect which allows the drug to accumulate selectively at the site action. EPR effect

increases drug concentration intercellularly which leads to less toxic effects.[114,115] Thirdly, NLCs have good biodegradability and biocompatibility therefore they can easily get metabolized into non-toxic products after complete drug delivery. They are removed from the body by the mononuclear phagocytic system.[116] The versatile nature of nanostructured lipid carriers plays an important role to encapsulate anticancer drugs.[36]

Approaches to enhance drug delivery to tumor cells by drug targeting

Currently, the main challenge in the delivery of anticancer drugs is to develop nanocarriers with selectivity for the specific targets. This will help to improve the therapeutic efficacy of anticancer drugs as well as will minimize the side effects associated with conventional chemotherapy.[117] Drug targeting to tumor cells can be achieved by two approaches i.e., passive targeting and active targeting.

Passive targeting

Passive targeting of NLCs can be possible if the solid tumor has leaky vasculature and defective lymphatic drainage which facilitate the accumulation of NLCs inside the tumor This phenomenon is called as Enhanced Permeation Retention (EPR) effect (Figure 1).[118,119] In passive targeting permeability of endothelium of blood vessels of tumor is enhanced than the normal cells. In metastatic cancers tumor also involves new vessels or surrounding vessels. These leaky vessels allow selective permeation of nanocarrier to the stroma of tumor. This feature does not apply to the small molecular drugs as they have low circulatory time thereby get removed immediately from the tumor. Therefore encapsulation of such drugs in a suitable nanocarrier can enhance the pharmacokinetic properties of drugs there by prolonging circulation time in blood and minimizing side effects caused because of Non-selectivity of this drugs.[120]

Because of the poor lymphatic system, interstitial pressure at the center of the tumor is more than the periphery. When the internal pressure is increased it results in the flow of external interstitial fluid which further reduces the diffusion of the drug towards the center of the tumor thereby permitting the drug to stay in interstitial fluid and this further increases drug retention time.[114]

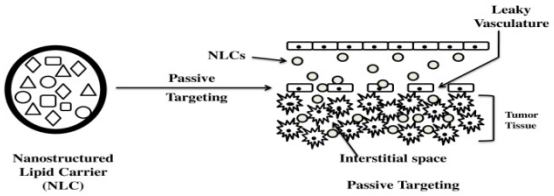

Figure 1: Drug delivery by passive targeting.

To achieve passive targeting NLCs should have properties like the size of NLCs should lie between 10-100 nm. Charge on NLCs should be anionic and neutral and NLCs should be safe from RES as it is involved in the removal of NLCs out of the tumor.[116,121]

Active targeting

Active targeting involves targeting nanocarriers to particular cells after extravasations. Active targeting depends on molecular recognition of cancer cells by interaction with specific receptors which are overly expressed on them and minimally expressed with normal cells. This molecular recognition can be by ligand-receptor interaction or antigen-antibody interaction.[122,123] Active targeting can be aimed at surface modification of nanocarriers with cancer cells specific ligands that will identify and bind to molecules or receptors that are complementary with each other on the surface of target cells (Figure 2). Therefore active targeting helps to achieve nanocarrier selectivity towards tumor cells.[124] Antibodies, vitamins, peptides can be used as ligands that can identify specific overexpressed receptors present on cancer cells.[125]

The choice of ligands will be based on the ability to bind to overexpressed receptors on tumor cells and not to normal cells. On the target cells, there should be the homogenous expression of targeted receptors. Monoclonal antibodies, peptides, antibody fragments are examples of targeting ligands. Ligand's binding affinity can influence tumor penetration because of the binding site barrier. When target cells are easily accessible, high binding affinity can be observed because of the flow environment of the bloodstream.[126,127] Targeted NLCs can be developed in such a way they will show passive endocytosis or endocytosis with specific interaction with receptors.[128]

Drug targeting by long circulating NLCs

Our immune system identifies nanostructured lipid carriers as foreign material after their intravenous administration. Therefore NLCs get immediately removed for systemic circulation by the mononuclear phagocytic system through surface recognition of NLCs. Site specific delivery cannot be achieved with unprotected NLCs as they are removed within seconds after the administration.[129]

After the intravenous administration, these nanocarriers in the bloodstream interact with opsonins by attractive forces such as hydrophobic or hydrophilic, van der walls, ionic or electrostatic. Without opsonins tagging on nanocarriers surface, phagocytic cells are not able to identify them as non-self-material. To remove NLCs, opsonization is considered an important step. To stop or inactivate this process attempts have been made to develop long circulating drug delivery system.[130]

To decrease immunogenicity and to impart long circulating properties, surface modification such as PEGylation is mostly used (Figure 3). Recirculation of nano-size NLCs can be improved with the use of high molecular weight PEG.[131,132] PEGylated

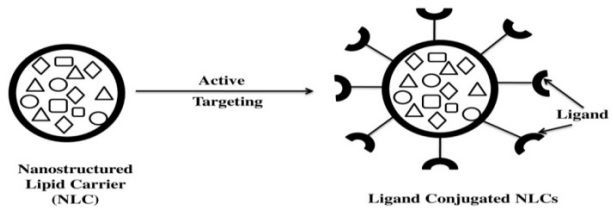

Figure 2: Drug delivery by active targeting.

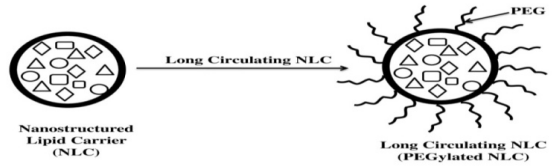

Figure 3: Long circulating NLCs.

10-hydroxycamptothecin NLC has produced long circulating effect in Kumming mice. There were 40 fold improvements in the maximum concentration of drug in the lungs than the free drug solution.[133]

CONCLUSION

Cancer is the second most cause of death worldwide. By understanding the complete microenvironment of tumor cells which limits the delivery of anticancer drugs we can come up with a better solution that is the formulation of nanostructured lipid carriers. Nanostructured lipids carriers can give targeted drug delivery of anticancer drugs to tumor cells by facilitating the specificity of anticancer drugs thereby minimizing side effects associated with conventional chemotherapy. They offer many benefits like high drug payload, P-gp efflux inhibition, Inhibition of MDR. They provide long circulating effect which helps to achieve controlled drug delivery. They show less toxicological profile because of their biodegradability and biocompatibility. Effective and specific drug delivery of anticancer drugs can be possible by considering different drug targeting strategies while formulating NLCs of anticancer drugs. Therefore NLCs can provide a new platform for selective delivery of anticancer drugs to the tumor cells and can be considered as a potential nanocarrier for cancer treatment.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NLCs: Nanostructured Lipid Carriers; **SLNs:** Solid Lipid Nanoparticles; **HPH:** High Pressure Homogenization; **O/W:** Oil in Water; **W/O:** Water in Oil; **DMSO:** Dimethyl Sulfoxide; **SEM:** Scanning Electron Microscopy; **TEM:** Transmission Electron Microscopy; **IV:** Intravenous; **MDR:** Multiple Drug Resistance; **P-gp:** P Glycoprotein; **EPR:** Enhanced Permeation Retension; **RES:** Reticuloendothelial System; **PEG:** Polyethylene Glycol.

SUMMARY

Cancer is a life-threatening disease that is associated with persistent tissue injury and uncontrolled cell growth. Because of the non-specificity of anticancer drugs, they kill normal healthy cells along with cancer cells which lead to severe side effects. To minimize such limitations associated with conventional chemotherapy, nanostructured lipids carriers can be developed. They offer many benefits like high drug payload, P-gp efflux inhibition, Inhibition of MDR. They provide long circulating effect which helps to achieve controlled drug delivery.

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