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Review Article

SOLID LIPID NANOPARTICLES: A NOVEL CARRIER FOR CHEMOTHERAPY

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ABSTRACT

The main goals of Solid Lipid Nanoparticles (SLN) in terms of drug delivery are to increase the bioavailability and efficacy of drugs, to control non-specific toxicity, immunogenicity, pharmacokinetics and pharmacodynamics of drugs. This review focus on, the potential of SLN in various types of chemotherapy such as cancer, parasitic infections and tuberculosis. The use of conventional chemotherapy is hampered due to obstacles such as poor specificity, side effects, drug resistance and poor stability of chemotherapeutic compounds. These obstacles may be partially overcome by encapsulating them as SLN. The new generations of SLN such as Nanostructured Lipid Carriers (NLC), Lipid drug Conjugates (LDC), Polymeric Lipid Hybrid Nanoparticles (PLN), long circulating SLN, improve the role of SLN as a versatile drug carrier for various types of chemotherapy. Various studies have suggested that SLN can improve the pharmacokinetics, biodistribution and stability of many chemotherapeutic agents. The results of various in-vitro and animal studies were found to be promising. In the near future, it can be predicted that SLN will further improve the chemotherapeutic drug delivery in a more specific, efficient and safer manner.

Keywords: Chemotherapy, Solid lipid nanoparticles (SLN), Polymeric lipid hybrid nanoparticles (PLN), Nanostructured lipid carriers (NLC)

INTRODUCTION

The term chemotherapy was introduced by Paul Ehrlich in 1907, initially referring to antiparasitic therapy, now refered more broadly to the use of any chemical compound that selectively acts on microbes or cancer. Chemotherapy is the treatment or prevention of disease by chemical substances that kill cells, specifically those of microorganisms or cancer. The drugs used in chemotherapy are also referred as chemotherapeutic agents or cytotoxic agents[1]. Use of conventional chemotherapy is hampered due to toxic side effects, poor specificity and drug resistance leading to a narrow therapeutic window of cytotoxic drugs. Hence for cytotoxic drugs a novel drug delivery system is required, for tumor specific drug delivery to increase the therapeutic index.

Safety and efficacy of a pharmaceutical agent can be greatly improved by incorporating drug into polymers or lipids. Particulate colloidal drug carriers are more promising in improving drug safety and therapeutic efficacy of chemotherapeutic drugs. Solid lipid nanoparticles (SLN) also referred as lipospheres are a new generation of colloidal drug carriers. SLN are submicron sized particles in the range of 50-1000 nm, made up of physiological lipids that remain solid at body and room temperature and was first introduced by Muller et al in 1991[2]. SLN can be prepared by using lipid(s), waxes and biocompatible surfactant(s) using methods like High pressure homogenization, Microemulsificaton, Emulsification-solvent evaporation, Emulsification-solvent diffusion, Multiple emulsion, Solvent injection etc [3-17]. In last two decades SLN have been proved to be a potential carrier for therapeutic [16-19], cosmetics and dermal [20-28], and diagnostic applications [29-31].

Solid Lipid Nanoparticles (SLNs) have attracted increasing scientific and commercial attention as colloidal drug carriers during the last few years. This is because SLN combine several advantages and avoid or minimize the disadvantages of other colloidal carriers such as lipid emulsion, liposome, and polymeric nanoparticles. Proposed advantages include:

- The possibility of controlled drug release and drug targeting [4,6,16-19]
- Generally less toxic as compared to some polymeric nanoparticles because physiological and biocompatible lipids are used [32-33].
- Protecting the labile and sensitive drugs from chemical, photochemical or oxidative degradation, due to immobilization of drug molecules by solid lipids [34] and reduce drug leakage as commonly observed in liposomes.
- the ease of scale-up and manufacture [35-38], flexibility in sterilization [6,39]
- Low cost of solid lipids as compared to phospholipids and biodegradable polymers.
- Avoidance of organic solvents.
- Both lipophilic and hydrophilic compounds can be encapsulated and delivered by SLN with modification in the formulation[11, 40].
- SLN have been proposed as a colloidal drug carrier therapeutic system for different administration routes such as oral [40-45], dermal [25-28], ophthalmic [46-49], pulmonary [50-52], rectal[53] and particularly for parenteral administration[18,54]

Barriers in conventional chemotherapy

i) Poor specificity: Poor specificity of cytotoxic drugs is due to poor biodistribution at cellular level. Effective therapeutic concentration at target site is difficult to achieve in traditional chemotherapy because cytotoxic drugs also have high affinity to other body tissues and serum proteins, which may also leads to increase in systemic toxicity. For more instance, cytotoxic drugs are also toxic to non-target cells like rapidly dividing cells of gastrointestinal tract and bone marrow [55].

ii) Side effects: Poor specificity of cytotoxic drugs results in complications of treatment or side effects. In traditional chemotherapy side effects are measured and reported as part of treatment evaluation. The side effects may be acute, chronic or permanent. Side effects cause inconvenience, discomfort and may occasionally be life threatening or fatal. All chemotherapies are associated with a wide range of side effects. However some side effects occurs more frequently like anemia, alopecia, depression, low blood counts, mouth sores, nausea and vomiting, neutropenia, thrombocytopenia and other side effects are drug specific e.g. Rifampicin can cause hepatotoxicity, Anthracyclines can cause cardiotoxicity. Thus poor side effect profile of cytotoxic drugs prevents doctors from delivering prescribed therapy at specific time that reduces the chance of achieving desired outcomes [56-58].

iii) Drug resistance: Resistance to chemotherapy can be developed at cellular level or non- cellular level which results in decreased therapeutic concentration at the target site. Cellular mechanism involve over expression of ATP dependent membrane associated drug efflux transporter in the target cell e.g. P-glycoprotein (P-gp), multi drug resistance associate protein, breast cancer resistance

protein. This type of cellular drug resistance is also known as multi drug resistance (MDR) phenotype [59, 60].

Other cellular mechanisms for drug resistance involve: Alteration in drug target e.g. tubulin, Detoxification of drug e.g. over expression of glutathione-S-transferase, Deficiency or modification of protein that direct the apoptotic pathway. Non cellular drug resistance associated with physiology of target tissue like poor blood supply, inappropriate physicochemical conditions like high interstitial pressure in tumor restrict the entry of cytotoxic drugs inside the tumor and lower pH at target site causing deactivation of some basic drugs. Lack of oxygen also reduces ability of cytotoxic drugs generating oxygen radicals [61-63].

Reasons for using SLN in chemotherapy

1. Enhanced permeability and retention (EPR) effect: This is a drug delivery strategy that utilized pathophysiological and anatomical imperfections of tumor tissues for tumor specific targeting. Macromolecules like proteins, polymer drug conjugates, nanoparticles and lipidic particles have demonstrated increased or selective accumulation in solid tumors. This phenomenon is known as EPR effect [64]. EPR effect is the characteristic of enhanced permeability of tumor vessels, imperfection in tumor vessels, high vascular density and defective lymphatic drainage in the tumor. Due to these pathophysiological characteristics of tumor cell, macromolecules easily enter into the extra vascular space in the tumor and slow venous return and poor lymphatic drainage in tumor allows macromolecules to be retained in the tumor which results in high local concentration [65-69].

   So passive tumor targeting of cytotoxic drugs can be achieved by incorporating them into SLN and the obstacle of poor specificity can be partly overcome.

2. Active tumor targeting may also be possible by altering biodistribution of SLN through physicochemical properties of surface to minimize systemic toxicity and target drug to specific site [70-75].

3. Encapsulation of chemotherapeutic drugs: Ranges of chemotherapeutic drugs are available for the treatment of various diseases like cancer, tuberculosis and parasitic infections. These drugs have distinct molecular structure and physicochemical properties which makes encapsulation of these drugs in a pharmaceutical carrier difficult. SLN can be used to incorporate variety of lipophilic, hydrophilic and ionic compounds. For more intense, SLN have inherent capability to incorporate lipophilic compounds effectively and the new generation of SLN like Lipid Drug Conjugate (LDC), Polymer-lipid hybrid nanoparticles (PLN) are utilized for encapsulating hydrophilic and ionic compounds.

4. Excipients used in the preparation of SLN are biocompatible and approved by regulatory agencies [76-78].

Limitations of SLN and strategies to overcome them

The properties of SLN lead to following challenges which limits the use of SLN for several chemotherapeutic agents to achieve effective chemotherapy:

(a) Entrapment of water soluble drugs

(b) Avoidance of Reticulo Endothelial System(RES)

(c) Controlled and extended release of drugs

To overcome aforementioned challenges various strategies have been developed to make SLN as a versatile carrier for chemotherapy. The details of these strategies are as following:

(a) Entrapment of water soluble drugs: Chemotherapeutic agents are a class of highly diversified compounds which shows different physicochemical properties. Hence some chemotherapeutic drugs are lipophilic and some hydrophilic in nature. During manufacturing of SLN, solid lipid need to be melted and dispersed as nano sized droplet into aqueous phase by mechanical means to obtained SLN with good entrapment efficiency where the drug needs to be adequately partitioned into these small droplets[16]. Hence lipophilic drugs e.g. Camptothecin; Paclitaxel can be efficiently entrapped into SLN due to their inherent ability to partition well into the lipid. There are also number of water soluble chemotherapeutic drugs available e.g. Mitomycin C, 5- Fluro Uracil (5-FU), and Floxiuridine (FuDR). In addition some lipophilic drugs are commonly administered in aqueous vehicles (e.g. 0.9% NaCl solution) by using their salt form. For example Doxorubicin and vincristin are mostly used as their hydrochloride salt. Encapsulation of these hydrophilic drugs into conventional SLN results in low drug loading into carriers, because very less amount of these drug partition into lipid phase during manufacturing and the prepared SLN are beneficial only where very small quantity of drug is required to achieve therapeutic response [79]. But this is not applicable to chemotherapy where high amount of drugs are required [80].

To increase the drug loading of water soluble drugs in SLN following strategies have been developed by researchers:

(i) Gasco et al used organic counter ion to form ion pair with charged drug molecule. They prepared stearic acid SLN of doxorubicin HCl and idarubicin HCl, and their loading improved by using decyl phosphate and hexadecyl phosphate. Significant increases in partitioning of these drugs into lipid were observed [81].

(ii) Lipid Drug Conjugate (LDC) Nanoparticles: This strategy involves formation of insoluble lipid-drug conjugate either by salt formation or covalent linking like ester linkage. Then the formed LDC was mixed into aqueous surfactant solution for preparation of SLN by homogenization or other methods [82].

(iii) Polymer Lipid hybrid Nanoparticles (PLN): This is the most recent strategy [83-85] which involve formation of complexation of drug and ionic polymer; this was previously studied for ionic cytotoxic drugs and chemosensitizers [86-90]. Charges on drug are neutralized with polymer counter ion and the formed complex is encapsulated into SLN. By using this approach, doxorubicin HCl and verapamil HCl SLN were prepared [83]. There was increased encapsulation efficiency from 20-35% to over 80%. Another strategy [86] suggested that by proper selection of drug-polymer and lipids having good compatibility, high partitioning of verapamil HCl in to lipid phase (upto33%) and upto 90% loading were observed.

All these aforementioned strategies cannot be applicable to the drugs which are highly water soluble and not having any charges. For these kinds of drugs, their lipophilic derivatives can be prepared by chemical synthesis. For example, Wang et al [72] encapsulated a lipophilic derivative of 5-FU which was 3', 5' – dioctanoyl-5 fluro-2' deoxy uridine (FuDR) into SLN. 5- FU is an antimetabolite which has low molecular weight having water solubility of 12.2mg/ml and present in unionized form. By preparing lipophilic derivative FuDR entrapment efficiency of over 90% was obtained. The only drawback of this approach is that it requires chemical synthesis and purification to prepare lipophilic derivatives. In addition, safety, stability and efficacy of these lipophilic derivatives should also need to be considered, which is a tedious task.

Avoidance of RES system*:* RES is important only when passive targeting of drug to lymph node, liver and spleen are desired. But if the drug is meant to target other sites, than RES clearance act as a major barrier to these drugs delivery by SLN. Uptake via RES can be avoided by coating of particles with hydrophilic polymers such as PEG, poloxamine etc. The proposed mechanism for this is that, these hydrophilic polymer results in adsorption of proteins on the surface of the particles which decrease opsonization in-vivo [91]. As a result particulate carriers become more resistant to RES clearance. These particles are also referred to as "long circulating carriers" or "stealth particles". Studies shows that these types of particles remain in circulation for long time, with half life of 55 hours in human subject and few hours in animal models [91-93]. The use of stealth SLN is at its infant stage, but the interest is increasing.

SLN safety or stability may be affected due to changes in the physicochemical properties, after coating with hydrophilic polymers; this should be considered during formulation of long circulating SLN. For more instance, Cavilli et al [94] prepared stealth SLN of doxorubicin using PEG 2000. For attachment of hydrophilic PEG onto the surface of SLN, PEG molecules were pre conjugated with lipophilic part like stearic acid, dipalmitoyl phosphotidyl ethanolamine to form stealth coating agent. Hydrodynamic volume of nanoparticles increased due to presence of hydrophilic polymer onto the surface. They have observed that by increasing the concentration of stealth coating agent average particle diameters were increased and zeta potential were decreased, as a result polydispersity index were decreased. Another study [95], showed that drug loading was unaffected in PEG coated SLN. Biodistribution studies of stealth SLN containing paclitaxel, doxorubicin 94-96 were also carried out. The details of these studies will be discussed in the next section. But in general, stealth SLN showed prolong residence time in systemic circulation and it may also be possible to prepare surface engineered SLN for active targeting to specific sites.

Controlled release of drugs: The release patterns of SLN are another limitation of this carrier for use in chemotherapy. The SLN developed in 90s have showed biphasic and uneven release profile. There was a quick release of large dose followed by non-uniform release [97]. The initial fast release of drug is also referred to as "burst release". This type of release is not suitable to deliver chemotherapeutic drugs, because due to burst effect large amount of these drugs quickly release in circulation or to the site of administration (local regional injection) which can leads to potential health hazards. The possible reason for this burst release may be due to the uneven distribution of drug in SLN due to improper selection of lipid or surfactants or manufacturing and storage conditions. For more instance, during SLN preparation many lipids (e.g. tripalmitin) may form perfect crystal lattice in solid state which provide space for large amount of drug molecules [34, 98, 99]. This will leads to expulsion of drug to outer surface of SLN. In addition, during long term storage polymorphic transition in lipid leads to lipid crystallinity, which may also result in expulsion of drug to outer surface of SLN [100]. Due to this deposition of drug at the outer surface, quick or burst release occurs [97]. Remedy for this problem is the adjustment of the production conditions [97]. Since lipid crystallinity is the main cause of burst release, this may be overcome by selection of lipids that do not form perfect crystals, like mono- or di-gycerides, or tri-glycerides with different chain length [18]. Burst release may also be reduced by rapid cooling of the lipid emulsion and/or by lowering surfactant concentration [16,101]. Another strategy was developed by Muller et al [22] to control the release pattern of drugs. This strategy involves the development of new generation of SLN also known as "Nanostructured Lipid Carrier" (NLC). In NLC, solid lipids are mixed with small amount of oils; as a result lipid crystallinity is reduced. In addition, NLC tend to be attractive carrier for chemotherapeutic drug delivery due to reduced burst release and increased payload of lipophilic chemotherapeutic drugs.

SLN as a novel carrier for chemotherapy*:* From last two decades several chemotherapeutic agents have been encapsulated in SLN and their in-vitro and in-vivo efficacy have been evaluated. Outcomes of these studies have been shown to improve the efficacy of chemotherapeutic drugs, simultaneously reduction in side effects associated with them. Improved stability of drugs, encapsulation of chemotherapeutic agents of diversified physicochemical properties, enhanced drug efficacy, improved pharmacokinetics and less in-vitro toxicity are the important features of SLN which make them a suitable carrier for delivering chemotherapeutic drugs [102].

In this section, role of SLN in various type of chemotherapy (Cancer, Tuberculosis and Parasitic Infection) have been discussed:

Role of SLN in cancer chemotherapy

The first in-vivo studies of SLN containing anticancer compound was carried out by Yang et al in 1999[54], they have used a chemically reactive compound camptothecin. Camtothecin is an anticancer plant alkaloid and is a proto type compound of class topoisomerase inhibitiors[103]. Camptothecin stabilizes the binding of topoisomerase I to DNA which lead to fragmentation of DNA in the G2 phase and leads to cell death. This activity depends upon the lactone ring of the drug molecule which can be hydrolytically opened and converted into the carboxylate. The study showed inactive carboxylate form of camptothecin formed. Only after release of camtothecin from SLN into neutral buffer medium[104] and in the acidic medium camtothecin remained as active lactone form. In other words, SLN are capable of predicting drugs which are more prone to hydrolysis.

The results of in-vivo studies of camptothecin-SLN(CA-SLN) in mice have show increased accumulation of CA-SLN in brain, heart and RES organs and comparison with camtothecin solution, CA-SLN show higher MRT and AUC. There was 18 fold enhancements in MRT, this is due to the coating of SLN with poloxamer. Higher concentration of CA-SLN in brain was attributed to transport of these SLN through BBB by endocytosis.

In 2000, Podio et al[105] studied the tissue biodistribution and transport across BBB of drug free stealth and non stealth SLN labeled with radiolabeled marker in rats. The average particle size was below 100 nm and the finding of this study showed localization of SLN in brain and cerebrospinal fluid (CSF). The study also demonstrated that after administration, SLN maintained their shape and size in plasma and lymph which confirms the findings of Cavilli et al [106].

The potential of Doxorubicin loaded stealth and non stealth SLN have been investigated in rats and rabbits by Cavilli and coworkers, for improved parentral delivery [94, 95]. In the first study [95], stealth and non stealth doxorubicin SLN were prepared by microemulsion template method. The pharmacokinetics and tissue distribution of doxorubicin loaded SLN were investigated in rats and compared with commercially available doxorubicin solution. The results demonstrated, low uptake of SLN by RES organs and there was a significant amount of doxorubicin detected in brain and CSF of rats. As compared to commercially available doxorubicin solution, there was significant increase in half life; peak plasma concentration and AUC. There was a 5- fold enhancement of peak plasma concentration for non stealth SLN and 7-fold enhancement for stealth SLN. Prolonged circulation time, upto 24 hours was also achieved with both stealth and non stealth SLN, while the drug was not present in animals after 180 min., injected with the solution. They suggested that prolong circulation time of SLN is depend upon amount of stealth agent present; by increasing the amount of stealth agent, circulation time also increases. As far as the cardiotoxicity of doxorubicin is considered, which limits its clinical use; there was low concentration of doxorubicin in the heart, when administered as SLN which showed low cardiotoxicity as compared to commercially available solution.

In another study [94], the pharmacokinetic and tissue distribution were carried out in rabbits using doxorubicin and stearic acid-PEG 200 as a stealth agent. This study also showed that the amount of doxorubicin in blood after injection is the function of stealth agent present. The result of this study confirms the findings of previous study[95], which attributed the brain targeting of stealth SLN. This may be due to retention of SLN in brain blood capillaries, which could create concentration gradient leading to increase in transport across the endothelial cell. Other possible mechanism may be transcytosis or endocytosis of SLN through the endothelial cell barriers, or permeation of SLN through tight junction between endothelial cells.

Amongest various anti cancer drugs, paclitaxel has been most extensively studied by researchers[107-111] to evaluate the potential of SLN. Koziara et al[108, 109] prepared paclitaxel loaded SLN by microemulsion template method and evaluated the potential of SLN for tumor delivery both by in-vitro and in-vivo. In the first study[108], the cytotoxicity of paclitaxel loaded SLN was evaluated in-vitro by using human glioblastoma cells like HCT-15 and U-118, to check the potential of these SLN in the treatment of brain tumor. In-situ rat brain perfusion was used for evaluation of drug brain uptake of SLN and results indicated increased brain uptake of SLN and increased cytotoxicity toward drug resistant tumor cells. In the second study[109], the potential of paclitaxel SLN were evaluated in-vivo by using HCT-15 mouse xenograft model. The findings of this study shows that paclitaxel SLN overcome the drug resistance in HCT-15

cell lines and in-vivo xenograft model when injected intra tumorlly. Significant efficiency was observed in the endothelial cell diffraction assays.

Lee et al [110], prepared stearically stabilized SLN of paclitaxel which demonstrated slow but time dependent release of drug. Results of in-vitro cytotoxicity studies on breast and human ovarian cancer cell lines by MTT assay were comparable to commercially available paclitaxel formulation.

In another study, cellular uptake and cytotoxcity of paclitaxel loaded SLN in A-549 cell lines were carried out[112]. Fluroscence technique was used to determined cellular uptakes of SLNs with different lipid materials. Cellular uptake ability of SLN with different lipid material was found to be in the following order: Tristearate SLN> Monostearate SLN> Stearic acid SLN> Comperitol ATO 888 SLN. Cellular toxicity of paclitaxel was greately enhanced by encapsulating as SLN matrix and it depends upon the ability of cellular uptake and drug loading of SLN. Polyethylene glycol monostearate (PEG-SA) and conjugated folic acid-Stearic acid (FA-SA) were also incorporated in monostearin SLN respectively. PEG-SA SLN enhanced the cellular uptake, but it did not increase the cytotoxicity whereas SLN modified with FA-SA enhanced the cellular uptake and cytotoxicity which may be due to improved endocytosis mediated by folate receptor. Since site of action of paclitaxel is microtubules present in the cytoplasm, these modified SLN are suitable carriers to deliver paclitaxel for tumor targeting. The finding of this study also revealed the potential application of SLN for therapeutic targeting of cancer.

Gasco et al studied the cellular uptake and cytotoxicity of SLN loaded with doxorubicin or paclitaxel by using two different cell lines, Human breast carcinoma cells (MCF-7) and Human promyelotic leukemia cells (HL60)[113]. Cytotoxicity of these SLN were compared to free drug solutions. There was no cytotoxicity observed for the two blank SLN on either of the cell lines even at highest concentration. Fluroscence microscopy results clearly indicated cellular uptake of fluorescent SLN. The cytotoxicity of Dox-SLN and PTX-SLN was higher than that of drug solutions on both cell lines. In addition, Dox-SLN was more cytotoxic to HL60 cells and PTX-SLN was more cytotoxic to MCF-7 cells. This study also confirms the increased uptake and accumulation of SLN in the tumor cells. Similar results have been reported for the cholesterol buterate, doxorubicin and paclitaxel loaded SLNs by using colorectal cancer cells (HT-29)[114].

Recently Zhang et al [115], prepared monostearin NLC conjugated with folic acid, of paclitaxel (PTX) and doxorubicin (Dox) in order to overcome MDR of cancer cells. Human breast cancer (MCF-7) cells, human ovarian cancer cells (SKOV3) and their MDR cells (MCF-7/ADR and SKOV3-TR30) were used for cytotoxicity and reversal activity. Activity of these NLCs was compared with taxol and doxorubicin solution. For sensitive human breast cancer cells (MCF-7), the PTX-NLC showed enhanced cytotoxicity compared to taxol. But for resistant cells (MCF-7/ADR) cytotoxicity of taxol was higher (nearly 30 folds) than in sensitive cells whereas in case of PTX-NLC very low cytotoxicity was observed. This meant that PTX-NLC completely reverse the PTX resistance in MDR cells. After modification with folic acid reversal power of PTX-NLC was significantly increased which may be due to folate receptor mediated endocytosis and increased cellular uptake could bypass the P-gp efflux. In case of Dox-NLC cytotoxicity of Dox was increased by about 7.5 folds against MCF-7/ADR. The reversal power of PTX-NLC and Dox-NLC were 34.3 and 6.4 folds respectively against MCF-7/ADR cells and reversal power were 31.3 and 2.2 folds for PTX-NLC and Dox- NLC respectively against SKOV3 and SKOV-TR30 cells. In short, the NLC modified with folic acid had improved reversal power for MDR human cancer cells.

Tamoxifan, a anti cancer drug used for breast cancer also used in SLN [116,117]. Fontana et al [116] developed tamoxifan SLN and in-vitro antitumor activity was carried out by using human breast cancer cells (MCF-7 cell lines). It was observed that the activity of tamoxifan SLN was comparable to free drug, but the usefulness of these SLN in cancer therapy is due to their prolong release of drug. Pharmacokinetic studies of tamoxifan citrate SLN was carried out by Reddy et al [117] and the results showed 3-3.5 fold increase in the half life and MRT of these SLN as compared to free drug which revealed prolonged circulation time of SLN that is useful for breast cancer therapy.

Wong Lun Ho et al, studied the uptake of doxorubicin (Dox) loaded PLN (Dox-PLN) in multi drug resistant breast cancer cells[85, 118]. Human breast cancer cell line MDA435/LCC6/MDR1 and murine breast cancer cell line EMT6/AR1 were used to investigate uptake and retention of Dox-PLN and both the cell lines were P-gp over expressing. P-gp is a membrane associated glycoprotein which actively transports structurally diverse compounds and many anticancer drugs [like vincristin, vinblastin, epipodophyllotoxin (etoposide), paclitaxel, docetaxel, topotecan, doxorubicin, daunorubicin, epirubicin, mitomycin-C, dactinomycin etc.] out of the cells leading to failure of effective chemotherapy[59, 119-121]. Effective chemotherapy is depend upon accumulation of drug into cancer cells and drug exposure time because mechanism of action of most anticancer drugs involve targeting to intracellular organelles, e.g. Dox disrupt the action of topoisomerase-II by intercalate between DNA base[122]. Treatment of both human and murine breast cancer cell lines with Dox-PLN showed enhanced uptake and retention of Dox in cells which was approximately 8 times more effective when compared to free Dox solution. Fluorescence microscopy and endocytosis inhibition studies were performed to explain the mechanism of drug uptake into P-gp over expressing cells. The results of fluorescence microscopy showed that Dox-PLN improve the drug localization in nucleus of MDA435/LCC6/MDR1 cells as compared to free drug solution. Endocytosis inhibition studies show that phagocytosis is an important pathway in membrane permeability of nanoparticles[85]. The study revealed that Dox-PLN are more beneficial in drug resistant cells. PLN allowing the drug molecule to bypass the efflux mechanism of P-gp. The possible mechanism of action for PLN to overcome MDR in P-gp over expressing cells may be because the drug in PLN enters in to tumor cells by combination of phagocytosis and simple diffusion. However the drug is physically associated with the solid lipids when internalized by cells. In this condition the drug cannot be easily removed by P-gp and results in to increase in intracellular drug concentration, which leads to chronic suppression of drug resistant tumor cell proliferation [85].

In another study by the same group[123] in-vivo potential of Dox-PLN was evaluated using murine solid tumor model. In this study, tumor morphology and histology were carried out and both approaches show that Dox-PLNs were effective in-vivo against breast cancer cells. After intratumorlly injection of Dox-PLN, extensive distribution of PLN was observed within the tumor cell which results in destruction of tumor cells. This high intra-tumor distribution may be the reason for superior in-vivo efficacy of Dox-PLN over Dox loaded microspheres. In addition the normal tissue toxicity is also quite minimal for Dox-PLN. There was no unusual morphology detected in the heart tissue of mice after 5-7 days of Dox-PLN treatment. The finding of this study suggests that improved therapeutic index may be obtained by PLN loaded with anticancer drugs and this may be useful for loco-regional treatment of breast cancer.

Hepatocellular Carcinoma (HCC) is the most common cause of cancer related death [124]. Docetaxel can be used in treatment of HCC and it is structurally similar to paclitaxel but more effective inhibitor of microtubule depolymerization[125]. In combination with other anticancer drugs it showed high efficacy in breast, gastric, pancreatic and urothelial carcinoma's patients [126-129]. Recently, Potential of Docetaxel loaded SLN for Hepatocellular Carcinoma was studied by Zehenghong Xu et al [130]. Targeting of docetaxel to hepatoma cells can be achieved by modifying the surface of nanoparticles with ligand that can bind to asialoglycoprotein (ASGP) receptor, which are highly located on the surface of human hepatoma cell lines. Hence galactosylation on the surface results in increased uptake of drug carrier into hepatoma cells by binding of particle with ASGP receptor [131, 132]. They developed hepatoma targeted SLN (t-SLN) for specific targeting to ASGP receptors. They used galactose moiety by conjugating DOPE (Dioleoyl phosphotidyl ethanolamine) with lactobionic acid. In-vitro release study showed initial burst release within the first day of about 18.2% followed by sustained release for

next 29 days of about 83.4%. Cytotoxicity of t-SLN, Non targeted SLN (n-SLN) and taxotre® were evaluated by MTT assay against hepatocellular carcinoma cell line BEL7402. Results showed that cytotoxicity of t-SLN was superior to n-SLN and taxotre®. Cellular uptake and subcellular localization study was also done by using rhodamine loaded SLN or t-SLN. There was much higher fluorescence intensity observed in cells treated with rhodamine loaded t-SLN. This may be due to enhanced internalization and ligand receptor recognization. These results also reveal the enhanced cytotoxicity of t-SLN because of better internalization. The results of histology suggested that t-SLN had no detrimental effect on both healthy liver and liver with fibrosis. In-vivo potential of these t-SLN were also evaluated by using murine model bearing hepatoma and compared with n-SLN and taxotre®. The t-SLN showed better antitumor efficacy and tolerance than n-SLN and taxotre®. There was 2.4 times higher accumulation of t-SLN in tumor compared with taxotre® after 6 hour of injection [130]. Finding of this study suggest that targeted nanoparticulate carriers of docetaxel could enhance its antitumor efficacy in-vivo with less systemic toxicity.

Bin Lu et al fabricated Mitoxantrone (MTO) SLN to improve the therapeutic efficacy of MTO against breast cancer and lymph node metastases[133]. Lymph node metastasis is one of the important factors in the effective treatment, since lots of lymph nodes are present around the breast. Lymphatic capillaries usually have open intercellular junction with a size range of 30-120 nm in the endothelium. Through this junction colloidal particle less than 100 nm can be passed into the lymphatic system [134]. MTO SLN was prepared by film dispersion ultrasonication method and having mean particle size of 61 nm. The study showed that the drug concentrations using SLN was much higher in local lymph nodes and lower in other tissues than the MTO solution. In addition no toxicity to the main tissues was observed after local injection of MTO SLN than MTO solution. After treatment with MTO SLN, the lymph node size of mice was approximately 3 times lower as compared to treatment with MTO solution [133].

Etoposide is an anticancer agent used in various malignancy including lymphomas. It inhibits topoisomerase-II and activates redox reactions to produce compounds that bind directly to DNA and cause DNA damage [135]. It has very short biological half life, hence prolong exposure to tumor cell may not be possible. To overcome this drawback etoposide has been encapsulated into SLN and studied for biodistribution and efficacy in Dalton's lymphoma tumor bearing mice [136-138]. Biodistribution studies of etoposide loaded positively charged SLN showed prolong circulation time, high blood concentration and significantly low uptake in RES organs. There was 14 folds higher distribution in brain for positively charged SLN than negatively charged SLN after 4 hours of injection [136]. Effect of route of administration of etoposide SLN were also carried out by Reddy et al [137]. In this study etoposide SLN were injected by intraperitoneal, intravenous and subcutaneous routes, where tumor uptake and biodistribution were determined. Highest tissue distribution of etoposide for different routes were found to be in the following order Intravenous>Intraperitoneal>Subcutaneous. But in the tumor uptake study there was 59 fold higher uptake of etoposide SLN compared to i.v. administration and 8 fold higher uptakes compared with intraperitoneal administration. In another study by the same group etoposide loaded SLN showed significantly higher apoptosis induction for prolong time and there was increase in survival time of tumor bearing mice, when compared with free etoposide[138].

SLN containing prodrug of 5-flurouracil was prepared by Yu et al [139], there was 37.52% higher accumulation in liver as compared to control clinical group, which demonstrate specific targeting to the liver by SLN.

To increase the chemical stability of all-trans-retinoic acid, Lim et al prepared it's SLN in powder form[140]. Results indicate improvement in the stability of all-trans retinoic acid when encapsulated in SLN form and the anti cancer activity of SLN powder in different cell line culture was approximately similar to free drug. There was reduction in the hemolytic potential of all-trans retinoic acid when incorporated into SLN powder form.

Another in-vitro cellular uptake study was carried out by using Vinrorelbine bitartrate[141]. Incorporation of this drug in PEG modified SLN showed significant uptake in MCF-7 and A-549 cells. In addition in-vitro anticancer activity of vinrolbine ditartrate was enhanced significantly after incorporation into SLN and PEG modified SLN.

Bondi et al prepared NLC of two synthetic derivatives (compound A and compound B) of anticancer drug temozolamide[142]. The prepared NLC showed increase in the effect of compound A and compound B on human hepatocellular carcinoma cell lines and on human prostate cancer cell lines, when compared with free drug.

In a study by Oyewumi et al, the potential of gadolinium SLN in targeted tumor delivery and in enhanced efficacy of neutran capturing therapy was shown [143]. They prepared PEG coated and folate coated SLN of gadolinium by microemulsion method. Increased cellular uptake and retention in cancer cell was observed for both PEG uncoated and folate coated PEGylated SLN which also revealed the enhanced efficacy of chemotherapeutic drug by SLN.

Role of SLN in anti parasitic chemotherapy

Parasitic diseases (like malaria, leishmaniasis, tryanosomiasis) are one of the major problems around the globe[144, 145]. Antiparasitic chemotherapy is the only choice of treatment for these parasitic infections, the reason for this is that these infections do not elicit pronounced immune response hence effective vaccination may not be possible [146]. In addition, as compared to other class of therapeutics very less drug discovery has been carried out for this class of compound, so the numbers of candidates are limited for the treatment and relatively few reports were published. Delivery of these drugs to intracellular region and to different locations is a major challenge. Hence a novel drug delivery carrier is required for effective treatment of parasitic infections. The main aim of parasitic chemotherapy is to minimize the side effects of antiparasitic drugs which can be achieved by targeting drug specifically to the parasite to maximum possible extent. Recently, a review has been published by Patravale et al, on various drug delivery approaches using colloidal carrier for treatment of parasitic diseases [147]. There are only few cases reported which focuses on the potential of SLN for delivering antiparasitic drugs.

The studies have shown the targeting potential of SLN to the brain [54,148]. This brain targeting may be useful in the parasitic diseases like cerebral malaria and CNS stages of trypanosomiasis. Gupta et al[149], have prepared transferrin-conjugated SLN of an anti malarial drug quinine dihydrochloride. The main aim of this study was to target the drug to the brain for the management of cerebral malaria. The results of fluorescence microscopy showed enhanced uptake of transferrin conjugated SLN in the brain tissues. Also much higher concentration of drug was observed in serum when drug SLN was administered intravenously. Thus this study also confirms the brain targeting potential of SLN.

In another study, LDC technology has been used to deliver a hydrophilic antitrypansomiatic drug diminazine diacetutate for the treatment of African trypansomiasis [150]. These LDC showed adsorption of Apolipoprotein-E, A-I, A-IV when incubated with human serum. These are the key factors for targeting drug to the brain and responsible for the nanoparticles delivery to the brain where the parasite trypansoma reside[151]. In-vivo study, showed presence of LDC in the endothelial cells of blood vessels in the brain.

Recently, Joshi et al [152] prepared NLC of an antimalarial drug artemether for intravenous delivery. Artemether is a potent antimalarial drug for the treatment of multi resistant malaria and cerebral malaria. It is available in oral and intramuscular oily formulations. The oral formulation has low bioavailability whereas oily formulation causes pain on injection. Antimalarial activity of artemether loaded NLC was evaluated in *Plasmodium benghei* infected mice and compared with conventional artemether injectable formulation. Cytotoxic studies showed that these NLC were less hemolytic, and as compared to marketed oily i.v. injection,

artemether NLC had significantly higher antimalarial activity with survival rate of 60% on the 31st day of the study. Artemether NLC remained in circulation more than 20 days indicating long circulating potential in-vivo [152].

Role of SLN in tubercular chemotherapy

Various drug carriers like liposome and polymeric nanoparticles have been used to encapsulate Anti Tubercular Drugs (ATD) and were proved to be successful in experimental tuberculosis [153, 154]. As reported, there are only few studies on SLN as a carrier for tuberculosis chemotherapy. Pandey et al, have explored SLN as an ATD carrier for oral and inhalable drug delivery [155,156].

In Pandey et al study [155] ,3 ATD were co-incorporated into SLN to evaluate the potential of these carriers in tuberculosis chemotherapy via the oral route, M. tuberculosis $H_{37}Rv$ infected mice were used for experimental tuberculosis. Drug distribution and pharmacokinetic studies showed that after oral administration of SLN all 3 drugs were detected in plasma upto 8 days and drug concentrations were above or at the minimum inhibitory concentration (MIC_{90}). While the free drugs were cleared within 12 hours from circulation after administration. All the 3 drugs were detected in the lungs, spleen and liver of mice upto 10 days after oral administration. There was 10-29 folds increase in mean resident time (MRT), AUC and relative bioavailability in case of ATD loaded SLN. Furthermore, in case of SLN only 5 oral doses administered every 10th day were required to clear all tubercule bacilli from the organs of M. tuberculosis $H_{37}Rv$ infected mice, while in case of free drug 46 doses were required to remove all the bacillis. The finding of this study suggested that SLN have great potential in the delivery of antitubercular drugs by reducing frequency of doses and improving patient compliance by better management of tuberculosis.

Future perspectives of SLN based chemotherapy

Target specific drug delivery for chemotherapy using SLN: Targeting of chemotherapeutic drugs to specific organ, cells, parasite can be achieved by SLN, by modifying the surface properties of SLN and by attaching target specific ligands to the surface. For example- recently a study carried out by Steven et al, developed folate receptor targeted SLN for delivery of paclitaxel-2' carbonyl cholesterol (Prodrug of paclitaxel) [157]. Since tumor cells overexposes the folate receptor. The targeted SLN showed greater cytotoxicity due to greater cellular uptake in-vitro and also improved animal survival in-vivo compared to non targeted SLN. This finding suggests that, in future more targeted SLN formulations will be developed for various drugs used in different types of chemotherapy.

1. Gene Delivery: Since Past few years gene therapy emerged as a new promising strategy for cancer management. The vehicle used for gene therapy should have good specificity to target cell and higher efficacy for transfection of genetic material to cancer cells. Viral vectors may result in unwanted immune response [158] and non viral transfection agents like dendrimers, peptide, cationic lipids, polymers and liposome have shown low in-vivo effectiveness [158-163]. Cationic SLN may make possible the delivery of genetic material in cancer treatment. Same in-vivo transfection efficacy were observed in cationic SLN and liposome formulated with same cationic lipids [163]. The intrinsic toxicity of delivery vehicle may also be minimized by using good combination of two tailed cationic lipids [164].

   Recently, Gasco et al[165] evaluated the transfection capacity of SLN-DNA vector in-vivo in mice. Nacked plasmid DNA is used as powerful tool for gene therapy but the main drawback is the rapid elimination from the systemic circulation after i.v. administration due to hepatic clearance or enzymatic degradation [166]. The results of this study revealed the transfection of SLN-DNA in liver and spleen, and protein expression was observed which were maintained for at least one week. This was the first in-vivo study supporting potential of SLN in gene therapy.

   In short, SLN has good prospect as a gene delivery vehicle for cancer management.

2. Combinational drug delivery: Combination of drugs may be used to achieve good response in chemotherapy which may not be achieved by single drug only. For example, to minimize or overcome the MDR phenotype chemotherapeutic drugs can be given along with P-gp inhibitors also known as "Chemosensitizer" e.g.- verapamil, cyclosporine-A, PSC-833 and GG918 [167,168]. But these chemosensitizers may lead to toxicity and pharmacokinetic interaction due to poor specificity and low potency for drug transporters [59]. These shortcomings may be overcome by incorporating them into drug delivery system such as SLN. Verapamil PLN and cyclosporine-A SLN were successfully formulated [83]. In the study by Wang et al [83], Doxorubicin and verapamil were co-encapsulated in a PLN system and it was observed that the PLN system delivered by both the agents (cytotoxic and chemosensitizing) simultaneously, without interfering in each other's release profile. In another study [118], doxorubicin and more potent P-gp specific GG918 were formulated in PLN system and evaluated in resistant cancer cell lines and the results revealed that the PLN system showed better cellular uptake and higher toxicity than the combination of free solution of doxorubicin and GG918, as well as than the Dox-PLN alone. In addition combination of 3 ATD drug in SLN showed reduction in dosing frequency and improved patient compliance, which are essential for better tubercular chemotherapy, as discussed earlier [155]. In brief, these findings suggest that combination of 2 or more drug exert good therapeutic results by formulating as drug combination in a SLN system leading to increased therapeutic advantages.

3. Recently Ahmadin et al, hypothesized the targeted delivery of saturated solution of an osmotic agent loaded SLN used to eradicate tumor cells. Sodium chloride (NaCl), Potassium chloride (KCl) and Calcium chloride ($CaCl_2$) can be used for this purpose but NaCl would be safer than KCl and $CaCl_2$ [169].

CONCLUSION

Chemotherapeutic drugs are class of unstable, reactive and toxic compound which have diversified physicochemical properties. SLN are a new generation of colloidal drug carriers having many advantageous and favorable qualities over existing colloidal carriers. The use of SLN in chemotherapy offers exciting possibilities such as drug targeting to specific sites like tumor cells, parasitic cells and organs, by modifying the surface properties of SLN. Modified form of SLN such as PLN, LDC, NLC, stealth SLN, targeted SLN offers encapsulation of various chemotherapeutic drugs.

Chemotherapeutic drugs encapsulated in SLN-systems have been shown to be superior to conventional dosage form, comparable to other drug carriers in terms of pharmacokinetics, drug efficacy and biodistribution. The results of in-vitro and in-vivo animal models are very promising. A number of SLN systems have shown good ability to overcome the obstacles that occurred in conventional chemotherapy. It is anticipated that, SLN will further improved the efficacy of chemotherapeutics for better management of various types of chemotherapy such as cancer, tuberculosis and parasitic infections.

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