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SOLID-LIPID NANOPARTICLES FOR THE TREATMENT OF CANCER

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ABSTRACT

The SLNs (Solid-Lipid nanoparticles) technology is one of the most promising drug carriers for bioactive chemical molecules. By enhancing a range of chemotherapeutics' anticancer effects, its current use in chemotherapy has changed how cancer is treated. It has excellent temporal and thermal stability, cheap preparation method and high manufacturing yield as they may be made from naturally existing sources. Additionally, mixing chemotherapeutic agents with LNPs reduces therapy resistance, decreases toxicities, increases drug concentration in cancer cells while decreasing concentrations in healthy tissue. Both in vitro and in vivo studies on SLNs for the treatment of cancer were extensive, with positive results in several clinical trials. The current paper gives a broad summary of the various SLN kinds that have been developed recently, as well as their uses and contributions to various malignancies.

KEYWORDS: Solid-Lipid nanoparticles, cancer, tumor, drug delivery system.

INTRODUCTION

Despite significant progress in clinical techniques and drug discovery, cancer remains the world's most common cause of death, trailing only cardiovascular disease.[1] According to GLOBOCAN's global cancer statistics 2020, 19.3 million new cases of cancer and approximately 10 million deaths have been resulted from cancer.[2] The complex and multifactorial pathogenesis complicates disease treatment. Furthermore, the development of multidrug resistance is the reason for the ineffectiveness of many anticancer treatments. As a result, a specific treatment is ineffective in all cases. Recurrence is common in several cases because cancer can acquire resistance to earlier treatments available.

To address these issues, it is widely acknowledged that nanoparticle-based drug delivery systems (DDS) with improved bioavailability and less adverse effects have an effective anticancer effect in comparison to free drugs.[3-7] Liposomal doxorubicin (LD) and pegylated liposomal doxorubicin (PLD) have entered phase II and III clinical trials, respectively, and have been accepted by the FDA for the treatment of breast cancer.[8]

Nanotechnology is presently a fast - growing field with application domains in health and drug treatment. Materials' particle sizes have shifted from the micro- to nano-scale as advanced technologies has advanced over the last couple of decades. Material particle size reduction at the nanometer scale tends to increase their total surface area through several orders of magnitude. Nanoparticles are particles with sizes ranging from 1 nm to 1000 nm.

Nanoparticles, dendrimers, nanotubes, micelles, and liposomes are a few examples of several forms of nano drug delivery systems. Combinational drug delivery systems based on nanotechnology boost bioavailability by improving permeability, retention, and targeting the cancer tissues.[9]

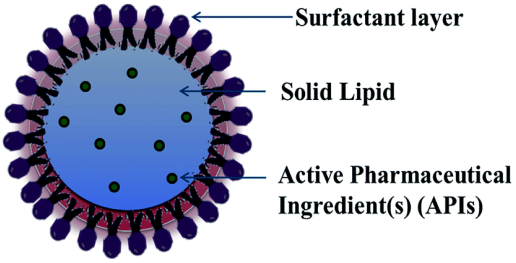

Figure 1: Solid lipid nanoparticles.

Mueller et al. (2000) and Gasco (1993) concentrated on the creation of SLNs for drug delivery in the early 1990s. The only benefits of SLNs are their biocompatibility, increased lymphatic absorption susceptibility, and sustained drug release.[10, 11] SLNs are typically between 50 and 100 nm in size. The solid-lipid core of SLNs used in the colloidal drug delivery technology maintains its solid phase at both room and body temperatures. The drug is typically dissolved or diffused in the solid core, which has a single layer of hydrophobic phospholipids

on top (Figure 1). Traditional colloidal carriers including emulsions, liposomes, and polymeric micro- and nanoparticles are substitutes to SLNs.[12]

Alleviation chemotherapeutics loaded SLN is extremely effective in the treatment of cancer. [10, 13] However, as shown by the findings of latest research investigations, they are able to successfully transporting contrast agents together with anticancer agents and providing combined diagnoses and treatment. Solid lipid nanoparticles (SLNs) coupled with c(RGDyK) were created as effective carriers to enhance the targeted delivery of IR-780 to the tumours, as Kuang and colleagues have shown in their study. The multifunctional cRGD-IR-780 SLN greatly increased the potency of photothermal methods, tumor-specific targeting, and serendipitous photography of in vivo travel of SLNs that included IR-780 iodide nanomedicine.[14]

WHY LIPID NANOCARRIERS FOR CANCER THERANOSTICS!

SLNs would be less harmful than polymers, have higher entrapment efficiency, higher loading, and bigger surface area, which enhance the activity of the drug contained in the lipid core.[15-17] SLNs are more durable and display prolonged drug release than liposomes, and they can even omit the sterilising process used to create liposomes. SLNs can surpass the limitations of nanoemulsions and nanocrystals in terms of drug solubilization in biofluids, which limit their therapeutic value. The SLNs contain highly purified triglycerides or waxes, calixarenes, and sterols as lipids. Table 1 provides a list of the solid lipids used in the SLN preparation process as well as the methodologies used.

Table 1: Solid lipids used in the preparation of SLNs.

Solid lipid	Chemotherapeutic agent	Methods of preparation
Trimyristin and soybean lecithin	Docetaxel	Highpressure Homogenization method
Stearic acid/Glyceryl monostearate	Tamoxifen	Solvent injection method
Compritol® 888 ATO	Camptothecin	Modified solvent emulsification
Stearicacid/Glycerylmonostearate	Emodin	Highpressure Homogenization method
Compritol®888ATO	Tryptanthrin	Hothomogenization method
Trimyristin	Paclitaxel	Homogenization method
Palmiticacid	Tamoxifen	Microemulsion and precipitation method

SLN delivery can solve the solubility and bioavailability issues that lipophilic drugs suffer. Bypassing the reticuloendothelial system, regulated and extended drug release, deposition of hydrophilic/hydrophobic agents, and delivery of the chemotherapeutic at the site of action are all capabilities of SLNs (Fig 2).[18] The Food and Drug Administration (FDA) has granted generally recognised as safe (GRAS) status to components used in the manufacture of SLNs. The history and origin of SLNs are very brief because clinical studies in cancer treatment were lacking.[19,20]

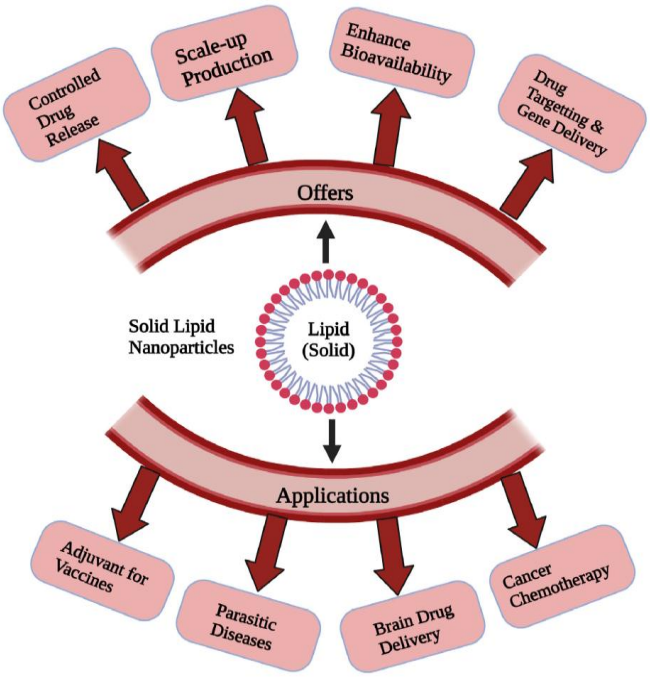

Figure 2: The Applications of SLN.

USES OF SLN IN VARIOUS CANCER THERAPIES

Liver cancer

One of the fastest-growing prevalent malignancies in the world is hepatocellular carcinoma (HCC), a primary malignancy of the liver. HCC has the foremost cancer-related mortality rate in China since the 1990s, and it has the third-highest mortality rate globally for all cancer-related disorders.[21] The liver serves as the most common organ for tumour metastases in regard to original malignancies. For the in-vitro and in-vivo administration of antisense oligonucleotide (AS-ODN) to liver endothelial cells, Bartsch and colleagues (2004) introduced stabilised lipid coated lipoplexes.[22]

Breast cancer

Breast cancer, which accounts for 29% of all female cancers worldwide, is the leading cause of cancer mortality in women.[23] Together with surgery, chemotherapy is still the recommended method of treating cancer.[24,25] Doxorubicin (DOX), docetaxel, and paclitaxel are among the anticancer drugs used in the first-line chemotherapy treatment strategy for breast cancer.[26]

But there are still challenges. First off, using DOX as a therapy has serious adverse effects like cardiotoxicity and hair loss.[27] Second, multidrug resistance (MDR) may enhance the number of drugs that are transported (efflux) out of tumour cells, which could lead to the ineffectiveness of cancer treatment.[28,29]

It is well established that nanoparticles are effective tumour targeting agents because of their enhanced permeability and retention (EPR) effect, which allows them to target tumours passively. As an additional benefit, covering up the particles with a polyethylene glycol/oxide (PEG/PEO) surface modification prevents the reticuloendothelial system from absorbing them, extending their circulation time.[18]

Colon/Colorectal Cancer

The chemotherapy of colorectal cancer is risky and has non-selective adverse effects that may necessitate hospitalizations and special care.[30]

Through the use of a strategic and original method to advance and refine the treatment (SMART) of CRC, hot and cold homogenization, the SLN-loaded 5-FU was produced. Unique PEGylated Lipids and a mixture of Surfactants were used to create the SLN. To assess the efficiency and cellular uptake of 5FU-SLN in HCT-116 cancer cells, cytotoxicity tests, clonogenic assays, flow cytometry, and confocal imaging were carried out. In trials on tumour effectiveness, 5FU-SLN dramatically reduced tumour development when compared to 5-FU, and its area-under the plasma concentration-time curve (AUC) was 3.6 times higher than that of 5-FU. In mice treated with 5-FU-SLN, the expression of HER2 receptors was significantly reduced. Compared to 5-FU, 5FU-SLN greatly reduced the formation of subcutaneous tumours in mice and was selectively toxic to HCT-116 cells.[31]

Despite the fact that there are clinically effective oral anticancer chemotherapies, the therapeutic effect mostly depends on drug absorption and is invariably accompanied by systemic adverse effects. Thus, the development of oral therapy systems featuring highly targeted drug delivery to cancer cells and less systemic drug absorption is desirable for the local treatment of colon malignancies. The hierarchical targeting of folate (FA) and dextran coated on SLN surfaces in a sequential layer-by-layer fashion by researchers demonstrates the effective accumulation and cell uptake of the doxorubicin and superparamagnetic iron oxide nanoparticles-loaded solid lipid nanoparticle (SLN) delivery system for chemo/magnetothermal combination therapy at tumours. The in vitro and in vivo characteristics highly supported the hypothesis that the dextran shells on SLN surfaces not only prevented the proton-coupled FA transporter on brush border membranes in the small intestine from moving the FA-coated SLNs into cells, but also improved particle residence in the colon by specifically associating with dextranase. Primary colon cancers were successfully inhibited when the hierarchically selectable SLN therapy system was evaluated for its in vivo anticancer effectiveness through oral route.[32]

Prostate cancer

Prostate cancer is a major cause of cancer-related death in men worldwide and is difficult to cure. In order to actively target prostate cancer cells, transferrin (Tf) bioconjugated solid lipid nanoparticles (SLNs) were created and loaded with curcumin (CRC). When compared to CRC-SLNs alone, Tf-CRC-SLNs significantly outperformed prepared blank Tf-SLNs in terms of in vitro anti-proliferative activity. Improved early apoptotic and late apoptotic or early necrotic populations were also seen in bioconjugated Tf-CRC-SLNs (6.4 percent and 88.9 percent, respectively) compared to CRC-SLNs and CRC solution.[33]

Glioblastoma

Gliomas are the most prevalent form of malignant brain cancer, and central nervous system (CNS) tumours are a substantial cause of illness and mortality globally. One of the dangerous and fatal forms of human cancer, glioblastoma multiforme (GBM), makes up 50% of all gliomas. Numerous methods have been explored to improve medication delivery to tumour tissue, and among them, the usage of nanostructures appears to be one of the most promising ones. This is because BBB comprises one of the major barriers to drug delivery to tumour tissue. A magnetic drug-delivery system was created as a result, with the goal of increasing BBB permeability to anti-tumor substances like nutlin-3a by using magnetic nanoparticles in conjunction with an external magnetic field. The ability to magnetically

direct the nanovectors toward a specific site to cross the BBB and release the medicine to GBM cells, inducing apoptosis, was demonstrated in vitro using Nutlin-3a and SPIONs that were encapsulated in SLNs.[34]

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