

# Importance of Solid Lipid Nanoparticles in Cancer Therapy

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## BIONANOTECH MEDICINE & BIOTECH

### Cancer Nanotechnology

#### ABSTRACT

A drug delivery system can be defined as a system that capable of releasing a carried bioactive agents in a specific location within the body at a specific rate. Anti- cancer drugs can be associated with colloidal carrier systems such as polymeric micelles, nanocapsules, liposomes and solid lipid nanoparticles, which can be actively targeted to specific tumor cell. The treatment of cancer is based on the delivery method. The cancer patients are using various anticancer drugs but these are less effective and have major side effects.

Solid lipid nanoparticles (SLNs) have been introduced as an alternative drug carrier system to drug delivery. Due to the disadvantages of the other colloidal carriers (liposomes, emulsions, and polymeric micro- and nanoparticles), SLN developed. In this study, we determined how SLN can be used for cancer therapy. As a result, substances which have anti-cancer properties loaded SLN formulations were significantly more effective than free substances on cancer therapy.

Keywords: Drug Delivery Systems, SLNs, Cancer Therapy.

#### 1. INTRODUCTION

Human cancer is a complex disease caused by genetic instability because of accumulation mutant alleles of proto-oncogenes, tumor-suppressor genes, and other genes that control, directly or indirectly, cell proliferation [1-2]. Most current anticancer agents do not greatly differentiate between cancerous and normal cells, leading to toxicity and major side effects. In addition, cancer is often diagnosed and treated too late, when the cancer cells have already invaded and metastasized into other parts of the body. At this stage, therapeutic modalities are limited in their effectiveness [3].

Nanotechnology has great potential to make an important role in prevention of cancer, detection, diagnosis, imaging and treatment. Controlled drug delivery technology represents one of the border areas of science, which

involves interdisciplinary combination of polymer science, bioconjugate chemistry, molecular biology and pharmaceuticals., contributing to human health care. The concept of drug targeting and controlled drug delivery are used in order to improve the therapeutic index of drugs by increasing their localization to specific organs, tissues or cells and by decreasing their potential toxic side effects at normal sensitive sites.

Nanoparticles have already been used to deliver drugs to target sites for cancer therapeutics or deliver imaging agents for cancer diagnostics. Due to their nanoscaled structure they are easily and more readily taken up by the human body [4-6]. Solid lipid nanoparticles (SLN) are one of the novel potential colloidal carriers systems during the last few years because SLN combine several advantages and avoid or minimize the disadvantages of other colloidal carriers [7].

Colloidal nanoparticles incorporating anticancer agents can overcome such resistances to drug action, increasing drug concentration in cancer cells, enhancing antitumor activity and reducing their toxicity towards normal cells. They can be endocytosed/phagocytosed by cells, with resulting cell internalization of the encapsulated drug. Higher tumor uptake, thanks to the small size and the hydrophilicity of the carrier device, as well as a sustained release of the drug could improve the efficacy of anticancer chemotherapy [8-9]. The purpose of this review, the potential of solid lipid nanoparticle as a carrier for controlled drug delivery used how to be effective in cancer treatment.

##### 1.1. Solid Lipid Nanoparticles

SLNs indicate lipids, which are used in the manufacturing of nanoparticles, are solid at room temperature and also at body temperature and with mean diameter approximately between 50 and 1000 nm [10].

SLN have several advantages;

- Controlled release of active drug over a long period and drug targeting,
- Small size,
- Generally less toxic,

- Protecting the labile and sensitive drugs from chemical, photochemical or oxidative degradation,
- Flexibility in sterilization
- Avoidance of organic solvents.
- Both lipophilic and hydrophilic compounds can be encapsulated,
- Incorporation of drug can reduce distinct side effects of drug,
- SLN have been proposed as a colloidal drug carrier therapeutic system for different administration routes such as oral, dermal, ophthalmic, pulmonary, rectal and particularly for parenteral administration [11-15].

## 1.2. Preparation Methods of SLN

Since the beginning of the nineties attention from various research groups has focused on an alternative to polymeric nanoparticles, the solid lipid nanoparticles.

The production of lipid microparticles by spray congealing was described by Speiser at the beginning of the eighties followed by lipid nanopellets for peroral administration [16]. Speiser created an initial nanoemulsion by using high speed mixing or ultrasonication; the nanoemulsion was subsequently spray dried to produce the 'nanopellets' [17]. Large scale production can be performed in a cost-effective and relatively simple way using high pressure homogenization leading to SLN. An alternative approach is the production of SLN via microemulsions [18].

There are different methods of SLNs preparation;

- High shear homogenization.
- Hot homogenization.
- Cold homogenization.
- Ultrasonication or high speed homogenization.
- Micro emulsion based SLN preparations.
- SLN preparation by using supercritical fluid.
- SLN prepared by solvent emulsification/evaporation.
- Double emulsion method.
- Spray drying method.

Basically, there are two approaches for SLN production hot and cold homogenization technique in high pressure homogenization which are the most common technique. For both techniques the drug is dissolved or solubilized in the lipid being melted at approximately 5±10 °C above its melting point [19].

### Hot homogenization technique:

The hot homogenization technique the drug loaded melted lipid is dispersed under stirring by high shear device (e.g. Ultra Turrax) in the aqueous surfactant solution of identical temperature. The hot homogenization technique is also suitable for drugs showing some temperature sensitivity. [20-22].

### Cold homogenization technique:

The cold homogenization technique is a suitable technique for processing temperature labile drugs or hydrophilic drugs. Lipid and drug are melted together and then rapidly ground under liquid nitrogen forming solid lipid microparticle.

- Cold homogenization has been developed to prevent:
- Temperature induced drug degradation
- Partitioning of hydrophilic drug from lipid phase to aqueous phase
- Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or supercooled melts [23].

The cold homogenization technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension [24]

## 1.3. Role of Solid Lipid Nanoparticles in Cancer Therapy

The studies of solid lipid nanotechnology are available the most new investigations, characterization, formulation and storage, drug loading properties and drug release in the literature [25-28].

The first in-vivo studies of SLN containing anticancer compound was carried out by Yang et al in 1999, they have used a chemically reactive compound camptothecin which known for anticarcinogenic properties [29].

Amongst various anti cancer drugs, paclitaxel has been studied by researchers to evaluate the potential of SLN [30-33]. In these studies, they demonstrated that paclitaxel loaded SLN have cytotoxic effect on various cancer cells (HCT-15, U-118, A-549 etc.) and 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 (MCF-7 and HL-60) [34]. They found that the cytotoxicity of Dox-SLN and PTX-SLN was higher than free drug solutions on both cell lines. A similar studies found that cholesterol butyrate, doxorubicin and paclitaxel loaded SLNs have more effective than free solutions by using colorectal cancer cells (HT-29) [35].

Tamoxifen, a anti cancer drug used for breast cancer (MCF-7) also used in SLN [36-37]. They were observed that the activity of tamoxifen-SLN was comparable to free drug, but the usefulness of these SLN in cancer therapy is because of their prolonged release of drug. But Reddy et al showed tamoxifen citrate of these SLN as compared to free drug which revealed prolonged circulation time of SLN that is useful for breast cancer therapy.

Lu and colleagues evaluated that the therapeutic effect of mitoxantrone loaded solid lipid nanoparticle (MTO-SLN) was promising in terms of either the breast cancer weight or the percent inhibition of the tumor [38].

Etoposide is another anticancer agent which used in various malignancy including lymphoma. To overcome this drawback etoposide has been encapsulated into SLN and studied for biodistribution and efficacy in Dalton's lymphoma tumor bearing mice [39-40]. These studies found that 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 drug.

Another in-vitro cellular uptake study was carried out by using Vinorelbine bitartrate [41]. Incorporation of this drug in PEG modified SLN showed significant uptake in MCF-7 and A-549 cells. Anticancer activity of this drug was enhanced significantly after incorporation into SLN and PEG modified SLN. Another study, Brioschi and colleagues demonstrated that cholesterylbutyrate solid lipid nanoparticles could be regarded as suitable and highly effective prodrug of butyric acid in vitro and in vivo studies [42]. Zhu and colleagues reported that podophyllotoxin loaded solid lipid nanoparticles (PPT-SLNs) have an effective long-term anti-cancer effect and can enhance the tumor cells apoptotic processes [43]. Xiang et al. found that dexamethasone acetate loaded solid lipid nanoparticles studied in lung-targeting delivery and they evaluated that compared to DXM-sol, DXM-SLNs had lower uptake by liver and spleen macrophages after intravenous administration and a significantly higher uptake by the lung [44]. Xu et al. studied the performance of docetaxel-loaded SLN targeted to hepatocellular carcinoma in 2009. They showed that nanocarrier of docetaxel could enhance its antitumor effect in vivo with low systemic toxicity for the treatment of locally advanced and metastatic HCC [45].

## 2. CONCLUSION

The application of nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. Lipid based on nanoparticle drug delivery technology presents significant opportunities for improving medical therapeutics, SLNs is a new era technology which has been taken over by the pharmaceutical industry. Combination of drugs and SLN may be used to potentially translate into targeted cellular and tissue-specific clinical applications designed to achieve maximal therapeutic effects with minimal side effects. Therefore, there is a need to develop suitable drug delivery systems that distribute the therapeutically active drug molecule only to site of action, without affecting healthy organs and tissues. A conceptual understanding of biological responses to nanostructure based drug delivery systems is needed to develop and it is expected to apply in cancer therapy in the future.

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