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Review

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Solid lipid nanoparticles in cancer therapy

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Abstract

The use of solid lipid nanoparticles in medicine and more specifically drug delivery is set to spread rapidly. Currently many substances are under investigation for drug delivery and more specifically for cancer therapy technology is the latest trend in the cancer therapy. It helps the pharmacist to formulate the product with maximum therapeutic value and minimum or negligible range side effects. Cancer is a class of disorders characterized by abnormal growth of cells that proliferate in an uncontrolled way and a major disadvantage of anticancer drugs is their lack of selectivity for tumor tissue, which causes severe side effects and results in low cure rates. Thus, it is very hard to target the abnormal cells by the conventional method of the drug delivery system. In harmony with these approaches, this review's basic approach is that the defining features of solid lipid nanoparticles are embedded in their breakthrough potential for patient care. This review article describes the possible way to exploit solid lipid nanoparticle technology to targeted drug therapy in cancer. We looked at the usefulness of solid lipid nanoparticles as a tool for cancer therapy.

Keywords: Cancer therapy, Solid lipid nanoparticles, Quantum dots

Introduction

Solid lipid nanoparticles are also referred to as "zero-dimensional" nanomaterials. This definition arises from the fact that all of their dimensions are in the nanoscale (under 100 nm), as opposed to one-dimensional nanomaterials, which have one dimension larger than the nanoscale (such as nanowires and nanotubes), and two-dimensional nanomaterials, which have two dimensions larger than the nanoscale (such as self-assembled monolayer films). Solid lipid nanoparticles (SLN) are colloidal drug carrier systems [1-3]. General ingredients include solid lipid, emulsifier and water. The term lipid is used generally in a very broad sense and includes triglycerides, partial glycerides, PEGylated lipids, fatty acids steroids and waxes. All classes of emulsifiers have been used to stabilize the lipid dispersion, emulsifiers such as poloxamer, polysorbates, lecithin and bile acids. They are very much like nanoemulsions, differing in lipid nature. The liquid lipid used in emulsions is replaced by a lipid solid at room temperature in SLN including high-melting point glycerides or waxes [2, 4-5]. Indeed, nanoparticles were initially thought to be designed as carriers for vaccines and anticancer drugs when they were first developed in about 1970. Several innovative research articles on solid lipid nanotechnology for drug delivery are available in the literature which describes extensive preparation techniques, characterization and types of SLN, investigation of their structural properties, factors affecting their formation and storage stability, drug loading principles and drug release

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characteristics [1, 6-9].

Use of SLN in various cancer therapies

Liver cancer

Hepatocellular carcinoma (HCC), a primary malignancy of the liver, is one of the most common tumors worldwide. The mortality rate from HCC is the third highest worldwide for any cancer-related diseases, and since the 1990s, HCC has been the cause of the second highest mortality rate due to cancer in China [10]. In addition to primary tumors, the liver is the most common organ where tumor metastases occur. Bartsch and coworkers (2004) proposed stabilized lipid coated lipoplexes for the delivery of antisense oligonucleotide (AS-ODN) to liver endothelial cells in-vitro and in-vivo [11].

Breast Cancer

Breast cancer is one of the most frequently occurring cancers in women and the second leading cause of cancer deaths in women. However, since 1989, the breast cancer mortality rate has decreased 1.8% per year, due to improvements in breast cancer prevention as well as treatment [12]. A major clinical obstacle in cancer therapy is the development of resistance to a multitude of chemotherapeutic agents, a phenomenon termed multidrug resistance (MDR). Chemoresistance can generally result from either of two means firstly, by physically impairing delivery to the tumor (e.g., poor absorption, increased metabolism/excretion, and/or poor diffusion of drugs into the tumor mass); secondly, through intracellular mechanisms that raise the threshold for cell death [13-17]. It is widely known that nanoparticles are beneficial tumor targeting vehicles due to their passive targeting properties by the enhanced permeability and retention (EPR) effect, whereby the added advantage of stealth shielding the particles with a poly ethylene glycol/oxide (PEG/PEO) surface modification avoids uptake by the reticuloendothelial system, thereby improving circulation time of the nanoparticles [18].

Colorectal Cancer

Colorectal cancer is the most common cancer in Western countries and is the second leading cause of cancer-related deaths in the United States, accounting for nearly 60,000 deaths each year [19]. Hyaluronic acid–coupled chitosan nanoparticles bearing oxaliplatin (L-OHP) encapsulated in Eudragit S100–coated pellets were developed for effective delivery to colon tumors [20]. SLN have been proposed as new approach of drug carriers [21]. SLN carrying cholesteryl butyrate (chol-but), doxorubicin and paclitaxel had previously been developed. However, doxorubicin is not so active against colorectal cancer [22]. SLN are in the colloidal size range and can be loaded with both hydrophilic and lipophilic drugs, depending on the preparation method [23, 24]. The composition of the warm microemulsions from which SLN are prepared is flexible, and can be varied to suit the type of drug and administration route [25].

Lung Cancer

Lung cancer is one of the leading causes of death worldwide [26]. Adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, which together make up the majority of lung cancers, are referred to as ‘‘non-small cell lung cancers’’ (NSCLCs). Patients with early stage NSCLC are typically treated with surgery; 5-year survival rates range from 25% to 80%, depending on the stage of the disease [27]. Current treatments for lung cancer have shown little success because they cannot cure disseminated tumors with an acceptable level of toxicity. The causes of lung cancers are generally characterized by mutations in p53 gene [28-31], which can lead to loss of tumor-suppressor function, increase of drug resistance, loss of mutational repair, increase of tumor angiogenesis, proliferation of cells, and inhibition of apoptosis [32]. Thus, one alternative strategy that has shown promise in the treatment of lung cancer is gene therapy. There are two main groups of vectors used in gene delivery: viral and non-viral vectors. Toxicity and immunogenicity concerns associated with viral vectors have led to an active interest in non-viral systems for gene delivery [33]. Among non-viral vectors, biodegradable nanoparticles have shown their advantage over other carriers by their increased stability and their controlled-release ability [34-35]. Typically, nanoparticles in gene delivery systems could be divided into two systems, cationic and anionic nanoparticles. Cationic nanoparticles systemsutilize the ionic interaction between the cationic polymers and the anionic plasmid DNA, forming stable polymer/lipids-DNA complexes [36-37]. Cationic lipid formulations, solid lipid nanoparticles (SLNs) have gained increasing attention as promising colloidal carrier systems [38]. As a substitution for viral delivery systems it was reported

the use of p53 gene/cationic lipid complexes for the treatment of early endobronchial cancer [39]. Despite their low potency compared to those of viral vectors, cationic lipids may present advantages in the context of long-term administration to multiple tumor sites dispersed over the bronchial epithelium. Moreover, most nonviral gene delivery systems that are being considered show no immunogenicity [40-42].

Brain Tumor

One of the best characterized lipid-based nanoscale compounds developed for brain tumor drug delivery are, SLN. These nanoparticles are prepared by high-pressure homogenization or micro-emulsion of solid physiologic lipids [43]. Although the exact mechanism by which SLN's cross the BBB and BTB is unknown, internalization is hypothesized to be mediated by endocytosis of SLN's by endothelial cells. The process of endocytosis is thought to be facilitated by the adsorption of circulating plasma proteins to the SLN surface [44]. The lipid matrix of SLN provides a means of loading drugs and protecting them from degradation. The unloading of drugs within target tumor tissues can also be controlled depending on the surface coating of the SLN and its constituent lipids [45]. Especially coating of the nanoparticles with the polysorbate (Tween) surfactants resulted in transport of drugs across the blood brain barrier [46]. SLN have the potential to revolutionize both preoperative and intraoperative brain tumor detection. The incidence of primary brain tumors in the United States has been estimated at approximately 43,800 per year [47-49]. Since the application of nanotechnology to the imaging of gliomas was proposed [50], there has been a rapid expansion of the application of nanodevices to the diagnosis and treatment of brain tumors. A wide variety of nanoparticle targeting options have been reported including peptides, cytokines, drugs, antibodies and ferromagnetic agents. When administered systemically, nanoparticles are cleared swiftly by the reticuloendothelial system. This process involves opsonization of nanoparticles, phagocytosis by macrophages and uptake in the liver and spleen [51]. Clearance of nanoparticles by the reticuloendothelial system can be partially blocked by the attachment of hydrophilic molecules to their surface [52]. However, common agents employed to achieve a hydrophilic coating such as polyethylene glycol or pluronic can be immunogenic or pro-inflammatory [53]. Passage of the BBB was suggested to be possible by the toxic effect of nanoparticles (about 200 nm) on cerebral endothelial cells [54], although for similar nanoparticles (about 300 nm) this was contradicted in another study. [55] In addition this effect was not found for a different type of nanoparticles [56]. Physical association of the drug to the nanoparticles was necessary for drug delivery to occur into the brain [55]. Also other SLN like manganese oxide was shown to translocate to the brain by the olfactory route [57], based on measurements of manganese in different parts of the brain.

Gastro-intestinal Cancer

In gastrointestinal cancers, drugs in SLP are given by oral route. SLN were introduced as a novel drug carrier system for oral delivery in the middle of 1990s [58]. The adhesive properties of nanoparticles are reported to increase bioavailability and reduce or minimize erratic absorption. [59], Absorption of nanoparticles occurs through mucosa of the intestine by several mechanisms namely through the Peyer's patches, by intracellular uptake or by the paracellular pathway. Pinto and Muller (1999) incorporated SLN into spherical pellets and investigated SLN release for oral administration [60]. SLN granulates or powders can be put into capsules, compressed into tablets or incorporated into pellets. For some of these applications, the conversion of the liquid dispersion into a dry product by spray-drying or lyophilization is useful or often necessary [60, 61]. However, the assessment of the stability of colloidal carriers in GI fluids is essential in order to predict their suitability for oral administration. Critical parameters have been widely overlooked in the design of new and efficent colloidal drug carrier systems for oral use: firstly, their stability upon contact with GI fluids since they are composed of biodegredable materials and particle size in nanorange maximizes the surface area for enzymatic degradation [62], secondly, particle aggregation due to environmental conditions of the GI tract leading decrease in the interaction capability of particles with the intestinal mucosa [63].

Nanoparticle and quantum dot for cancer treatment

The introduction of nanoparticles in the field of cancer research has recently improved diagnosis, targeting and drug delivery with the use of nanotubes, liposomes,

dendrimers and polymers [64-66]. Other nanoparticles, such as quantum dots, possess excellent photophysical properties and prove to be an elegant alternative to the traditional bioimaging tools [67]. Quantum dots are one of the most rapidly evolving products of nanotechnology, with great potential as a tool for biomedical and bioanalytical imaging. Their superior photophysical properties [68] and sometimes multifunctional surfaces are suitable for applications in various biological models [69]. Semiconductor quantum dots and nanoparticles composed of metals, lipids or polymers have emerged with promising applications for early detection and therapy of cancer. Quantum dots with unique optical properties are commonly composed of cadmium contained semiconductors. Cadmium is potentially hazardous, and toxicity of such quantum dots to living cells, and humans, is not yet systematically investigated. Therefore, search for less toxic materials with similar targeting and optical properties, is of further interest. Despite advances in neurosurgery and radiotherapy the prognosis for patients with malignant gliomas has changed little for the last decades. Cancer treatment requires high accuracy in delivering ionizing radiation to reduce toxicity to surrounding tissues. Recently some research has been focused in developing photosensitizing quantum dots for production of radicals upon absorption of visible light. In spite of the fact that visible light is safe, this approach is suitable to treat only superficial tumours [70]. Quantum advances in nanotechnology have the potential to revolutionize multiple aspects of the diagnosis and treatment of brain tumors in the future [71].

Radionuclide nanoparticles for cancer treatment

Nanotechnology is also enabling highly efficent radiotherapy, such as the injection of single doses of an atomic nanogenerator at kilobecquerel (nanocurie) levels into mice bearing solid prostate carcinoma or disseminated human lymphoma induced tumor regression and prolonged survival, without toxicity, in a substantial fraction of animals [72]. In another study, metal nanoshells with tunable optical resonance were shown to induce irreversible thermal damage to tumour cells when exposed to near infrared light [73]. Currently, clinical trials on targeted radionuclide therapies are mostly based on small molecules both for targeting and delivery that include antibodies, smaller peptides [74-75], or the radiolabeled biotin/avidin pair [76]. Advancement in the area of internal radionuclide therapy may further be enabled by using different carrier materials with higher radionuclide loads exhibiting different behavior in-vivo such as liposomes, dendrimers, and other structures with sizes of the order of several nanometers.

Magnetic nanoparticles for cancer treatment

Magnetic nanoparticles (MNPs) are being actively investigated as the next generation of magnetic resonance imaging (MRI) contrast agents [77] and as carriers for targeted drug delivery [78-79]. As therapeutic tools, MNPs have been evaluated extensively for targeted delivery of pharmaceuticals through magnetic drug targeting [80-81] and by active targeting through the attachment of high affinity ligands [82-84]. Huh *et al* (2005) recently described how superparamagnetic iron oxide (SPIO) nanoparticles can be used to detect cancer in-vivo using a mouse xenograft model [85]. In this investigation, the nanoparticles were conjugated to herceptin, a cancer-targeting antibody. Harisinghani *et al* (2003) utilized SPIO nanoparticles in human patients with prostate cancer to detect small metastases in the lymph node. In this case, the nanoparticles were coated with dextran for retention in the blood stream and gradual uptake into the lymph nodes where they are internalized by macrophages [86]. MNPs have been examined extensively as MRI contrast agents to improve the detection, diagnosis, and therapeutic management of solid tumors. Currently, clinical imaging of liver tumors and metastases through reticulo-endothelium system mediated uptake of SPIOs has been capable of distinguishing lesions as small as 2–3 mm [77, 87]. Another clinical application of ultra superparamagnetic iron oxide MNPs under evaluation is their use in improving the delineation of brain tumor boundaries and quantify tumor volumes [88, 89].

Future trends

SLN constitute an attractive colloidal drug carrier system due to successful incorporation of active compounds and their related benefits. Although most of the technologies have focused on the delivery of single chemotherapeutic agents to the tumors, it is increasingly becoming clear that an integrative approach may work better than a reductionist approach. Nanotechnology platforms can provide the unique niche within this space by enabling multimodal

delivery with a single application. Although SLN's may be used for drug targeting, when reaching the intended diseased site in the body the drug carried needs to be released. So, for drug delivery biodegradable nanoparticle formulations are needed as it is the intention to transport and release the drug in order to be effective. Interestingly pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs and up to recently did not realize that carrier systems themselves may impose risks to the patient. Nevertheless, we believe that the next few years are likely to see an increasing number of nanotechnology-based therapeutics and diagnostics reaching the clinic.

Conclusion

Solid lipid nanoparticle, although in its nascent stage, has a great potential to cure the cancer, with least side effects. It is the technology that will grow in years to come, and probably, the human race will have a 100% cure to cancer.

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