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REVIEW ARTICLE

Nanoparticulate Carrier Systems for Anticancer Drug Delivery: A Review

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Abstract
Nanoparticles are particulate dispersions or solid particles with a size in the range of 10-1000 nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanoparticles have been investigated as drug carriers, because they provide a great opportunity due to their advantageous features: (i) various formulations using organic/inorganic materials, (ii) easy modification of targeting molecules, drugs or other molecules on them, (iii) effective delivery to target sites, resulting in high therapeutic efficacy and (iv) controlling drug release by external/internal stimuli. Because of these features, therapeutic efficacy can be improved and unwanted side effects can be reduced. Nanoparticles are particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained.

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INTRODUCTION

Cancer has been one of the major social and health concerns for the last ten decades, More than 11 million people are diagnosed with cancer each year, and cancer accounts for about 7 million deaths/year 12.5% of deaths worldwide), making this disease a huge factor in worldwide mortality. The incidence of cancer is expected to increase continuously as the world population ages, and it has been estimated that there will be 16 million new cancer cases every year by 2020 and despite tremendous efforts to treat cancer, there has been very little actual improvement in cancer therapeutics over the past 50 years.[1] In order to substantially improve effective cancer therapy, we must vastly improve our knowledge of cancer pathophysiology, discover new anticancer drugs, and develop novel biomedical technologies.

It is well established that nanomedicine is currently attracting a worldwide interest of researchers who aim to dedicate this technology to develop novel approaches in cancer imaging, molecular diagnosis and targeted therapy.[2] Anticancer drug delivery systems are of the most investigated research areas in nanomedicine. Numerous investigations have shown that incorporating anticancer agents in nanoparticulate or microparticulate carriers would provide a useful means for controlling the tissue and cellular distribution profiles of these agents.

CANCER AND NANOTECHNOLOGY

Nanotechnology is an area of science devoted to the design, construction, and utilization of functional structures on the nanometer scale (often 100 nm or smaller). Nanotechnology for cancer consists of three main areas:

(1) Nanodetectors for sensing proteins and cancer cells,
(2) Nanoparticle or nanovector formulations for high-contrast imaging, and
(3) Nanotechnology-based drug delivery and therapeutic formulations.

Cancer nanotechnology is currently under intense development for applications in cancer imaging, molecular diagnosis and targeted therapy. The basic rationale is that nanometer-sized particles, such as biodegradable micelles, semiconductor quantum dots and iron oxide nanocrystals, have functional or structural properties that are not available from either molecular or macroscopic agents. When linked with biotargeting ligands, such as monoclonal antibodies, peptides or small molecules, these nanoparticles are used to target malignant tumors with high affinity and specificity.

In the context of nanomedicine-based therapeutics, effective cancer therapy requires drug delivery to cancer tissues, meaning that a drug delivery system should hold the anticancer drug in the blood and then allow a burst or continuous drug release at the cancer. For this purpose, a variety of lipid-based drug delivery systems have been developed in the form of emulsions, liposomes and lipid-core micelles.

Cancer Therapeutics and Various Nanotechnology Platforms

Various nanotechnology based platforms that can be used for cancer therapy include liposomes, nanopartilces, micelles, dendrimers, hydrogels, etc., which are shown schematically in Fig 1.

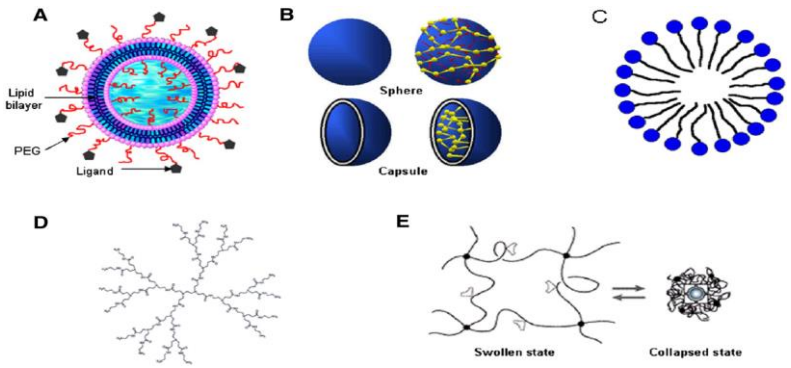

Fig 1. Schematic representation of nanotechnology based cancer therapies A) Liposomes, B) Nanoparticles, C) Micelles, D) Dendrimers, E) Hydrogels

Nanoshells

Nanoshells are nanoparticle beads that consist of a silica core coated with a thin gold shell.[3] Manipulation of the thickness of the core and the outer shell permits these beads to be designed to absorb and scatter specific wavelengths of light across the visible and near-infrared (NIR) spectrum. Their primary application is in thermal ablation therapy by exploiting their ability to absorb light. Meanwhile, their ability to scatter light has potential for cancer imaging.

The most useful nanoshells are those that have a silica core diameter of ~120 nm with a 10-nm layer of gold shell, because these strongly absorb NIR light (~800 nm) and can create intense heat that is lethal to cells. This NIR light can penetrate several centimeters of human tissue without causing harm, because tissue chromophores do not absorb much energy in the NIR range. Antibodies can be attached to nanoshells to get them to specifically recognize and target cancer cells (e.g., breast adenocarcinoma cells overexpressing human epidermal growth factor receptor-2) *in vitro*.

The benefit of the nanoshell mediated approach is that that the energy can pass through the healthy tissue and leave the neighboring cells intact, while killing only the tumor cells that have been targeted by the nanoshells.

Carbon Nanotubes

Carbon nanotubes are rolled-up sheets of carbon atoms, forming hollow tubes only about one nanometer wide. Gold nanoshells are tiny spheres (in this case, of silica) coated with a thin layer of gold.[4] The trick to getting nanotubes and nanoshells to stick only to cancerous cells is that so far, researchers have used both folate (Vitamin B) and antibodies. Cancer cells have an unusually high number of receptors for folate, and nanostructures coated in folate pass easily into cancerous cells. Antibodies promise even greater selectivity; for example, a nanostructure can be coated with antibodies that bind to proteins found only on the surface of melanoma cells.

Once the nanotubes are stuck to the cancerous targets, they are poised to kill in one of two ways. Their hollow interiors can carry anticancer drugs, or they can be zapped with infrared radiation, the same relatively harmless form of radiation that causes sunlight to feel warm and that turns on your TV remotely.

Recently, Zhang *et al.* have demonstrated that carbon nanotubes carrying short (or small) interfering RNA (siRNA) can rapidly enter tumor cells, then release the siRNA to exert RNA interference on target gene expression.[5]

Dendrimers

Dendrimers are spherical polymers that are normally less than 5 nm in diameter. Their key useful feature is the polymer branches that provide vast amounts of surface area to which therapeutic agents and targeting molecules could be attached (Fig. 2).

Fig 2. Structure of a Typical Dendrimer

In addition to improving drug properties such as solubility and plasma circulation time, polymeric carriers can also facilitate the passive targeting of drugs to solid tumors. This targeting is possible because of the increased permeability of tumor vasculature to macromolecules and because of limited lymphatic drainage. The unique properties of dendrimers, when compared with linear polymers, make them interesting candidates for the development of delivery systems for anticancer drugs.[6]

Quantum Dots

Quantum dots (nanocrystals) are composed of 10–50 atoms, and they confine electron-hole pairs to a discrete quantized energy level. When excited with ultraviolet light, they fluoresce in different neon colors depending on their size, which determines the energy level of the quantum dot. Quantum dots can be also be attached to various proteins and receptors to monitor with which molecules they interact and in what part of the cell they are found. Most recent advances have attempted to use quantum dots as carriers for siRNA, similar to the use of carbon nanotubes in that capacity.[7] As cells are impermeable to quantum dots, they must be coated with special molecules or antibodies to facilitate their uptake by cells. Since semiconductors are poisonous heavy metals, toxicity is a huge obstacle to clinical application of quantum dots for humans.

Liposomes

The development of liposomes as drug delivery vehicles can be considered one of the earliest forms of nanomedicine. These phospholipid bilayered membrane vesicles (Fig 3) can range from 100 nm up to 5 μm in size and have been utilized for the delivery of small molecules, proteins and peptides, DNA, and MR imaging contrast agents.[8] An advantage of liposome encapsulation is that there *in vivo* behavior has been well established with processes such as PEGylation resulting in long circulation times. Another favorable feature of liposomes is the ability to encapsulate a large number of MNP cores and deliver them together, avoiding dilution, to a target site.

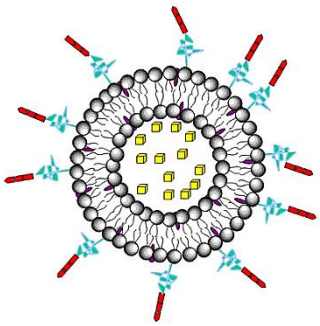

Fig 3. Drug encapsulation in liposomes

Polymer Micelle

Polymeric micelles are spherical, nanosized (10–100 nm) supramolecular constructs with a core–shell structure resulting from the selfassembly of amphiphilic block copolymers in aqueous environments. The hydrophobic core acts as a solubilizing reservoir for poorly water soluble agents, while the hydrophilic micellar corona, in turn, forms a hydrating layer on themicelle surface to hinder plasma protein adsorption and subsequent rapid phagocytic clearance by the RES. Manymicelle types have been proposed as carriers for anticancer therapeutic and diagnostic agents including paclitaxel, doxorubicine, cisplatin and Gd-DTPA.

Hydrogels

Some new promising radiopharmaceuticals systems are based on their ability to become locally gelatinized after a lag of time in order to be retained in the tissue. Chitosan, fibrin and alginate are good examples of these systems. Chitosan is a linear polysaccharide composed of randomly distributed β-(1–4)-linked d-glucosamine (deacetylated unit) and Nacetyl- d-glucosamine (acetylated unit). It is produced commercially by the N-deacetylation of chitin, which is the structural element in the exoskeleton of crustaceans.[9] Chitosan is a bioadhesive substance, and readily binds to negatively charged surfaces such as mucosal membranes.

Indeed, the N-deacetylation of chitin yields a cationic polymer, which has a pH-dependent aqueous solubility in water. Chitosan exists in a liquid form when the pH is around 4.0 or lower, while when it is injected into the body, it can be gelatinized at higher physiological pH values. Due to these characteristics, chitosan has the potential to be retained at the injected site.

Challenges for Delivery of Nanoparticles

It is believed that localization and accumulation of nanoparticles preferentially in tumors may be achieved by enhanced permeability and retention of nanoparticles based on passive extravasation of particles b400 nm in most tumors.[10] This is attributed to the leakiness of tumor vessels caused by openings between defective endothelial cells, wide interendothelial junctions, incomplete or absent basement membrane, loosely attached or absent pericytes (cells that provide support for the endothelial cells), and large numbers of transendothelial channels or pores. Whether it be through the physical enhanced permeability and retention effect or the use of specific targeting molecules, nanoparticles may successfully reach the tumors, but their ability to penetrate the tumor mass may be impaired because of barriers created by abnormal tumor physiology. Abnormal tumor structures, such as physically compromised vasculature, abnormal ECM, and high interstitial fluid pressure, can create constraints that thwart effective delivery of nanotherapeutics.

CONCLUSION

Different radiolabelled nano- and microcarriers have been elaborated for passive or active targeting of tumors with promising results in spite of the fact that not all these targeting mechanisms are actually clearly understood. Many of these carriers have been successfully applied in both preclinical and clinical studies showing a great conceivability to improve the quality of tumor detection and to enhance the therapy outcome in terms of tumor-selective radiation delivery. However, different major points will have to be addressed before moving forward to a full exploitation of their potential in clinical use. These points include, among others, the radiochemical stability and radioisotopes leakage, especially in liposomes and micelles, which induce severe toxicities and imply the necessity to find better chelating agents with higher affinity. Another concern is the practically limited control over isotope release profiles, synthesis methods, carrier size and size distribution and both the number and localization of functionalized branches in water soluble polymers. The carrier design and targeting strategies would vary according to the type, location of tumor and the administration methods (local or systemic). Novel nano- and microcarriers design with high specificity towards defined tumors, improved pharmacokinetic data and simpler highly effective radiolabelling methods will constitute decisive steps for potential clinical applications in the battle against cancer. Furthermore, the combination of the more recent imaging multimodalities and the use of these specific tumor-targeting carriers can significantly contribute to the improvement of both cancer imaging and radiotherapy.

DECLARATION OF INTEREST

It is hereby declared that this paper does not have any conflict of interest.

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