



Improved Targeted Delivery for Chemotherapeutic Drugs

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Date of Receipt- 17/09/2016
Date of Revision- 16/10/2016
Date of Acceptance- 30/10/2016

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COMMENTARY

Drug delivery systems offer the potential to improve the therapeutic index of chemotherapeutic agents via targeting the antitumor drug to its desired site of action, and hence, increasing the drug concentration in cancer cells and decreasing its concentration in healthy cells. Several nano-sized drug carriers, such as nanoparticles, liposomes, micells and polymer-drug conjugates, have been investigated in order to minimize side effects of anticancer drugs and enhance the antitumoral drug efficacy in cancer therapy.

Nanoparticles represent the most broadly studied drug delivery systems and afford strong benefits for delivering chemotherapeutic drugs as they protect drugs from degradation *in vivo*, provide targeting to diseased tissue, and control drug release at the target site.

In this regards, Kim et al.¹ modified the biocompatible and biodegradable glycol chitosan with hydrophobic cholanic acid that resulted in the formation of nano-sized drug carrier (HGC) with average size of 300-500 nm and used as a carrier for cisplatin which is a pivotal antitumor agent that is used in the treatment of a variety of malignancies,

including lung, bladder, testes, ovary, head and neck. Cisplatin was encapsulated into the hydrophobic cores of HGC nanoparticles by a dialysis method. The antitumor efficacy of cisplatin-HGC nanoparticles was evaluated *in vivo* and showed an improvement in the tumor targeting ability due to the prolonged circulation and enhanced permeability and retention of cisplatin-HGC nanoparticles in tumor-bearing mice and confirmed by higher antitumor efficacy and lower toxicity compared to free cisplatin using non-invasive live animal imaging technology.

Mesoporous silica nanoparticles (MSNs) seem to be a more promising candidate for drug delivery due to their prominent high surface area and large pore volume which allow the loading of massive amounts of drugs, and the sustained release of drug due to the slow diffusion causing local drug concentration². It seems that polyethylene glycol plays a role of increasing the residence time of MSNs in the systemic circulation, while D-Galactosamine enriches the MSNs in HepG2 cell line³. The antitumor drug; doxorubicin was encapsulated in the internal surface of MSNs, whereas, polyethylene glycol-galactose was grafted onto the external surface of MSNs and the loaded doxorubicin showed a pH-responsive release profile and higher cytotoxicity against the

HepG2 cell line by MTT measurements, which is a highly desirable characteristic for tumor-targeted drug delivery⁴.

Actually, hydrogels are gaining attention as smart drug carrier systems due to their ability to trigger the drug release into the desired site in response to external stimuli such as pH, temperature, ultrasonic irradiation, magnetic and electric field. Thus, these hydrogels have tremendous applications in controlled drug delivery. Moreover, the multi-stimuli responsive drug carriers could be more effective in delivering the drug to the targeted tissue when complicated diseases as tumors are involved. According to the delivery administration, hydrogel-based devices can be used for oral, nasal, ocular, rectal, vaginal, epidermal and subcutaneous applications⁵.

It is well known that tumor tissues have higher temperature and lower pH value than normal tissues. Therefore, temperature sensitive polymers could be used in tumor local hyperthermia therapy due to the increasing selectivity of drugs towards tumor cells and the decreasing toxicity to normal tissues as these polymers circulate in blood vessel at 37°C and precipitate on the heated cancer tissues around 42°C⁶.

Likewise, a dual temperature/pH-sensitive poly(N-isopropylacrylamide-co-acrylic acid) nanogel (PNA) was used as a carrier for the antitumor drug doxorubicin. This nanogel altered to hydrophobic state under hyperthermia of 43°C and liberated doxorubicin promptly in the acidic medium of tumor cells. So the cellular uptake and cytotoxicity of DOX-PNA nanogel were enhanced at higher temperature and lower pH value, suggesting a great potential application in tumor hyperthermia therapy⁷.

Similarly, in an attempt to increase cellular delivery and cytotoxicity of chemotherapeutic drugs, many researchers have investigated the encapsulation of antitumor drugs into stable liposomes coated with polyethylene glycol (PEG-liposomes) in terms of conveying drugs to cancerous tumor, reducing volume of distribution and ultimately reduced systemic toxicity. Among drugs, doxorubicin has been used as an example of such encapsulation to enhance passive tumor targeting and tumor growth inhibition⁸.

Docetaxel is the most commonly used chemotherapeutic agents for treating solid tumors, particularly lung cancer, causing inhibition of cell division and subsequent cell death. However, its efficacy is limited by its failure to reach the target site of action. Alternative dosage forms have been suggested including microspheres technology, where Wang et al.⁹ developed docetaxel-loaded chitosan microspheres using the emulsion crosslinking method in order to release the drug to a maximum extent in the lung tissue and minimize the exposure of healthy tissues which was confirmed by pharmacokinetics and biodistribution studies.

5-Fluorouracil (5-FU) is an effective chemotherapy for the treatment of different kinds of cancer including; stomach, colorectal, liver, breast and brain tumor through inhibition of DNA replication, leading to cell death. However, 5-FU has limitations such as short biological half-life due to fast degradation, toxic side effects on bone marrow and non-selective action against healthy tissues. For successful cancer treatment, Kevadiya et al.¹⁰ reported that polyacrylamide/Na⁺-MMT (Montmorillonite) composite hydrogel could be used as a carrier for 5-FU as the acrylamide and MMT has been successfully conglomerated to form composite gels with higher degree of swelling and faster drug release.

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