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Nanoparticles: A Suitable Drug Delivery System for Cancer Treatment

Poonam Jaggi^{1*}, Harshit Joshi² and Jagmeet Singh³

¹Department of Biotechnology, Amity University, Noida, New-Delhi, India

²Department of Pharmaceutics, Smriti College of Pharmaceutical Education, Indore (Madhya Pradesh), India

³Department of Biotechnology, Lovely Professional University, Jalandhar, India

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*For Correspondence

Poonam Jaggi, Department of Biotechnology, Amity University, Noida, New-Delhi India.

E-mail: Pnm.jaggi@gmail.com

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ABSTRACT

Application of nanotechnology in delivery of drugs is set to broaden rapidly. Currently, many drug delivery systems are under investigation for cancer therapy. Cancer in general is a disease which is characterized by the uncontrolled growth and multiplication of cancerous cells. Even though conventional therapies have enhanced patients' survival, they also have numerous drawbacks. For example, conventional cancer chemotherapy has the therapeutic agents that distribute non-specifically in different tissues of the human body, thus affecting both cancerous as well as normal cells. This non-specific distribution of drugs to normal cells, tissues, and organs causes excessive toxicities; and thereby causing numerous adverse drug reactions including alopecia, weakness, organ dysfunction etc, causing poor quality of life for cancer patients. The pharmaceutical sciences are using nanoparticles to decrease the toxicity and side effects of drugs. Recently, studies have shown exceptional growth of investigation and applications in the field of Nano science and nanotechnology. There are promising results revealing that nanotechnology, as applied to medicine and drug delivery, can bring major progress in the diagnosis and treatment of cancer.

INTRODUCTION

Nanoparticles can be defined as being submicron (i.e. less than 1 micrometer) colloidal systems generally made of polymers either biodegradable or non-biodegradable polymers. According to the method of preparation of nanoparticles, Nano spheres or Nano capsules can be prepared. Nano spheres are matrix systems in which the drug is dispersed throughout the particles [1-4]. While Nano capsules are reservoir based vesicular systems in which the drug is confined to an aqueous or oily cavity which is surrounded by a membrane usually made of a polymer [5].

If designed and optimized properly, nanoparticles can act as a carrier for delivery of drug to the targeted tumor site. At the tumor level the mechanism of drug accumulation takes place by passive diffusion and by convection across the leaky, hyper permeable tumour vasculature [6]. The site specific targeting can also be done by active targeting [7]. Control release of the drug can also be achieved by controlling the structure of the nanoparticles, polymer used, and its association with the carrier.

Nanoparticles for Tumor Tissues Targeting and Delivery

Conventional nanoparticles

The association of a drug to conventional carrier systems causes modified drug bio distribution profile, as it is primarily carried to the mononuclear phagocytes system which includes liver, spleen, lungs and bone marrow. Once the nanoparticle reaches into the bloodstream, conventional nanoparticles i.e. surface non-modified nanoparticles undergo opsonisation and are massively cleared by the fixed macrophages of the mononuclear phagocytes system organs [8]. This was illustrated in mice administered with doxorubicin incorporated into poly (isohexylcyanoacrylate) Nano spheres. Increased concentrations of the cytotoxic drug doxorubicin were found in the liver, spleen and lungs, in contrast to the counterpart mice administered with free doxorubicin [9]. In a similar manner, when the anticancer drug actinomycin D was adsorbed on poly-(methyl cyanoacrylate) Nano spheres, higher concentration was primarily found in the lungs of the rats [10]. However, in case actinomycin D was

incorporated with a slower biodegradable poly(ethyl-cyanoacrylate) Nano spheres, than poly-(methyl cyanoacrylate) nanospheres, the accumulation of drug was primarily found in the small intestine of rats. Similarly, when vinblastine was incorporated into the same Poly-(ethyl-cyanoacrylate) Nano spheres, the drug concentration was found at higher levels in the spleen of the rat [11].

Consequently, both associated drug (physicochemical properties of the drug, localization in the Nano spheres whether it is adsorbed or incorporated) as well as the polymeric composition (type of polymer, hydrophilicity-hydrophobicity; biodegradation profile) of the nanoparticles have an immense influence on the drug distribution profile in the reticulo-endothelial organs [14]. However, the accurate primary mechanism was not fully understood, but it was seen that this outcome was rapid (within 0.5 or 3 hours) and was found to be compatible with endocytosis as well [14].

Such predisposition of mononuclear phagocytes system macrophages for endocytosis/phagocytosis offers a chance for efficient delivery of therapeutic agents to these cells, employing conventional nanoparticles. This alteration of bio distribution can be beneficial for the chemotherapeutic treatment of mononuclear phagocytes system confined tumors. For e.g., hepatocarcinoma or hepatic metastasis which arise from the digestive tract or bronchopulmonary tumors (primitive tumors or metastasis) and gynaecological cancers together with 'non small cells tumor' as well as 'small cells tumors', myeloma and leukemia. When conventional nanoparticles are employed as carriers for chemotherapeutic agents, some degree of cytotoxicity against the Kupffer cells or other targeted macrophages can be anticipated, as the class of chemotherapeutic drugs being employed is capable to induce apoptosis in these cells [12,13]. Treatments designed for frequent administrations (with dosing intervals less than 2 weeks that is the period of restoration of Kupffer cells) could possibly result in a deficiency of Kupffer cells, which in turn could cause a decreased uptake by liver, and consequently results in decreased therapeutic efficacy of the drugs for hepatic tumors. Additionally a probable risk for bacteraemia can also not to be excluded [12-14].

In addition to this conventional carriers also target the bone marrow, which is already a significant but very unfavorable site of action for most of the chemotherapeutic drugs. Therefore, chemotherapy with such carriers may elevate myelosuppressive effects. Conventional nanoparticles ensure a better safety profile than free chemotherapeutic agents, while it acts on normal tissues. For e.g., decrement of cardiac accumulation of drugs [14], in addition to genotoxicity of mitomycin C and farmorubicin [15-55] has also been related.

Long-circulating nanoparticle

Since the effectiveness of conventional nanoparticles is bounded by their extensive capture by the macrophages of the mononuclear phagocytes system after IV administration, other Nano particulate mechanisms must be taken into consideration to target tumors, which are not localized in the mononuclear phagocytes system area. A great deal of research has been devoted to developing Stealth nanoparticles, which are undetected by the macrophages [16]. Stealth nanoparticles are characterized by an extended half-life in the blood compartment [17,18,56-59]. This allows the stealth nanoparticles to selectively extravagate into the pathological sites, like tumors with a leaky and hyper permeable vasculature. Subsequently such long-circulating nanoparticles are believed to be able to directly target most tumors located outside the mononuclear phagocytes system regions.

The size of the colloidal carriers as well as the characteristics of their surface are of chief importance for the biological fate of nanoparticles, since these parameters can avoid their uptake by macrophages of mononuclear phagocytes system. A high curvature (resulting in a small size: less than 100 nm) and/or a hydrophilic surface are needed, in order to decrease the opsonisation reactions and consequent clearance by macrophages. A key breakthrough in the research of the nanoparticles field consisted in employing excipients like hydrophilic polymers, polyethylene glycol, polyamines, poloxamers, and polysaccharides to proficiently coat conventional nanoparticle surface [19]. Coatings from these excipients offer a dynamic cloud of hydrophilic and neutral chains at the particle surface of the nanoparticles, which repels the plasma protein. Hydrophilic polymers can be attached to the surface in two ways, either by adsorption of surfactants on the surface or by introducing of block or branched copolymers. Coating the conventional nanoparticles with surfactants so as to obtain long-circulating carrier, has been the first strategy employed to direct tumor targeting *in vivo* [60-65].

The second approach consists of linkage of amphiphilic copolymers covalently, generally used for getting a protective hydrophilic cloud on nanoparticles, as it avoids the likelihood of rapid coating desorption upon dilution or subsequent to contact with blood components. This methodology has been used with poly-(lactic acid) (PLA), poly-(caprolactone) and poly-(cyanoacrylate) polymers, which were associated chemically to PEG [20-22,66,67]. Although these copolymers have not been used until now as nanoparticles in chemotherapy of cancer, it is possible that this type of construction is extensively investigated.

Another significant approach consists in targeting the tumor with long-circulating drug carrier and then irradiating of tumor site in case of photo dynamic therapy (PDT) [23,68-72].

Local administration: Subcutaneous or intratumoral

Contrasting to water-soluble molecules, which are quickly gets absorbed across the blood capillary wall and pass into circulation, small particles administered locally infiltrate into the interstitial space around the administered site and are slowly absorbed by the lymphatic capillaries into the lymphatic system [24,25,73-75]. For that rationale, subcutaneously or injection given locally (in the peri-tumoral region) nanoparticles can be employed for lymphatic targeting, i.e. as a means for chemotherapy against lymphatic cancers or metastases. For e.g., the chemotherapeutic drug aclarubicin adsorbed onto activated carbon particles was analyzed after administering it subcutaneously to mice, against a murine model (P388 leukemia cells) of lymph node metastases [26,76,77]. The same system was also employed in subjects following intratumoral and peritumoral injections, as a local regional chemotherapy adjuvant for breast cancer [26]. In both administrations, this carrier system showed distribution selectively high levels of free aclarubicin to the regional lymphatic system and low levels to the rest of the body [26, 27,78-80].

Inorganic Nanoparticles

Recently, inorganic nanoparticles have found to interact with biological systems have drawn extensive attention in biology and medicine. Such nanoparticles are considered to have potential as novel intravascular probes for both diagnostic as well as therapeutic purposes. Significant issues for successful nanoparticle based drug delivery system include the ability to target specific types tissues and cell types, and escape from the biological particulate filter (the RES)..

Amongst the inorganic materials, magnetite has been explored most extensively for cancer therapy and diagnosis [28-39,81-84]. Magnetite nanoparticles were used directly or dispersed in the polymeric matrix as cores. They have been used chiefly in the hyperthermia treatment of cancer [38,85-90] and, in some cases, for magnetic field-assisted targeting of nanoparticles. Recently, inorganic nanoparticles have found to interact with biological systems have drawn extensive attention in biology and medicine. Such nanoparticles are considered to have potential as novel intravascular probes for both diagnostic as well as therapeutic purposes. Significant issues for successful nanoparticle based drug delivery system include the ability to target specific types tissues and cell types, and escape from the biological particulate filter (the RES)..

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Liposomes and Lipid Nanoparticles

A wide variety of drug carriers have been investigated as a means of improving the therapeutic efficacy of drugs. Amongst these drug carriers, liposomes have been widely studied as a drug delivery option to target tissues. Liposomes are fundamentally non-toxic, biodegradable as well as non-antigenic because they are an assembly of amphiphilic phospholipids such as phosphatidylcholine, phosphatidylserine etc that are one of the constitutive components of biomembranes. Many scientists have reported that certain drugs, including anti-tumor and anti-bacterial drugs, entrapped in the liposomal cavity could alter their biodistribution as well as its pharmacokinetics [40-42,95-96]; the significantly larger therapeutic advantages of these drugs have been shown.

In addition, attempts have been made to introduce antibodies and ligands onto the surface of liposomes in turn to improve the therapeutic effect of drugs incorporated into the liposomes by enhancing the targeting efficiency [42-45,97,98].

A typical example of these liposomal drugs, the immunostealth liposome developed by Maruyama et al., designed a new type of long-circulating immunoliposome [46], i.e. the PEG-immunoliposome with antibodies attached at poly ethylene glycol terminals. The presence of unbounded PEG (not bonded to the antibody) does not interfere with the binding of the terminally linked antibodies to the antigens. This type of immunoliposome demonstrated better targeted delivery than the normal immunoliposomes to the targeting organ of both lung endothelial cells and solid tumor tissue. This was caused because of the free PEG chains effectively avoiding the RES uptake of liposomes; this resulted in the increased blood concentration and the enhanced target binding of immunoliposomes.

Lipid emulsions have also been considered as promising drug delivery system to target tissues [47-49]. An emulsion is basically a heterogeneous mixture of two or more immiscible liquids (hydrophilic and hydrophobic) with the emulsifier or surfactant used to stabilize the dispersed droplets. They have certain merits like good biocompatibility, biodegradability, physical stability and ease of large-scale manufacturing. In addition to this, they can include hydrophilic, hydrophobic and amphipathic drugs due to their structural characteristics. Many researchers have revealed the validity of the lipid emulsions as a parenteral drug delivery system [50-52,99]. For example, Kurihara et al. demonstrated that the lipid emulsion could be effective as an injectable carrier to achieve tumor delivery of lipophilic palmitoyl rhizoxins [50,99,100].

CONCLUSION

The development of nanoparticles as a drug delivery system is presumed to have a huge impact on the clinical approaches for chemotherapy. The capacity to specifically target nanoparticles together with the controlled delivery of a therapeutically active agent provides a powerful new method to treat cancer. By rationally designing and optimizing nanoparticles based on advanced knowledge of cancer biology and the tumor microenvironment, better efficacy can be achieved. Additionally, nanoparticles that are capable to by-pass the RES and can carry imaging agents and deliver multiple drugs are now being developed for improved detection, diagnosis and treatment of cancer. The application of nanotechnology to cancer has already produced some stimulating results and holds even bigger promise for patients suffering from cancer in the future.

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