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REVIEW ARTICLE

Nanoparticle Based Drug Delivery System: Milestone for Cancer Therapy

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ABSTRACT

The challenge of modern drug therapy is the optimization of the pharmacological action of the drugs coupled with the reduction of their toxic effects *in vivo*. The prime objectives in the design of drug delivery systems (DDS) are the controlled delivery of the drug to its site of action at a therapeutically optimal rate and dosage to avoid toxicity and improve the drug effectiveness and therapeutic index. DDS has improved many of the pharmacological properties of conventional ("free") drugs including particulate carriers which are primarily composed of lipids and/or polymers and their associated therapeutics. It alters the pharmacokinetics (PK) and biodistribution (BD) of the associated drugs or functions as drug reservoir or both. Nanoparticles provide a range of new opportunities to increase the targeting of currently approved diagnostic and therapeutic agents to cancers. Nanoparticles carrying a chemotherapeutic can reduce the undesirable distribution of such agents. The problems related to cancer chemotherapy can partially be overcome by direct intratumoral delivery of controlled release biodegradable nanoparticles (NPs).

KEY WORDS: Nanotechnology**,** Cancer, Drug Delivery System, Nanoparticles

INTRODUCTION:

It has been observed that many of the problems that hinder the clinical applications of particulate DDS get solved by several DDS formulations. It has shown advantages in *vivo* delivery of new drugs and ligand targeted therapeutics. Some of the problems exhibited by free drugs that can be ameliorated by the use of DDS are given below (Table 1). The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. Liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction in toxicity or side effects. The applications of liposomes were found to be limited due to the inherent problems such as low encapsulation efficiency, rapid leakage of water soluble drug in the presence of blood components and poor storage stability. Polymeric nanoparticles have been found to offer specific advantages over liposomes. They help to increase the stability of drugs/proteins and possess useful controlled release properties (Vila et al., 2002; Mu et al., 2003). Nanoparticles offer wide advantages in drug delivery system. The particle size and surface characteristics of nanoparticles can easily be manipulated to achieve both passive and active drug targeting after parenteral administration. They control and sustain the release of the drug during transportation and at the site of localization, altering its organ distribution and subsequent clearance so as to achieve increase in drug therapeutic efficacy and lower side effects. It has been found that controlled release and particle degradation of such nanoparticles could be readily modulated by the choice of matrix constituents. Further, drug loading is relatively higher and the drugs can be incorporated into the systems without any chemical reaction, which is an important factor for preserving the drug activity. These particles can further be modified to achieve site-specific targeting *via* attachment of targeting ligands to their surface or use of magnetic guidance. Nanoparticle based drug delivery system can be administered through various routes including oral, nasal, parenteral, intra-ocular and so on. The conventional chemotherapy has encountered several problems like normal tissue toxicity, poor solubility, stability and high incidence of drug resistant tumor cells. Cytototoxic agents which are administered conventionally are found to bind extensively and indiscriminately to body tissues and serum proteins in a highly predictable manner, with the result only a small fraction of the drug reaches the tumor site. Further, cancer cells have a defence mechanism characterised as cellular drug resistance or multidrug resistance (MDR) phenotype which involves active efflux of a broad range of cytotoxic drugs out of the cytoplasm by membrane bound transporters (Baird and kaye, 2003). In addition cancer cells tend to be more resistant to chemotherapy due to various drug permeation barriers which makes it difficult to achieve high intratumoral drug concentration in solid tumors. This type of drug resistance or sometimes referred as “non-cellular” drug resistance may further lead to compromised clinical outcomes even

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though an anticancer drug may has strong *in vitro* efficacy. The most important goal of drug delivery is to minimize the exposure of normal tissues to these drugs while maintaining their therapeutic concentration in tumors. The problems related to cancer chemotherapy can partially be overcome by direct intratumoral delivery of controlled release biodegradable nanoparticles (NPs). NPs are colloidal carrier systems, which have been shown to improve the efficacy of the encapsulated drug by overcoming drug resistance as well as by providing sustained drug effect (Brigger et al., 2002). Biodegradable poly (hydroxy acids) such as the copolymers of PLA (poly lactic acid) and PLGA (d, l-lactide-co-glycolide) are being extensively used in biomedical applications because of their biocompatibility, ability to encapsulate various drug molecules and sustained release properties. One particularly interesting application of nanoparticule is the drug brain delivery accompanied with the local sustained release of the new large therapeutic molecules available to treat the CNS. Due to their poor stability in biological fluids, rapid enzymatic degradation, unfavourable pharmacokinetic properties and lack of diffusion toward the CNS, they may be advantageously formulated in brain targeted protective nanocontainers (Pardridge, 2001). These drugs in comparison to conventional drugs possess a high intrinsic pharmacological activity. The small dose requested for therapeutic efficiency easily fits the loading capacity of nanoparticles and do not require the administration of large amount of potentially toxic nanoparticle excipient. Further, it has been found that transferrin receptors are over expressed in most cancer cells by two to tenfold more than in normal cells. The transferrin-conjugated nanoparticles have been demonstrated to have enhanced cellular uptake and retention than unconjugated nanoparticles (Sahoo et al., 2005)

Problem	Implication	Effect of DDS
Poor solubility	A convenient pharmaceutical format is difficult to achieve, as hydrophobic drugs may precipitate in aqueous media. Toxicities are associated with the use of excipients such as Cremphor (the solubilizer for paclitaxel in Taxol).	DDS such as lipid micelles or liposomes provide both hydrophilic and hydrophobic environments, enhancing drug solubility.
Tissue damage on extravasation	Inadvertent extravasation of cytotoxic drugs leads to tissue damage e.g. tissue necrosis with free doxorubicin.	Regulated drug release from the DDS can reduce or eliminate tissue damage on accidental extravasation.
Rapid breakdown of the drug in vivo	Loss of activity of the drug follows administration e.g. loss of activity of camptothecins at physiological pH.	DDS protects the drug from premature degradation and functions as a sustained release system. Lower doses of drug are required.
Unfavorable pharmacokinetics	Drug is cleared too rapidly, by the kidney, for example, requiring high doses or continuous infusion.	DDS can substantially alter the PK of the drug and reduce clearance. Rapid renal clearance of small molecules is avoided.
Poor biodistribution	Drugs that have widespread distribution in the body can affect normal tissues, resulting in dose-limiting side effects such as the cardiac toxicity of doxorubicin.	The particulate nature of DDS lowers the volume of distribution and helps to reduce side effects in sensitive, nontarget tissues.
Lack of selectivity for target tissues	Distribution of the drug to normal tissues leads to side effects that restrict the amount of drug that can be administered. Low concentrations of drugs in target tissues will result in suboptimal therapeutic effects.	DDS can increase drug concentrations in diseased tissues such as tumors by the enhanced permeability and retention (EPR) effect. Ligand-mediated targeting of the DDS can further improve drug speci-ficity.

Table No. 1. Non-ideal properties of drugs and their therapeutic implications.

PLGA (POLY (LACTIC-CO-GLYCOLIC ACID) NANOPARTICLES FOR ANTICANCER DRUG DELIVERY:

Particulate drug carrier systems encapsulating drugs have emerged as promising approach in anticancer treatment by improving the therapeutic index of drugs by preferential localization at target sites (Bisht and Maitra, 2009). Nanoparticles formulated from the biocompatible and biodegradable polymer poly (d, l-lactide-co-glycolide) (PLGA) have shown the potential for various drug delivery applications (Sahoo and Labhasetwar, 2003). These nanoparticles can be designed to slip between intercellular spaces, enter cells or transport directly through biological barriers to access disease sites either by modifying the surface characteristics or by attaching any suitable ligand on their surface (Das et al., 2009). Biodegradable and biocompatible PLGA is perhaps the most widely investigated biomaterial for making NPs for controlled release and sustainable drug delivery (Blanco et al., 2005; Kilic et al., 2005; Olivier, 2005). It has been found that PLGA has a solid safety profile and sustained drug release (Lupi et al., 2004; Gavini et al., 2004; Panyam et al., 2002). PLGA like other natural polyesters undergoes hydrolysis upon implantation into the body, forming biocompatible and metabolizable moieties such as lactic acid and glycolic acid that are eventually removed from the body by the citric acid cycle (Panyam et al., 2003). PLGA NPs are generally made by emulsion solvent evaporation or by solvent displacement techniques (Jain, 2000). Drugs encapsulated inside the NPs can be released at a sustained rate through diffusion and by the degradation of the NPs. Many lines of evidence suggest that the degradation rate of PLGA can be controlled by changing block copolymer composition and molecular weight (Lin et al., 2000). Accordingly, the release rate of encapsulated drugs can be altered from lasting for days to months.

CHARACTERIZATION OF PLGA NANOPARTICLES:

PARTICLE SIZE:

Particle size and size distribution are the most important characteristics of nanoparticle systems. These determine the *in vivo* distribution, biological fate, toxicity, targeting ability, drug loading, drug release and stability of nanoparticles. Studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over microparticles as a drug delivery system (Panyam and Labhasetwar, 2003). Due to their small size and relative mobility, nanoparticles have relatively higher intracellular uptake and are available to a wider range of biological targets. Particle size affects the drug release rate of the particles. Since smaller particles have larger surface area, most of the drug associated remains at or near the particle surface, which leads to fast drug release, however, due to the large cores, larger particles allows encapsulation of more drug and therefore slow diffusion outside (Redhead and Davis, 2001). Particle size also affects the rate of degradation of the polymer which is found to increase with increasing particle size (Dunne and Corrigan, 2000). Photon-correlation spectroscopy or dynamic light scattering is the fastest and the most routine method of determining particle size. It requires the viscosity of the medium to be known and determines the diameter of the particles by Brownian motion and light scattering properties (Swarbrick and Boylan, 2002). Results obtained by this technique are usually verified by scanning or transmission electron microscopy (SEM or TEM).

ZETA POTENTIAL:

The zeta potential of a nanoparticle is commonly used to characterise its surface charge (Couvreur et al, 2002). It reflects the electrical potential of the particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (+/-) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles. The zeta potential can also be used to determine whether a charged active material is encapsulated within the centre of the nanocapsule or adsorbed onto the surface.

MORPHOLOGY:

To ascertain the overall shape and morphology of PLGA nanoparticles, atomic force microscopy (AFM) and/or electron microscopy techniques such as scanning electron microscopy (SEM) and Transmission electron microcopy (TEM) are used.

SURFACE PROPERTIES OF NANOPARTICLES:

After intravenous administration nanoparticles are easily recognized by the immune system of the body and are then cleared by phagocytes from the circulation, the process referred to as opsonisation (Muller and Wallis et al, 1993). For successful drug targeting , there should be minimum opsonisation and prolonged circulation of these particles *in vivo* which can either be achieved by surface coating of nanoparticles with hydrophilic polymers/surfactants or formulation of these particles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, polyoxamer, poloxamine and polysorbate 80 (Tween 80). Studies have shown that PEG conformation at the nanoparticle surface is of utmost importance for

preventing opsonisation due to the opsonin repelling function of the PEG layer.

STABILITY AND STERILISATION:

In general lyophilised polymeric nanoparticles exhibit a high stability, they do not require special storage conditions and may be stored in the refrigerator at 2 - 4°C (Huncharek et al., 1998). Radiation sterilisation is the method of choice for the sterilisation of nanoparticles. Indeed, routine sterilization techniques are often inapplicable due to physicochemical properties of the nanoparticles. The sterile filtration is not feasible because the sizes of the nanoparticles are close to or above the pore size of the sterile filters, heat sterilisation is not possible because of the heat sensitivity of most nanoparticle materials (Kreuter, 2006). It has been found that irradiation not only protects the physicochemical parameters (mean particle size, polydispersity, molecular weights and aggregation stability) of the nanoparticles (both empty and drug loaded) but also prevents the radiolysis of the drug (Maksimenko et al., 2008).

NANOPARTICLES FOR DRUG DELIVERY INTO THE BRAIN:

The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. The BBB is characterized by relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. It effectively prevents the passage of water soluble molecules from the blood circulation into the CNS and can also reduce the brain concentration of lipid soluble molecules by the function of enzymes or efflux pumps (Chen et al., 2004). Consequently, the BBB only permits selective transport of molecules that are essential for brain function. Strategies for nanoparticle targeting to the brain rely on the presence and interaction of nanoparticles with specific receptor-mediated transport systems in the BBB. Polysorbate 80/LDL, transferrin receptor binding antibody (such as OX26), lactoferrin, cell penetrating peptides and melanotransferrins are found to be capable for delivering a self non transportable drug into the brain *via* the chimeric construct that can undergo receptor-mediated transcytosis (Kreuter, 2004; Ji et al., 2006; Gabathuler et al., 2005). Poly (lactic-co-glycolic acid) (PLGA) transferrin-conjugated nanoparticles have also been found to transport cytostatics across the blood-brain barrier (BBB) (Jorg and Svetlana, 2008).

RECENT ADVANCES IN NANOPARTICLES AS CANCER THERAPY TOOLS:

Drug development is a difficult and expensive process. For a cancer drug to make it to clinical use, it not only has to be effective against cancer cells, but also needs to have low toxicity, good stability and good solubility. Many promising drugs such as wortmannin failed clinical development because they failed one or more of these requirements. Nanoparticle drug delivery is a breakthrough technology and has the ability to overcome these limitations. It has been observed that the nanoparticle formulation of wortmannin decreased toxicity and increased stability, solubility and effectiveness. Additionally, nanoparticle wortmannin showed improved efficacy to radiotherapy dramatically and was more effective than the most commonly utilized chemotherapeutics (Karve et al., 2012). Literature has revealed that nanoparticles bear stratigies for multifunctional targeting in cancer therapy including antibody based targetting, peptide based targetting, small molecule-based targetting, aptamer-based targeting and so on (Yu et al., 2012). In recent years, fluorescent silica nanoparticles (FSNPs) have received immense interest in cancer imaging. FSNPs are a new class of engineered optical probes consisting of silica NPs loaded with fluorescent dye molecules. These probes exhibit some attractive features, such as photostability and brightness, which allow sensitive imaging of cancer cells (Santra, 2010). In brief, now-a days nanotechnology based cancer therapy plays a pivotal role, providing the technological power and tools that enable those developing new diagnostics, therapeutics, and preventives to keep pace with today's explosion in knowledge.

CONCLUSION:

Nanoparticles provide a range of new opportunities to increase the targeting of currently approved diagnostic and therapeutic agents to cancers. Nanoparticles carrying a chemotherapeutic can reduce the undesirable distribution of such agents. Certain tumors are located in difficult to reach sites such as the brain. Nanoparticles can access these sites by avoiding the systemic clearance by the RES and have the capacity to move across the blood brain barrier (BBB). Nanoparticles integrated with the diagonostic or therapeutic agents can either freely release these agents or undergo their own decomposition for the release to occur. Improvements in targeting can lead not only to increased efficiency of these agents but also to increased signal-to-noise ratios for diagnostics and better efficacy to toxicity ratios for therapeutics.

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