Chapter 7
Nanotechnology-Based Drug Delivery Systems: Past, Present and Future

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7.1 Introduction

Conventional method of drugs delivery is problematic due to the low efficiency rate, poor biodistribution and selectivity. Those limits perhaps can be overcome by using controlled drug delivery system. Controlled drug delivery system works by transporting the drug to the target action site, thus lowering side effects to other tissues. The delivered drugs can be protected against rapid degradation, providing more concentrated drugs available in the target tissue by means requiring low dosage of drug (Wilczewska et al. 2012). The technology provides means of bypassing liver as to avoid the first pass metabolism. Cell-specific targeting is a way of attaching drugs to their specifically designed carriers.

Development in nanotechnology has pointed out the potential of nanoparticles with the size less than 100 nm, as drug carriers. Nanoparticles are ranging 10–1000 nm in size. Dissolve, entrapping, encapsulation or attaching drugs to the matrixes of nanoparticles. Nanoparticles are gaining interest due to their large surface area, and their ability to adsorb and carry other compounds.

7.2 Nanocarriers Used in Drug Delivery System

Optimized nanocarriers are easily taken up by cells compare to macromolecules. Such nanocarriers used in drug delivery systems are polymers, liposomes, dendrimers, solid lipid nanoparticles, etc. For a successful targeted therapy, the mean of the drug conjugation to its nanocarriers and its targeting strategy are

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important (Suri et al. 2007). Adsorption or covalent linking of the drug to the surface of nanocarriers or encapsulation of the drug in the nanocarriers is possible. Covalent linking is above the other ways due to the ability to control specific amount of drug molecules attach to the nanocarriers. Cell-specific targeting can be done either by active or passive mechanism.

Active mechanism—The attraction of drug-nanocarriers conjugate to the affected site by using recognition ligands which are attached to the surface of conjugate antibodies, etc. It can also be achieved by physical stimuli manipulation (e.g., pH, temperature, etc.).

Passive mechanism—A result of enhanced vascular permeability and retention (EPR) in leaky tissues of tumors. The drugs will be released upon the arrival of the drug-nanocarrier conjugates at the affected tissues. A controlled drug release can be achieved by the changing physiological environment (e.g., pH, temperature, etc. or via enzymatic reaction) (Nevozhay et al. 2007).

Undesirable effects of nanoparticles depend on their size, shape, concentration, surface chemistry, administration route, reaction of the immunity system and residence time in the bloodstream. Factors that can affect the toxicity of nanoparticles should be considered. Toxicological studies are important when doing new drug delivery system formulations. However, their size can be a reference basis for generalization. Smaller particles have higher surface area. So they are more reactive, thus more toxic. Generally accepted, nanoparticles with less than 100 nm diameter have optimal pharmacokinetic characteristics which are suitable to be used in vivo. Smaller nanoparticles may be excreted via renal clearance and tissue leakage meanwhile the larger ones are removed through phagocytosis and via macrophage.

7.2.1 Liposomes

Reportedly, liposomes increase the drugs solubility and improve their pharmacokinetic properties in term of the rapid metabolism, lower side effects, and increase of anticancer activity (in vivo and in vitro) (Sunderland et al. 2006). Factors such as pH, osmotic gradient, composition of the liposome and the surrounding environment, affect the drug release from liposomes (Santos Giuberti et al. 2011). Liposomes interaction with cells can occur via adsorption, endocytosis, fusion and lipid transfer. Examples of drugs in liposomal formulations are anticancer drugs (Santos Giuberti et al. 2011), serotonin (neurotransmitter) (Afergan et al. 2008), antibiotics (Uner and Yener 2007), anti-inflammatory (Paavola et al. 2000), and antirheumatic drugs.

Reports on clinical outcomes and side effects—Photodynamic therapy (PDT) which is based on intense pulsed light (IPL) and spray (0.5% 5-aminolevulinic acid encapsulated in liposome), used in inflamed facial acne treatment (Yeung et al. 2011). Turkova et al. (2011) has performed the comparison between efficacy and safety of deoxycholate and lipid (liposomal) amphotericin B formulations (AMBF) in the treatment of invasive fungal disease in neonates. It was reported that the usage of deoxycholate amphotericin B is cheap, effective, and safe as a first-line therapy.

Safdar et al. (2010) has evaluated nephrotoxicity associated with amphotericin B lipid complex (ABLC) and liposomal amphotericin B (L-AmB) in patients receiving antifungal therapy and prophylaxis, and found no significant difference of nephrotoxicity for both drugs. Modified liposomes contain specific proteins or antigens, etc., that can be used to design drugs assigned to specific target tissue. Biswas et al. (2012) presented hydrazine-functionalized poly (ethylene glycol)—phosphatidylethanolamine (PEG-PE)-based amphiphilic polymer that operates various ligands which were reversible model ligands monoclonal antinucleosome antibody 2C5, antimyosin antibody 2G4, and glycoproteins concanavalin A (Con-A).

In the study of Kim et al. (2003), they investigated modified cationic liposomes either by PEG-grafting or PEG-adding as plasmid DNA transfection complexes. They tested on the toxicity, mitochondrial targeting and delivery efficacy of paclitaxel (PTX), the model drug. They concluded that TPP PEG-PE is a possible and safe drug delivery system.

7.2.2 Nanoparticles Based on Solid Lipids

Types of carrier systems based on solid lipid matrix- Solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and lipid drug conjugates (LDC) (Wissing et al. 2004). They have been exploited for dermal, peroral, parenteral, ocular, pulmonary, and rectal delivery. SLN are composed of solid lipids with major component of purified triglycerides. It provides good stability and tolerance, protecting drugs from degrading, and controlled drug release. However, few disadvantages were pointed out such as low capacity for loading, drug expulsion after crystallization, and high amount of water of the dispersions (Muller et al. 2002). NLC and LDC are modified lipids based nanoparticles. NLC are made of the mixture of solid lipids and liquid lipids. Three types: imperfect type, multiples type and amorphous type. NLC are exploited for dermal delivery. LDC is a soluble drug-lipid conjugate, linked by covalent bond or salt formation (Muller and Keck 2004).

7.2.3 Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are made of synthetic polymers, and may be classified as biodegradable e.g., poly (L-lactide) (PLA), poly glycolide (PGA), non-biodegradable such as polyurethane, based on behaviours shown in vivo. The PNPs are coated with nonionic surfactants for avoiding immunization and intermolecular interactions. Only after polymerization or during the process that the drugs can immobilized or encapsulated on PNPs surface. Drugs release are either through desorption, diffusion or by nanoparticles erosion in target tissue (Tong et al. 2011). Immobilizations of retinyl acetate (RA) on ethyl cellulose (EC) have been a stepping stone in the improvisation of aqueous stability and photostability.

Biodegradable thermo-responsive chitosan-*g*-poly (*N*-vinylcaprolactam)-biopolymer was used to deliver 5-fluoro-uracil to cancer cells. The hypothesized mechanism of the drug release is conformational changes following swelling during the transition of temperature known as lower critical solution temperature (LCST) in which significant release above LCST was shown in vitro. Results showed high toxicity to cancer cells but lower to normal ones (Rejinold et al. 2011). Reported by Kumari et al. (2010), minimal toxicity is associated with PLGA usage as drug delivery. Such nanoparticles has high biocompatibility rate with tissue and cells. Drug-biodegradable polymeric nanocarrier conjugates are stable in blood, non-toxic, non-thrombogenic, non-immunogenic, and non-inflammatory (Rieux et al. 2006).

7.2.4 Dendrimer Nanocarriers

The structure of dendrimers consists of a core, dendrons, and surface active groups. The core is an atom or molecule with dendrons (arms) attached to it. Factors that affect the usability of dendrimers are the selection of a core, monomers type and surface functional groups. The cytotoxicity depends on the material of the core and is greatly influenced by the nature of dendrimers surface (Caminade et al. 2005). Simultaneous interactions are possible between the surface functional groups with certain amount of receptors.

Encapsulation of drugs internally in dendrimers, chemically attached or physically adsorbed to the surface are ways to attach the drugs to dendrimers, and the choices depends on the properties of the drugs. Encapsulation is used when the drugs are toxic, low solubility and labile. Meanwhile, chemical bonding controls the number of covalent bonds and thus, control the number of drugs attached to the dendrimers surface (Singh et al. 2008). The selectivity of both methods can be enhanced by the attachment of targeting agents (e.g., folic acid) to the surface. The dendrimers surface provides attachment platform for specific ligands such as folic acid, PEG, antibodies, etc. (Wilczewska et al. 2012). Such attachment can improve the surface activity, biological and even physical properties of the dendrimers.

The structure and distribution of drugs or genes inside a common dendrimer known as poly (amido amide) (PAMAM) has been investigated. When compared with free cisplatin, PAMAM shows several advantages such as highly accumulated drug in solid tumors, low rate of drug release, and less toxicity effects in other organs (D'Emanuele and Attwood 2005). Other drug applications in PAMAM dendrimers are anticancer drugs, including doxorubicin, 5-FU, methotrexate, and anti-inflammatory drugs such as ibuprofen, indomethacin or piroxicam. Their toxicity is affected by their size and charge in which higher generation (G4-G8) PAMAM dendrimers exhibit toxicity due to higher density of cationic charge (Shah et al. 2011). Toxicity studies on the cationic and anionic dendrimers using Caco-2 has concluded anionic dendrimers has lower cytotoxicity compared to the other one (Kitchens et al. 2006). Destabilization of cell membranes and cell lysis has been observed after the introduction of positively charged dendrimers. Roberts et al.

(1996), has observed that cationic PAMAM caused a decrease in cell viability. They also tested on toxicity of cationic PAMAM Starburst® in mice and found no side effects occurred due to high concentration of low generation cationic dendrimers. G4 dendrimers that have amino terminal groups were found to be toxic, impairing the growth and development of embryos of zebrafish. Dendrimers with carboxylic acid functional groups exert no effects on zebrafish embryos. Dendrimers can modulate the release of cytokine and chemokine which is helpful in therapy and yet, cause major side effects (Duncan and Izzo 2005).

7.2.5 Silica Materials

The ones used in drug delivery system are classified as xerogels and mesoporous silica nanoparticles (MSNs) (Wei et al. 2010). Advantages are biocompatibility, high porosity, and functionalized easiness. They are often chosen for biological purposes. Silica xerogels has an amorphous structure that is highly porous and bigger surface area. The porous structure is influenced by the parameters of synthesis (Echeverria et al. 2010). Sol-gel technique is a common way to form silica xerogels filled with drugs. Modification in the synthesis conditions, such as reagents ratio, temperature, catalyst concentration and drying pressure, alters the xerogels properties in controlled drug release (Czarnobaj 2008). Example of drugs loaded using this technique are phenytoin, doxorubicin, cisplatin, nifedipine, diclofenac, metronidazole and heparin. The best known types of MSNs are MCM-41 and SBA-15 (Wei et al. 2010). The MSNs possess more homogenous structure, lower polydispersity and bigger surface area for adsorption of therapeutic agents (Di Pasqua et al. 2009).

7.3 Advantages of Nanocarriers for Drug Delivery

Without nanotechnology, the potential of a few therapeutics including nucleic acids and small molecules as a part of diseases treatment would not be proven. Polymeric and micelle-based-nanocarriers have hydrophobic core which are able to encapsulate poor water soluble drugs meanwhile, the hydrophilic surface helps to enhance water insoluble drugs delivery (Lukyanov and Torchilin 2004). Delivery of nanoparticulate drugs can improve the stability of payload in which the encapsulated drugs can be protected against enzymatic degradation (Mao et al. 2001).

Liposomal and virus-based nanocarriers can mimic natural environment of protein which allows protein to be stabilized and expressed naturally (Steinmetz 2010). Another main advantage is the ability of nanocarriers to specific targeting. Tumors-passive targeting can be achieved through the enhanced permeation and retention (EPR) effect. Vessels of tumors are often disorganized with enlarged gap junctions, thus promoting the permeation and retention of nanocarriers and subsequently,

continuous releases of therapeutic substances (Kratz and Warnecke 2012). However, EPR effect is highly diversified between different tumours.

Delivered therapeutic drugs can often cause side effects on healthy tissues. However, with the formulation and design of active targeted nanocarriers, the release of therapeutics can be controlled sustainably. With the ability of multiple encapsulation and diversified therapeutic effects, would help to reduce not just the side effects, but the dosages too (Acharya and Sahoo 2011).

7.4 Nanoparticles Application (Healthcare/Medical)

7.4.1 Targeted Drug Delivery

The limitation of anticancer drugs is due to poor selectivity and poor diffusion. Patients undergoing chemotherapy for cancer are still facing life-threatening side effects due to the lack of drugs that are more specified for tumour cells. To overcome this problematic issue, cytotoxic drugs should be transported to specific sites of tumours. The concept of targeted drug delivery involves the modification of drugs or nanocarriers with specific ligand that can interact selectively with the marker present on the surface of the target cell. The crucial part of the concept is the identification of distinctive properties of the marker on the target cell surface which cannot be found or expressed in normal cells. This particular active targeting have been gaining attention and not just due to the limitations of conventional treatments, but through the discovery of new carcinogenic molecular targets and the clinical studies involving monoclonal antibodies (MAbs) and other molecules that target specific markers (Karra and Benita 2012).

Monoclonal antibodies (MAbs) have been used in targeting the surface of target epitopes. Their binding to tumour's specific marker has been covalently linked to specific targeted cancer drugs. So these mAb-immunoconjugates can be used to deliver drugs to specific targeted tumours. One example is the humanized anti-CD33 antibody-alicheamicin conjugate Mylotarg, used in acute myeloid leukemia treatment (Huang et al. 2009).

In 1981, targeting cancer using mAbs had been described by Milstein. Clinical demonstrations were done for antibody-based tissue targeting; using 17 FDA's approved mAbs. In 1997, mAb rituximab (Rituxan) was approved for the treatment of non-Hodgkin's lymphoma patients (Peer et al. 2007). One year later, Trastuzumab (Herceptin) was approved for the treatment of breast cancer. It was an anti-HER2 mAb binded to ErbB2 receptors (Albanell and Baselga 1999). Vascular endothelial growth factor (VEGF) was found to be the promising angiogenesis inhibitor, thus few approaches to targeting VEGF have been investigated. The best VEGF inhibition approach studied is the Bevacizumab (Avastin), which was approved as the first anti-angiogenic agent for the treatment of colorectal cancer in 2004 (Ferrara 2005). Over 200 antibody-based delivery systems are clinically studied. Broad studies have

opened up to other options of targeting ligand tools such as aptamers, peptides, and growth factors, etc.

Since nanocarriers have higher ratio of surface area to their volume, there is possibility for targeting purposes, in achieving higher ligand density on the surface. Polymers and lipids are the common vectors used for drug delivery. A dozen of polymer drug conjugates have been clinically tested. Examples are anti-endothelial immunoconjugates, fusion proteins and caplostatin (First polymer-angiogenesis inhibitor conjugates) (Peer et al. 2007). Meanwhile, there are biodegradable polymers containing entrapped drugs such as Goserelin (Zoladex) and Leuprolide (Leupron Deprot), which are made of polylactideco glycolide entrapping luteinizing hormone releasing hormone, used for prostate cancer treatments. Carmustine (Gliadel) was used to treat brain cancer (Duncan 2006). There are also some polymer-drug conjugates and polymer-protein conjugates being developed for protein and gene delivery. The first practical use of polymer-protein conjugates as anticancer agents was in the early 1990s in which SMANCS and PEGylated proteins were introduced. Further studies into these polymer-protein conjugates were done. Polymer-drug conjugates were designed in late 1970s and studies involving HPMA copolymer conjugates and PGA conjugates (Duncan 2006).

7.4.2 Drug and Vaccine Delivery

Containment and prevention of diseases are depending on the key role of vaccines. Vaccine administration system is one of the obstacles involved. The delivery of the materials for vaccines administration should be in a good manner and should show high therapeutic effects. The enhancement of vaccine adjuvants in improving the quality of cellular and humoral immunity are possibly being swapped with the use of nanoparticles that improves the delivery of antigens to immune system. Some of the proved nanoformulations include MF59 (Novartis) (Wilson 2015). Other formulations using nanomaterials includes dendrimers, liposomes, micelle, etc. Nanoparticles as delivery tools benefited in ways that they can target specific tissues, dosage reduction as well as low toxicity effects, and improve the efficiency of drugs delivery. The size of nanoparticles is important for the drugs biodistribution in-vivo and influencing the cellular mechanism such as phagocytosis, endocytosis, and so on.

Nanoparticles too can facilitate the delivered antigens interaction with the Antigen Presenting Cells (APCs). Nanovaccines have received a lot of attentions due to their beneficial properties in overcoming the limitations of immunotherapy effects including low interactions with APCs, and instability of macromolecules. These immunomolecules can either be encapsulated within or conjugated on surface of polymeric nanoparticles. The usage of same nanoparticles with different surface charges in different studies has reported that nanoparticles with cationic groups were internalized more due to higher affinity for proteoglycans present on the cells surface (Gonzalez-Aramundiz et al. 2012).

Poly lactic-co-glycolic-acid is a biodegradable polymer that has been extensively studied as a delivery carrier as they can be packed as nanoparticles or microparticles according to the nature and formulations of delivery. Encapsulated antigens modifies physico-chemical properties of the nanodrugs delivery that it affects the results of assays on stability, surface charge, size and biodistribution cannot be extrapolated from one to another molecule using the same encapsulating particle. The properties of the antigen can be changed when it is encapsulated, and so the stability, functional structure and immunogenicity are in need of verification. Altogether, nanoparticles administration in lab animal testing using intraperitonial injection shows good protection against infections meanwhile oral administration shows less efficiency. One exception is the system that used chitosan or alginate as the DNA vaccine encapsulator. There is only one licensed vaccine commercialized in Canada (Ross et al. 2015).

Such important part in some studies is that the adjuvant effect of the nanodelivery system is almost potent as the loaded antigen itself and has been reported in mammals with the use of liposomes. Alum salts are the common immune adjuvants being used due to their "inflammasome" mechanism that leads to the increased of danger signals and subsequently, activate immunity. They still have few drawbacks in terms of inability to induce many cellular responses, degradation once being freeze-dried and multiple administration long term. These drawbacks have set researchers to find solutions and thus, emulsions may be the best suggested system to be used in immunotherapy. Few water-in-oil emulsions were developed and were able to formed depot at the site of injection, attracting immune cells; however the adversed reactions have maximized their application. Oil-in-Water (O/W) emulsions were used as the alternative adjuvants of vaccine and one example is the MF59™, the first O/W emulsion approved as influenza vaccine adjuvant in 1997 (Wilson 2015).

Liposome is also one of the proposed alternatives for the immunity responses stimulation. Due to their phospholipid bilayers structure, they have the capability to encapsulate antigens and deliver them to APCs, ease the cross transportation of antigens and stimulate immune responses. One unique benefit of these carriers is that there is possibility of immunostimulants co-encapsulation.

Virosomes are the most advanced liposomal structure developed as nanovaccine and one licensed example developed for influenza is the Inflexal V in which, two glycoproteins of influenza (Hemagglutinin (HA) and neuraminidase) are integrated onto the liposomes' surface either covalently or by electrostatic interactions. This increases the chance of capturing the antigens and APCs processing. The high immunotherapeutic effect of this component is due to the fusion of HA protein with the endosomal membrane and aiding in the escape of virosomes and thus, antigen will not be destructed. The antigen will be available for class I antigen presentation (Smith et al. 2013). Despite of all the promising potentials for nanovaccines development, intensive studies should be done to develop nanoformulations that can be applied in immunotherapy.

7.5 Conclusion

The modification or adaptation of nanotechnology either in therapeutic therapy or as diagnostic tools for diseases is the stepping stones for breakthrough of the technology. Nanocarriers in drug delivery system are designed to improve the therapeutical and pharmaceutical application of conventional drugs. Incorporation of drugs into nanocarriers can protect the drugs from enzymatic degradation as well as high possibility of specific targeting and controlled release. Nano-carrier-drug conjugates are more specific and effective. By accumulating drugs at the target sites, they can reduce toxicity and side effects in normal tissues and thus, lowering the drugs dosages.

However, there are challenges including developing protocols for toxicity testing, improving drug loading, transport and release, etc. that have to be met yet. A real breakthrough can be achieved solely through the painstaking performance in nanotherapy. Nanotherapeutic of diseases may contribute success or improvement in cancer treatment. Moreover, immobilization of such antibodies, growth factor or folic acid on the nanoparticles surfaces will improve the selectivity of drug carriers. Applications of nanoparticles such as in therapeutic treatments and diagnosis, in medicine are set to spread wider.

7.6 Future Perspectives

The nanotechnology of drug delivery offers considerable advances but major needs for drug carriers are still unmet. The keyword for controlled drug transportation is control, and can be achieved if there is flexibility in; modulation of size of drug carrier, stability, biocompatibility, and the rate of independency of drug delivery with the surrounding environment.

These properties are in need of improvement in order to be clinically used but considering the results of in vivo and in vitro studies, they are subject of interest. Throughout the development of drug delivery system up until now, tremendous improvement has been made. Yet, there are still challenges needed to be deal with such as scaling up the process of bringing therapeutic substances or drugs into the market, as well as developing multifunctional drug carriers that fulfil the biological and therapeutic requirements.

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