Pharmaceutical Nanotechnology: Strategies and Techniques of Drug Therapy, Disease and Delivery through Pharmaceutical Biotechnology

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Abstract

The health industry is enormous today and will only get larger as the baby-boomers reach old age. With such a huge customer based and an increasing demand, pharmaceutical industries will respond to patient's demands by expanding their technologies. As drugs become more complex and increasingly toxic, new modes of drug delivery systems are necessary to transport them to the desired sites in the body. For this reason the renowned pharmaceutical companies are applying new methods and technologies. One of the most comprehensive technology is pharmaceutical nanotechnology. Pharmaceutical nanotechnology offers new tools, opportunities and scopes, on many areas in diagnostics and therapeutics. Pharmaceutical nanotechnology is now well-established as specialized area for drug delivery, diagnostics, prognostic and treatment of diseases through its nano-engineered tools. Pharmaceutical nanotechnology provides opportunities to improve materials, medical devices and help to develop new technologies where existing and more conventional technologies may be reaching their limits. In short, recent development, market realization of various pharmaceutical nano-tools and global interest shown by scientists, governments

and industries ensure that there is tremendous potential and scope of nano-based drug delivery system in near future.

Keywords: *Pharmaceutical nanotechnology, Drug delivery, Diagnosis, Prognostic, Nano-engineered tools.*

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1. INTRODUCTION

Nanotechnology is a rapidly growing science of producing and utilizing nano-sized particles, that measure in nanometer. In other words, nanotechnology is the art of characterizing, manipulating and organizing matter systemically, at the nanometer scale, which has created a revolution in science, engineering, technology, drug delivery and therapeutics. The size of typical accessible structures is in the sub-micrometer range, being within the limits of optical resolution and barely visible with a light microscope or scanning electron microscope. This scale is about 1/1000 smaller than structures that could be resolved by the naked eye, but still 1000 times larger than an atom. Recent developments are addressing the size range below these dimensions and because of a typical structure and size is in the nanometer range, the methods and techniques are defined as nanotechnology (Aboofazel, R.et al., 2010). There are many treatments today that takes a lot of time and are also very expensive. Using nanotechnology in pharmaceutical field, quicker and much cheaper treatments can be developed. Medical nanomaterials may also include smart drugs that become active only in specific circumstances. Yoshihisa Suzuki from Kyoto University has designed a novel drug molecule that releases antibiotic only in the presence of an infection. Suzuki bound the molecule of gentamicin to a hydrogel using a newly developed peptide linker. Robert A. Freitas has designed an artificial red blood cell called respirocyte, a spherical nanorobot of about the bacterium size. Artificial engineered microbes are already being used to produce human hormones, for example. Human DNA is incorporated in the genome of the bacteria, which then start to produce human hormones, used to cure endocrine diseases. There is another aspect for using pharmaceutical nanotechnology.

Normally, drugs work through the entire body before they reach the disease affected area. Using these nanotechnology pharmaceuticals, the drug can be targeted to a precise location which would make the drug much more effective and reduce the chances of possible side-effects (Misra, R.et al., 2010). Pharmaceutical Nanotechnology provides a unique approach and comprehensive technology against cancer through early diagnosis, prediction, prevention, personalized therapy and medicine. Target-specific drug therapy and methods for

early diagnosis of pathologies are the priority research areas in which nanotechnology would play a vital part (Darshana, P. and Joshi, K. 2012).

2. PHARMACEUTICAL NANOTECHNOLOGY BASED SYSTEM

Developing a drug delivery system that optimizes the pharmaceutical action of a drug while reducing its toxic side effects in vivo is a challenging task (Jain, N.K. et al., 2007). These challenging task can controlled by using pharmaceutical nano-systems. Pharmaceutical nanotechnology consisting of two basic types, which are nano-materials and nano-devices, which play a key role in pharmaceutical nanotechnology and other fields. The nano materials are made from biomaterials; these are used in orthopedic or dental implants or as scaffolds for tissue engineered products. Their surface can be modified or coatings can be done which enhances biocompatibility with the living cells. These are further classified into two such as nanocrystalline and nanostructure materials (Jain, N.K. et al., 2007). Nanocrystals can be reduced their size through grinding in special mills and the resulting drugs can be applied intravenously as nanosuspensions or bronchially through an inhaler. This small size enhances the surface/volume-ratio and bioavailability of almost insoluble pharmaceuticals. Nanostructured materials are processed forms of nanomaterials with special shapes and functions. These include quantum dots, dendrimers, fullerenes and carbon nanotubes. Nanomaterials are widely used in drug delivery where they can increase drug solubility and, additionally, can lead to controlled release and/or drug targeting. They are used in anti-cancer treatment, gene delivery, inhalers, hormone delivery through the skin, drug delivery through the eye and in oral and vaccine delivery systems. A lot of companies employ nanoparticles in anti-cancer treatment. Nanodevices are miniature devices in the nanoscale and

some of which include nano- and micro-electromechanical systems (NEMS/ MEMS), microfluidics (control and manipulation of micro or nano-litre of fluids), and microarrays (different kind of biological assay e.g. DNA, protein, cell, and antibody). Examples include biosensors and detectors to detect trace quantities of bacteria, airborne pathogens, biological hazards, and disease signatures and some intelligent machines like respirocytes (Rangasamy, M et al., 2011).

3. TYPES OF PHARMACEUTICAL NANOSYSTEMS WITH THEIR APPLICATIONS

(i) Liposomes

The first type of nanomaterial that are applied in drug delivery was lipid vesicles, known as liposomes, which was first described in 1976 (Semete, B. et al., 2010). Liposomes are spherical vesicles composed of amphiphilic phospholipids and cholesterol, which self-associate into bilayers to encapsulate an aqueous interior. The amphiphilic phospholipid molecules form a closed bilayer sphere in an attempt to shield their hydrophobic groups from the aqueous environment, while still maintaining contact with the aqueous phase via the hydrophilic head group. (Bawarski, W.E. et al., 2008). Because a liposome can encapsulate an aqueous solution with a hydrophobic outer membrane, hydrophilic solutes cannot pass through the lipids. So, lipsomes can carry both hydrophobic molecules (its outer membrane) and hydrophilic molecules (the inner aqueous core). Depending upon their size and number of bilayers, liposomes can be classified into three categories: multilamellar vesicles, large unilamellar vesicles, and small unilamellar vesicles. Liposomes can be classified in terms of composition and mechanism of intracellular delivery into five types: conventional liposomes, pH-sensitive liposomes, cationic liposomes or immunoliposomes, and long-circulating liposomes (Bawarski W.E.et al., 2008). The liposome delivers its contents to the appropriate site by having its lipid bilayer fuse with bilayers of the cell membrane. By making liposomes in a solution of DNA or drugs (which would normally be unable to diffuse through the membrane) they can be (indiscriminately) delivered past the lipid bilayer. Liposomes have been intensively investigated for their use in cancer therapy. The effectiveness of drug

delivery systems can be attributed due to their small size, reduced drug toxicity, controlled way of drug release, because of its modification of drug pharmacokinetics and biological distribution (Misra, R.et al., 2010).

(ii) Dendrimers

Dendrimers are globular, highly branched, and synthetic polymers consisting of an initiator core and multiple layers with active terminal groups. These layers are

comprised of repeating units and each layer is called a generation. The core of a dendrimer is denoted as generation zero. The specific molecular structure of dendrimers enables them to carry various drugs using their multivalent surfaces through covalent conjugation or electrostatic adsorption (Zhang, L. et. al., 2008). Dendrimers used in drug delivery and imaging are usually 10 to 100 nm in diameter with multiple functional groups on their surface, rendering them ideal carriers for targeted drug delivery (Bawarski W.E.et. al., 2008). One of the advantages of dendrimers is that they are similar in size to many proteins and biomolecules like insulin, cytochrome C and haemoglobin. 2nd generation dendrimers have a width similar to that of DNA (2.4 nm), and 5th and 6th generation PAMAM dendrimers have similar widths to cellular lipid membranes (~5.5 nm)]. Dendrimers can be loaded with drugs using the cavities in their cores through hydrophobic interaction, hydrogen bond, or chemical linkage. Recently, researchers in Michigan developed a polyamidoamine-based G5 dendrimer, which has a diameter of about 5 nm and more than 100 functional primary amines on the surface. By attaching folate as the targeting molecule and methotrexate as the therapeutic agent, the G5 dendrimer was about 10 times more effective than methotrexate alone in prohibiting tumor growth (Zhang, L. et al., 2008). However, Dendrimers have demonstrated great potential in the delivery of anticancer therapeutic agents, when they have a polycationic surface, which can form multiple interactions with a number of target receptors. The polycationic surface is, however, also the main disadvantage in therapeutic delivery applications, due to their toxic effect on cell membranes (Semete, B.et al., 2010). "Newkome dendrimers and dentrons'' are now commercially available. PAMAM dendrimers are available directly from Dendritech.

(iii) Carbon nanotubes

Carbon nanotubes are carbon cylinders composed of benzene rings that have been applied in biology as sensors for detecting DNA and protein, as diagnostic devices for the discrimination of different proteins from serum samples and as carriers to deliver drug, vaccine or protein (Darshana, P. and Joshi, K. 2012). Single-walled carbon nanotubes have been used as a platform for investigating surface–protein and protein–protein binding, as well as to develop highly specific

electronic biomolecule detectors (Kewal K. and Jain.2005). Carbon nanotubes are hexagonal networks of carbon atoms. Length and diameter of these tubes are 1nm and 1-100nm in length. Nanotubes are of two type's single walled nanotubes (SWNTS) and multi walled nanotubes (MWNTS). These are small macro molecules have unique size, shape and remarkable physical properties (Sinha N et al., 2005). Single Layer Graphene Oxide, Graphene Nanoplatelets , Functionalized Graphene Nanoplatelet , Multi Walled Carbon Nanotubes Prices, Graphitized Multi Walled Carbon Nanotubes Prices, OH or COOH Graphitized Multi Walled Carbon Nanotubes, OH Functionalized Carbon Nanotubes, COOH Functionalized Carbon Nanotubes, NH2 Functionalized Carbon Nanotubes, Short Carbon Nanotubes, Industrial Grade Carbon Nanotubes etc. are good examples of commercial products.

(iv) Quantum dots

QDs are used to track individual glycine receptors (GlyRs) and to analyze their dynamics in the neuronal membrane of living cells, for periods ranging from milliseconds to minutes (Kewal K. and Jain.2005) . In recent years, semiconductor quantum dots (QDs) have attracted the attention of many research groups because of their scientific and technological significance in microelectronics, optoelectronics and cellular imaging (Darshana, P. and Joshi, K. 2012). Quantum Dots are semi conducting materials consisting of a semi conductor core coated by a shell to improve optical properties. Their properties originate from their physical size which ranges from 10-100A0 in radius (The

Nanotech Revolution in Drug Delivery 2007). Quantum dots are widely used in biological applications that require fluorescence, including DNA array technology, cell biology and immunofluoresence assays, particularly in the immunostaining of proteins, microtubules, actins and nuclear antigens (Michalet, X. et al., 2005). The most commonly used QDs are cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide (InAs). In bioimaging these particles serve as contrast agents, providing much greater resolution than existing fluorescent dyes. These particles can absorb white light and re-emit it within nanoseconds with different bulk band gap energies corresponding to different combinations of particles (Bawarski W.E.et al.,

2008). Commercially available products are Lead Sulfide (PbS) EviDot® Quantum Dots, PbS EviDots® (850nm - 1500nm) Specifications etc.

(v) Polymeric nanoparticles

Polymeric nanoparticles are being developed as effective delivery vehicles due to their passive tumour-targeting properties, which lead to the ability to enhance the efficacy and reduce the side effects of chemotherapeutic drugs. In addition, this unique capacity of nanoparticles to preferentially accumulate in and around the tumour mass also grants a platform for improved tumour diagnostics, hereby laying the foundation for the development of multi-functional nanoparticle systems in cancer therapy(Lilian E van Vlerken, L. E. V. V. and Amiji, M. M. 2006). Polymeric nanoparticles" is the collective name for nanospheres and nanocapsules. These are solid colloidal particles ranging in size from about 10 to 500 nm(Semete, B.et al., 2010). These nanoparticles provide alternative to above mentioned nanosystems due to inherent properties like biocompatibility, non-immunogenicity, non-toxicity and biodegradability(The Nanotech Revolution in Drug Delivery 2007). Polymers suitable for preparing nanoparticles include: poly(alkylcyanocrystalates), poly(mythylidene malnolate 2.1.2), polyesters, e.g., poly(lactic acid), poly(e caprolactone), and their copolymers. For the nanosphere preparation natural macromolecules, such as proteins and polysaccharides, non-polar lipids, and metal oxides and silica, can also be used (Kubik, T.e. al., 2008).

Some important commercial products are Onco TCS, AeroLEF, Basulin, Hepacid, Transdrug, Xyotax etc.

(vi) Polymeric micelles

A polymer micelle is a nanoparticle structured by one hydrophilic shell and one hydrophobic core. It can be divided into two main categories: hydrophobically assembled micelles and polyion-complex micelles . The former ones usually consist of amphiphilic copolymers with a hydrophobic block and a hydrophilic block. Balance between those two blocks in an aqueous medium induces spontaneous formation of nano-sized particulates. For most block copolymers, poly (ethylene glycol) (PEG) is used as a hydrophilic block. Different micelle

properties originate from the nature of hydrophobic core-forming materials, which include biodegradable polyesters such as poly(lactic acid) (PLA), poly(e-caprolactone) (PCL), and poly(glycolic acid) (PGA) (Kim, S., et al., 2010).These are usually of less than 100nm and their hydrophilic surface protects their nonspecific uptake by reticuloendothelial system. Micelles formed in solutions as aggregates in which the component molecules are arranged in a spherical structure with hydrophobic core shield from water by a mantle of hydrophilic groups. These are used for systemic delivery of water insoluble drugs. Commercially available products are CrEL-paclitaxel formulation, Phenylboronic Acid-Installed Polymeric Micelles etc.

(vii) Metallic nanoparticles

Nanoparticles of various metals have been made yet silver and gold nanoparticles are of prime importance for biomedical use, a large number of ligands have been linked to nanoparticles such as sugar, peptides, proteins and DNA. They have been used for active delivery of bioactive, drug discovery, bioassays, detection, imaging and many other applications due to surface functionalization ability, as an alternative to quantum-dots (Rangasamy, M et al., 2011). Commercially available products are CdSe: ZnS QDs, palladium and copper metal nanoparticles, silver and gold metal nanoparticles etc.

(viii) Fullerenes

A Fullerene is any molecule in the form of a hollow sphere, ellipsoid or tubular structure composed entirely of carbon. They are commonly referred to as "Buckyballs" – named after Buckminster Fuller who designed geodesic physical structures and buildings based on this geometry. A Buckyball is a carbon based hollow geometric sphere, first found in soot developed from a laboratory experiment (Andrew, W, et al., 2000). Fullerenes are similar to carbon nanotubes in that their molecular framework is entirely composed of an extensive p-conjugated carbon skeleton. They are typically synthesized by poorly understood empirical methods; for instance, the vaporization of graphite by resistive heating yields grunge from which fullerenes can be isolated chromatographically (Faraji,

A. H, et. al., 2009). . Fullerenes can very efficiently bind and inactivate radicals that play a crucial role in the development of diseases of the central nervous system (e.g. Parkinson, Alzheimer) and cardiovascular diseases (Barbel, V. W, et. al, 2004). C60 and C70 (99% purity) [MER Corp. (Tucson, AZ)], C76, C78 and C84 etc. are the suitable examples of fullerenes.

4. APPLICATION OF PHARMACEUTICAL NANOTECHNOLOGY

From the concept of the Nanotechnology, the current approach to Pharmaceutical based therapy in which drug is systemically absorbed by whole body in order to affect a single localized organ, according to which that organ, or diseased part of it , should be targeted with molecular precision. The pharmaceuticals in current rely on slight differential selectivity of binding or uptake , and a dose sufficient to be effective against the diseased organ is likely to have significantly deleterious effects on the body as a whole when weak binding and uptake are summed over the entire rest of the body. The pharmaceutical nanotechnology has been also focusing the following applications.

(i) Drug delivery

Nanoparticle-based drug delivery has many advantages, such as enhancing drug-therapeutic efficiency and pharmacological characteristics. Because nanoparticles improve the solubility of poorly water-soluble drugs, modify pharmacokinetics, increase drug half-life by reducing immunogenicity, increase specificity towards the target cell or tissue (therefore reducing side effects), improve bioavailability, diminish drug metabolism and enable a more controllable release of therapeutic compounds and the delivery of two or more drugs simultaneously for combination therapy (Sanvicens, N, et al., 2008).

(ii) Tissue Engineering

Nanotechnology can help to reproduce or to repair damaged tissue. "Tissue engineering" makes use of artificially stimulated cell proliferation by using suitable nanomaterialbased scaffolds and growth factors. Tissue engineering

might replace today's conventional treatments like organ transplants or artificial implants (Reddy, J. R. K, et al., 2007). Nanotechnologies and microtechnologies can be merged with biomaterials to generate scaffolds for tissue engineering that can maintain and regulate cell behavior (Khademhosseini, L, et al., 2005).

(iii) In gene therapy

Liposomes measuring less than 100 nm can be used for delivery of genetic material into cells. Liposomes incorporated with polyethylene glycol and galactose target liver cells effectively due to their rapid uptake by liver Kupffer cells. Thus gene therapy may be tried with such liposomal nanoparticles for various liver disorders such as Wilson's disease and hereditary hemochromatosis (Faraji, A. H, et al., 2009). Moreover, polymeric nanoparticles have been applied in gene therapy to breast cancer cells, resulting in antiproliferative effects (Abhilash, M, et. al., 2010).

(iv) Molecular Diagnostics

The combination of nanoparticles with other nanotechnology-based materials has the potential to address this emerging challenge and provide technologies that enable diagnoses at the level of single cells and single molecules (Sanvicens, N, et. al., 2008). In bioimaging QDs particles (The most commonly used QDs are cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide (InAs)) serve as contrast agents, providing much greater resolution than existing fluorescent dyes(Bawarski W.E.et. al., 2008).

(v) Stem cell therapy

Nanoparticles may prove effective tools for improving stem cell therapy, new research suggests. Chemical engineers have successfully used nanoparticles to enhance stem cells' ability to stimulate regeneration of damaged vascular tissue and reduce muscle degeneration in mice, they report in a study published online on October 5 in Proceedings of the National Academy of Sciences(Abhilash, M, et. al., 2010). Bulte et al. report the use of iron oxide nanoparticles to develop

magnetodendrimers that can be used to label human neural stem cells (NSCs) and mesenchymal stem cells (MSCs) through nonspecific membrane adsorption processes (Bulte, J.W.M, et. al., 2001). Noth et al. report the use of super paramagnetic iron oxide particles to label human mesenchymal stem cells to track their migration using MRI after transplanting it for cartilage repair (Heymer,A et. al., 2008). In stem cell therapy magnetic nanoparticles coupled to antibodies are added to a blood or bone marrow sample that contains the target adult stem cells. The magnetic particles bind the target cells, which then can be recovered using a magnet. This technique is used in cell therapies to isolate adult stem cells that are then retransplanted in the patient e.g. to treat blood disorders or cardiac diseases (Barbel, V. W, et. al., 2004).

(vi) Cancer treatment

Colloidal drug delivery modalities such as liposomes, micelles or nanoparticles have been intensively investigated for their use in cancer therapy. The

effectiveness of drug delivery systems can be attributed to their small size, reduced drug toxicity, controlled time release of the drug and modification of drug pharmacokinetics and biological distribution (Suril et. al., 2007).

(vii) Artificial organs and implants

Another field where the achievements of nanotechnology can be practically applied is creation of artificial cells, tissues and organs. Artificial cells are being actively investigated for use in the replacement of defective or incorrectly functioning cells and organs, especially related to metabolic functions (Kewal K. and Jain., 2005).

(viii) Drug discovery

Pharmaceutical Nanotechnology helps in identification and validation of target by identifying the protein present on the surface or target surface. Nanotech will enhance drug delivery process, through miniaturization, automation, aped and reliability of assays. Single walled nanotubes are successfully used to identify

surface protein of pathogen. Quantum dots- track individual glycine receptors and to analyze their dynamics in the neuronal membrane of living cells, for periods ranging from milliseconds to minutes. Gold nano particles, nanobodies (smallest, available, intact antigen-antibody fragments) produced by ablynx are some commonly used nanomaterials in diagnosis (The Nanotech Revolution in Drug Delivery 2007). The ADMET profile of new discovered drug entity can be modified by using Pharmaceutical nanotechnology.

5. FUTURE ASPECTS OF PHARMACEUTICAL NANOTECHNOLOGY

Pharmaceutical companies are in trouble. With patent expirations on numerous “blockbuster” drugs on the rise, large pharmaceutical companies are searching for new competitive business strategies. In America, drug revenues worth $70–$80 billion will potentially be lost by 2011 as various drugs go off-patent. Most of the new drug are failed to reach in the market due to their bad ADMET profiles. In recent years, various nanotechnologies have been employed

successfully to tackle drugs with low water solubility. Numerous pharmaceutical companies are using nanotech to revisit shelved drugs that were “difficult” from a formulation point of- view due to their solubility profiles (Bawa *et. al*, 2002). Medical diagnosis, proper and efficient delivery of pharmaceuticals, and development of artificial cells are the medical fields where nanosize materials have found practical implementations. As *suggested* by Freitas, the application of nanotechnology to medicine, nanomedicine, subsumes three mutually overlapping and progressively more powerful molecular technologies (Kubik, T., *et al.,* 2005).The `smart medicine` or `magic bullet`, targeting solely the organ of interest, has not yet been invented , but at least the conceptual basis of what is required is clear ; the drug needs to be addressed to its target ,much a letter is addressed to a addressee. One very interesting and novel future strategy is to devise a nanomachine, which can detect and attack pathogen simultaneously, detect the change in molecular event during diseased state, and also monitor the efficacy of treatment. Such devices would have a small computer, several binding sites to determine the concentration of specific molecules, and a supply of some ‘poison’ that could be released selectively. Similar machines equipped with specific ‘weapons’ could be used to remove obstructions in the circulatory system or identify and kill cancer cells. It has been also proposed that nanorobots

may be modified bacteria and viruses that already have most of the motorization and target delivery of genetic information(Kubik, T., *et al.,* 2005) .

6. CONCLUSION

Nanotechnology is now widely regarded as the enabling technology of the 21st century. Today nanostructured materials and nanotechnology techniques are being used to produce better composite materials, materials with enhanced catalytic activity, hardness and scratch resistance, and a wide range of consumer products (such as cosmetics and sunscreens) that improve human life. Pharmaceutical nanotechnology has emerged as a discipline having enormous potential as a carrier for spatial and temporal delivery of bioactives and diagnostics and provides smart materials for tissue engineering. It offers new tools, opportunities and scope, which are expected to have a great impact on

many areas in disease, diagnostics, prognostic and treatment of diseases through its nano-engineered tools. Pharmaceutical nanotechnology provides opportunities to improve materials, medical devices and help to develop new technologies where existing and more conventional technologies may be reaching their limits. It raises new hope to industries by providing new patentive technologies in view of revenue loss caused due to off-patent drugs. In future it will provide us the new nanotechnology such as smart medicine and nanorobots to make significant contributions to disease detection, diagnosis, therapy, and prevention.

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