Nanomedicineand its potential in Medical Applications: A Review

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1. Introduction

The concept of nanotechnology was essentially introduced in the famous talk '*There's plenty of room at the bottom*' by Nobel Laureate and renowned physicist Dr. Richard P. Feyman in December 1959. In his talk, Dr. Feyman outlined the possibility of manufacturing an object at the atomic/molecular scale andthat can also 'maneuver at [cellular] level'. He believed these objects could be used for various applications ranging from storing information to miniaturized computing. The term 'nanotechnology' however was coined in 1974 and the field has since achieved several significant milestones in medicine, physics, chemistry and engineering over the past four decades.

Nanotechnology is derived from the greek word 'nanos' meaning 'dwarf' and is used to signify particles/objects having a size of about 10^{-9} meters. To put things in perspective, one nanometer can be about 1/80,000 the diameter of a human hair or the width of a sheet of paper [1]. The term 'nanomedicine' was later coined to distinguish the vast field of nanotechnology from its application in medicine and diagnostics. The Medical Standing Committee of the European Science Foundation (ESF) defines nanomedicineas "the science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body"[2]. Nanomedicine is a relatively new andexplosivelygrowing field with immense potential in finding improved and more effective means of diagnosis and treatment of a variety of dangerous and incurable diseases inflicting mankind today.

The field of nanomedicine has numerous advantages over existing treatment modalities including greater stability of therapeutic agent within the body, comparatively accurate and site-specific delivery of the encapsulated agentas well as reduced systemic toxicity. The ideal nanoparticle should have a diameter of greater than 10 nm(nanometer)to prevent rapid clearance by kidneys. However, they should also maintain a size less than 200 nm(nanometer) to prevent removal by the reticuloendothelial system (RES) which includes the spleen and liver [3]. For transportation of therapeutic drugs or proteins, various nanocarriers can be used. The most prominent carriers used today include liposomes, micelles, dendrimers, polymeric nano/micro particles as well as biological vehicles such as viruses[4].The various components of nanoparticles and their unique roles in treatment and diagnosis are explained briefly below.

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2. The functional components of Nanoparticles

2.1. Carriers

Liposomes are basically phospholipid bi-layered carriers having a hydrophilic (water-loving) outer layer and core as well as a hydrophobic (water-repelling) layer in between. Water-soluble drugs are encapsulated within thecore and on the outer layer while drug insoluble in water and incorporated in between (Figure 1). Therefore liposomes can be used to delivering multiple therapeutic agents at the same time for combinational therapy. One of the first liposomes to be approved for human use is Doxil in 1995, for treatment of AIDS associated Kaposi's Sarcoma [5]. As the cell membranes in our body are also made of phospholipid layers, these liposomes will not have any toxic effects upon administration. Micelles are similar to liposomes, however, they contain only a single phospholipid layer. As a result, the core is hydrophobic while the shell is hydrophilic. Genexol PM is a micelle formulation that is currently undergoing clinical trials in the USA for treatment of various cancers. It has already entered the Korean market for treatment of breast and lung cancer. Dendrimers consist of a single atom or molecule in the center from which branched tree-like structures arise. These structures can be used for specifically targeting the cells of interest as explained in later sections. Polymeric nano/microparticles are being researched extensively as these carriers can be manipulated to suite their application. Polymers used for drug delivery today include natural, synthetic and stimuli-sensitive "smart" polymers. Polymers obtained from nature include gelatin, albumin (from blood plasma), chitosan (from crab shells), alginate (from algae), collagen (from tissues in animals). For example, Abraxane® is an albumin-based nanoparticle formulation in the market for treatment of breast cancer if chemotherapy is ineffective or if there is a relapse in the disease [6].Some of the prominent synthetic polymers studied today for NP preparation include poly (lactic-co-glycolic acid) (PLGA), poly (ε-caprolactone) and poly (ethylene glycol (PEG)[7]. Smart polymers tend to change their properties in response to environmental stimuli. For example, poly (N-isopropylacrylamide) (PNIPAAm) is a temperature-sensitive polymer that shows hydrophilic characteristics at temperature below ~35^{o}C and hydrophobic characteristics above 35^{o}C. This property is exploited to load drugs into the nanoparticles at low temperatures and release drugs abruptly when the particle is exposed to body temperature.

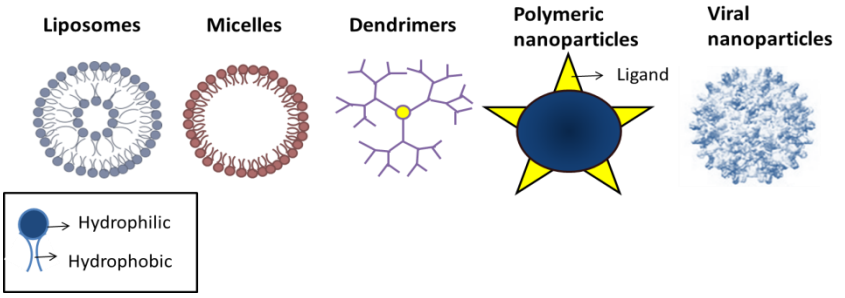

Figure 1: Schematic representation of different types of nanoparticles being studied today

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Based on the material being used nanoparticles can show different release profiles for the encapsulated agent. For example, PLGA is well known for showing a sustained release of the therapeutic drug over a period of 3 weeks or more depending on the polymer type used. This ensures a steady dosage of the drug, which is more convenient than providing medication at frequent intervals. PNIPAAm and natural polymers generally show a sudden burst release of a major portion of the encapsulated drug within a few hours to days of administration.

2.2.Diagnostic agents

Once the nanoparticles are administered it is important to track them within the body to ensure accurate administration. For this purpose, imaging agents such as iron oxide, gadolinium, quantum dots or fluorescent dyes can be used. Iron oxide and gadolinium containing particles can be detected within the body using magnetic resonance imaging (MRI). The area of accumulation of the particles will appear significantly darker during MRI than the surrounding regions not containing nanoparticles. Incorporation of fluorescent dyes or quantum dots within the particles enables tracking via optical imaging. Quantum dots (QDs) are essentially nano-sized particles prepared using semi-conductor metals. QDs prepared using the same material can emit lights of different wavelengths during imaging based on the size of the particle. QDs are particularly helpful in deep-tissue imaging following administration[8].

2.3.Therapeutic agents

Current methods of therapy for treatment of diseases such as cancer lack specificity as the entire body is exposed to the administered drug (eg :chemotherapy). This can cause adverse effects on the healthy tissues and organs depending on the toxicity level of the drug being given. Therapeutic payloads used for encapsulation within NPs so far include drugs, proteins, small interfering RNA (siRNA) and DNA plasmids. Nanoparticles carrying a variety of therapeutic drugs for treatment of diseases ranging from skin wound healing to cancer are currently being extensively researched and perfected. Sometimes, proteins and growth factors are also encapsulated within nanoparticles for delivery to damaged or diseased organ to promote cell growth and thereby tissue regeneration. siRNA-encapsulated nanoparticles are also being studied for cancer therapy. siRNA has shown the ability to silence genes thereby crippling the ability of the cells to grow and multiply [9]. Nanoparticles are also being studied for gene therapy. For this purpose, therapeutic DNA is encapsulated and delivered to the region of interest to replace damaged genes and thus treat genetic disorders.

2.4.Targeting agents

Three different targeting mechanisms currently exist for accurate delivery of nanoparticles to the target organ: passive, active and magnetic targeting. Passive targeting is based on the enhanced permeability and retention effect (EPR) prominently seen in cancer cases. The blood vessels supplying blood to tumor regions are known to be defective and leaky. The nanoparticles in the blood can escape from the blood vessel and arrive at the tumor region for release of

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therapeutic drug. The poor lymphatic drainage system in the region prevent removal of these particles from the body [10]. For active targeting, nanoparticles can be tagged with cell-specific antibodies or peptides that can specifically recognize and bind only to the targeted cell type. As a result, the nanoparticles will specifically accumulate within the cells of interest and release the therapeutic payload thus providing efficient treatment[11]. Nanoparticles incorporating iron oxide have the added advantage of being guided to the region of interest using an external magnetic field. The particles will move in the direction of the magnetic field, after administration thus arriving at the targeted site quickly for delivery of its payload[12].

3. Future outlook

Research today is steadily moving towards the development of multi-functional biocompatible and degradable nanoparticles that can be simultaneously used for imaging, concurrent delivery of multiple payloads as well as accurate targeting of the organ of interest. Although advances made in the field of nanomedicine seems exciting and promising, extensive research and clinical trials still need to be conducted before these nanocarriers can be approved for use in humans. Attempts are being made to transfer nanoparticle formulations from bench to bedside in a cost-effective and efficient manner so that its benefits are available to the several thousands of people affected by various diseases.

Nanomedicine is a growing field with a lot of untapped potential that is being exploited to find effective treatment methods for various diseases existing today. The exponential growth in this field since its inception and results obtained so far demonstrates its feasibility in therapeutic and diagnostic applications.In the future, we can expect the development of intelligent “nanorobots” that can travel within the body in search of diseases or damaged tissues and provide treatment on the spot to prevent progression of the disease.

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