WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

SJIF Impact Factor 7.421

Volume 8, Issue 4, 184-198 Review Article ISSN 2278 – 4357

NANOTECHNOLOGY AND ITS IMPLEMENTATIONS IN VARIOUS DISEASE STATES: A COMPREHENSIVE REVIEW

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Article Received on
12 Feb. 2019,

Revised on 04 Mar. 2019,
Accepted on 25 Mar. 2019

DOI: 10.20959/wjpps20194-13522

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ABSTRACT

With the progression of time and science, disease curability has increased, but so has the emergence of new diseases. Autoimmune diseases are the latest enemy of mankind in the path to a long and healthy life. Diseases like Cancer, Rheumatoid Arthritis and Diabetes Mellitus are the newest threats to humanity along with diseases like AIDS, Tuberculosis and Cardiovascular Diseases which claim a significant number of lives every year throughout the world. In order to diagnose and treat such diseases, targeted drug delivery is the best approach. Again, these diseases exhibit different signs and symptoms in different patients. In this case, patient targeted drug therapy can help in customizing the drug molecule to treat an individual patient's ailments. The best way to achieve targeted and customized drug therapy is by employing the latest innovative approach in pharmaceutics—Nanotechnology. Nanomedicine can be used to both diagnose and treat diseases in a site-specific manner. In this scientific review, the various methods of nano drug delivery and their implementations in detection and treatment of various disease conditions have been discussed.

KEYWORDS: Nanotechnology, Nanomedicine, Nanoparticles, Targeted Drug Delivery, Cancer, Rheumatoid Arthritis

INTRODUCTION

Nanotechnology is the latest innovation in the field of modern technology. Tremendous development has taken place in this field in the recent decades. The term 'nanotechnology'

can be described as the design and development of matter on an atomic, molecular and supramolecular level in order to create new materials with attributable size range. The measurement of nanotechnology is conducted in at the nanoscale, which is about 1 to 100 nanometers and the word nano being the prefix of nanotechnology comes from the Greek word '*nanos'* for 'dwarf'.[1] Physicist Richard Feynman first brought the ideas and concepts behind nanoscience and nanotechnology to the forefront at an American physical society on December 29, 1959.

Nanotechnology has been used in the fields of electronics, energy, space and food as well. However, the greatest impact of this technology has been witnessed by the healthcare system.[2-3] It is now used for diagnosis, screening and treatment of diseases. This branch of science is generally referred to as 'nanomedicine'. Various therapeutic agents including antiviral, anticancer, anti-inflammatory, hormonal and biological macromolecular drugs are now being developed utilizing the concept of nanomedicine to ensure better treatment of disease with less side effects. With conventional drug therapy it is difficult to avoid side effects and obtain therapeutic efficacy within a short period of time. But this can be avoided by the development of nanomedicine as the drugs are developed in nanoscale. Most of the pathological and physiological processes occur inside the cells, so effective treatment of diseases can be achieved as nanomedicine provides targeted drug delivery. This strategy is known as personalized medicine of healthcare system as drugs are designed on the basis of genetic, phenotype and environmental factors which can influence the safety and efficacy of treatment.[4] With the changes in disease pattern and mortality rates it has become very crucial to introduce newer technologies and better methodology options for various chronic ailments like cancer, neurodegenerative and metabolic disorders to ensure safer treatment. This review focuses on the types of nanoparticles as nanomedicine and insight of its application in various disease conditions.

NANOPARTICLES FOR DRUG DELIVERY

The area of nanotechnology is under constant growth and continuously new methods and types are being invented by researchers all over the world. There are different types of nanoparticles based on their size, shape, surface property and chemical composition for therapeutic effectiveness and treatment. Some of them are described below-

1. Micelles

Micelles are lipid based preparations which contain a hydrophobic core in which hydrophobic substance such as pharmacologic compounds can be incorporated. They are colloidal aggregates of surfactants which are created on immersion in water. Micelles are monolayered which means they can incorporate one hydrophilic drug at a time. They are smaller in size compared to liposomes so they can ensure better uptake of drug at target sites with better therapeutic efficacy and low toxicity. Recently, micelles have been developed for the delivery of drugs for cancer and genetic disorder.[2][5]

2. Dendrimers

Dendrimers are highly branched, three-dimensional, nanoscopic macromolecules with a tree-like structure. It has three main components: a central core, repetitive branching units, and functional end groups on the outer layer of repetitive branching units. It is usually synthesized by two major methods: the divergent method and convergent growth.[6-7] The sphere shaped dendrimers have low molecular size but have high molecular weight. They are used to transport drug by incorporating drugs in the central core or bound to their surfaces through hydrophobic or electrostatic interactions. Besides, drugs can also be attached with the terminal functional groups of dendrimer surface. Because of their size, shape and unique physical properties they are a promising vehicle for cancer therapy and gene delivery.[8]

3. Liposomes

Liposomes are the most widely used nanoparticles for delivery of drugs. They are vesicular formulations which are formed by a lipid bilayer composed of natural or synthetic phospholipid and cholesterol molecules with hydrophobic and hydrophilic parts. The hydrophilic part is directed towards the aqueous phase which forms the internal core of liposome and the hydrophobic part of lipid bilayers are directed towards each other. Liposomes are the best suitable vehicle system for drugs with limited solubility. If drug is hydrophilic, it can be incorporated in the aqueous internal core of liposome while hydrophobic or lipid soluble drugs can be inserted in the hydrophobic portion of lipid bilayer. Because of versatile properties of incorporating of both hydrophilic and hydrophobic drugs and ease of surface modification this nanoparticle is suitable for gene, protein, peptide delivery; and also delivery of antiviral, anticancer and antibacterial drugs.[9]

4. Fullerernes

Fullerenes are crystalline particles composed of carbon atoms in the form of hollow sphere or tube. If fullerene is in spherical shape, it is known as buckyballs while the cylindrical ones are known as carbon nanotubes or buckytubes. Fullerenes have hexagonal rings similar to graphite and they may also have pentagonal or sometimes heptagonal rings. The fullerene core is very hydrophobic and further complexation can be made by addition of functional groups to the core. They can be made water soluble by adding hydrophilic functional groups and thus can become suitable carriers for drug and gene delivery to cells.[8]

5. Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) consist of lipid phase which is solid at room temperature and where the drug is normally incorporated and surfactants are used for emulsification and stabilization of the dispersion. They have high hydrophobic drug loading capacity because of solid hydrophobic core with monolayer of phospholipids coating compared to liposomes. Because of their size, large surface area and drug loading capacity it is an attractive carrier system for various pharmaceuticals and gene delivery.[10-11]

6. Nanoemulsion

Nanoemulsions are mixture of two-phase insoluble liquids in which colloidal particles acts as carrier of drug with nanoscale size. Various surfactants are used to stabilize nanaoemulsions. In pharmaceuticals, nanoemulsions are widely used due to their several advantages such as improved physical stability, bioavailability of drugs and masking disagreeable taste of drugs.[2][12]

7. Polymeric Nanoparticle

Polymeric nanoparticles consist of biodegradable and biocompatible polymer. It protects drug from *in vitro* and *in vivo* degradation and thus provide controlled and sustained delivery of drug at targeted site. Thus, they achieve better therapeutic effectiveness and reduce side effects.[13] They are used as adjuncts in vaccines and act as drug carriers where drugs can be dissolved, entrapped, encapsulated or chemically attached. Polymeric nanoparticles are divided into two broad classes of nanocapsules which is a vesicular system and the other one is a matrix system known as nanosphere.[14]

IMPLEMENTATION OF NANOMEDICINE THEORY

Nanomedicines are targeted drug therapies that are designed as per particular patient and disease requirements. In recent years, nanotechnology is being employed to diagnose, detect and treat many diseases which were previously thought to be untreatable. Mostly an approach to treat previously untreatable diseases, nanotechnology is growing exponentially at present. A few of the accomplishments in nanotechnology sector are discussed below—

Cancer

Cancer is the main cause of mortality in the 21st century especially in developed countries.[4] It is assumed that about 13 million people will die because of cancer annually by 2030.[15] Tumor specificity is not obtained by the use of conventional chemotherapeutic agent and shows dose-dependent toxicity. To overcome these limitations nanomedicines have been developed to treat this life-threatening disease and to improve the quality of life and total life span of patients by ensuring better therapeutic effectiveness.[16] Nanomedicine provides targeted delivery of drugs to the tumor cells at a sustained and controlled rate over a period of days or even weeks without affecting healthy cells with reduced side effects and thus overcoming the effects of multi-drug resistance. Besides, development of drugs as nanoparticle protects drugs from degradation and less amount of drug is needed for achieving therapeutic efficacy. Enhanced Retention and Permeation Effect also known as EPR effect is used to deliver drugs to the tumor site which allows nanocarrier accumulation in the region of tumor and permeation by passive diffusion.[4] Various types of nanocarrier systems are used to deliver anticancer drugs like micelles, liposomes, polymeric nanoparticle, solid lipid nanoparticle and dendrimer. Nanomedine can also be designed to respond to external stimuli like temperature, light or magnetic fields to allow targeted release of drug in tumor site.[16] In the last decade several nanomedicines for cancer treatment have been released in the market and now are being used in clinics while several others are now in clinical trial phase.[3] The examples of some anticancer drugs developed as nanomedicines are shown in Table 1. In cancer treatment, nanoparticles should be effectively combined with both diagnostic and therapeutic agents to reduce chances of toxicity.[17]

However, there are some factors that need to be considered while designing nanoparticles for cancer treatment. First of all, the types of nanocarriers to be used in delivery of drug should be chosen based on its compatibility with the drug so that the pharmacokinetic properties of drug are not affected by the type of carrier itself. Besides, there are some nanoparticles where

biodegradable polymer is used which are less toxic but are removed from the body quickly without exerting any sustained effect. These types of nanoparticles should be used when repeated treatment options are needed in cancer therapy. But if sustained effect is required for weeks or days then nanoparticles should be chosen such like carbon nanotubes that are not easily degraded by limiting its repeated use.[17] A few nanomedicines are available in the market for cancer treatment. This is because extensive research is needed to develop nanomedicine with effective bio-distribution and targeted efficiency and in future, it is hoped that more nanotechnology based efficient drug treatment options will be developed thereby reduce mortality rate of cancer patients.

Table 1: Anticancer Nano-therapeutics in the Market.

Drug name	Brand name	Company	Type of nanoparticle	Indication	Status	Reference
Daunorubicin	Daunoxome	Galen Limited	Liposome	Kaposi's sarcoma	Marketed	[18][4]
Doxorubicin	Doxil	Janssen Pharmaceutica	Stealth liposome	Kaposi's sarcoma; refractory ovarian cancer; refractory breast cancer	Marketed	
Amphotericin B	Ambisome	Astellas Pharma	Liposome	Fungal infections	Marketed	
Vincristine	Marqibo	Talon Therapeuticals	Liposome	Leukemia and melanoma	Marketed	
Pacilataxel	Tocosol	Oncogenex Technologies	Nano-emulsion	Various tumors	Marketed	
Leuprorelina	Eligard	Tolmar Pharmaceuticals	PEGylated polymeric nanoparticles	Prostate cancer	Marketed	

Cardiovascular Disease

Cardiovascular disease has become the most widely spread disease in the recent years. A massive number of deaths is occurring every year due to cardiovascular disease in both developed and under developed countries. Myocardial infraction (MI), coronary artery disease, deep vein thrombosis and pulmonary embolism; all falls under the category of cardiovascular disease.[19] Oral medication and surgical interventions were the only treatment options in the last few decades for cardiovascular disease but now more research is taking place in order to introduce treatment options like nanotechnology for efficient treatment of such diseases. Nanoparticles ensure targeted drug delivery either by active or passive targeting.[20] In active targeting, tissue or cell specific ligands are incorporated into the nanocarrier or drug itself. Passive targeting involves accumulation of nanomedicine into the target site by EPR effect. Like cancer, in cardiovascular disease represents tissue structure

and several biomarkers that act as target site for nanomaterials. For example, in MI, the blood vessels in the left ventricle becomes leaky thereby allowing penetration of nanoparticles into the tissue. Besides, in cell injury and inflammation adhesion molecules used to recruit cells acts as target site for nanoparticles.[21] The examples of some nanomaterials for cardiovascular disease are given in Table 2. However, more development and research is needed to design effective nanomedicine for cardiovascular disease to reduce the mortality rate by cardiovascular disease as there are few fully developed nanomedicine for this disease compared to cancer.

Table 2: Nanomedicines for Treatment of Cardiovascular Diseases.

Drug name	Brand name	Company	Type of nanoparticle	Indication	Status	Reference
Rapamycin	Rapamune	Wyeth Pharmaceuticals	Nanocrystal	Immunosuppressive	Marketed	[4]
Tricor	Fenofibrate	Abbott Laboratories	Nanocrystal	Hypercholesterolemia associated with cardiovascular risk	Marketed	

Neurodegenerative Disorders

A great number of people has been affected by neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and strokes in recent decade. The occurrence of these conditions is going to increase as the number of aging population keep increasing with the expansion of life span over the next decade.[22-23] The treatment of neurodegenerative disease is limited by the Blood Brain Barrier (BBB) which is impenetrable by water soluble molecules and often hydrophilic drugs become degraded in the blood stream before reaching to the brain. Thus, a high dosage is needed for achieving the desired therapeutic effect, resulting in repeated dosing and increased chances of side effects or toxicity. Only lipophilic molecules with molecular weights below 400 Da are able to cross the BBB by transcellular lipophilic diffusion.[22] These limitations can be overcome by development of drugs using nanotechnology which results in sustained and controlled effect with reduced toxicity. The pathways by which drugs are delivered across the barrier include diffusion, paracellular transport, carrier- mediated transport, receptor- mediated transcytosis and adsorptive transcytosis.[24] However, extensive research is currently underway to develop nanomedicine according to each neurodegenerative disease pattern for better efficacy of treatment and making it clinically available.

AIDS

Acquired Immune Deficiency Syndrome (AIDS) caused by Human Immunodeficiency Virus (HIV) is responsible for millions of death worldwide. There is reduction in the number of helper T cells impairing immune system in the body thus leads to various life-threatening opportunistic infections. The current treatment involves the combined use of at least three antiretroviral (ARV) drugs to increase the life span of HIV infected patients which is also known as Highly Active Antiretroviral Therapy (HAART). However, this treatment regimen does not eradicate HIV infections from all parts of the body especially from some major anatomical sites such as brain, spleen, lung, liver and kidney.[25-28] Besides, there are some other factors that limit the efficacy of the drug molecules like drug resistance, toxicity, poor drug solubility and stability. All these factors give rise to the necessity of new formulation design of drugs. Targeted drug delivery systems like nanoparticles can overcome these obstacles and provide the desired drug effects. So, improved safety and therapeutic efficacy with reduced dosage regimen and side effects can be obtained by formulation of ARV drugs as nanoparticles. However, development of ARV drugs as nanoparticle is still in preclinical study stage and extensive research is needed before these drug products can become commercially available.[25]

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic autoimmune disease. It affects the joints, and is characterized by inflammation of the synovial joints and if not treated, it ultimately leads to bone erosion and irreversible disability.[29] The etiology of RA may be genetic or environmental like smoking, infection and diet. However, the exact reason which results in RA is not yet known.[30] The conventional treatment in RA with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Glucocorticoids (GC), Disease-Modifying Anti-Rheumatic Drugs (DMARDs) and Biological Agents require long term use of drugs which results in increased dosage regimen and often targeted action is not obtained. This causes damage to other healthy organs and ultimately leads to severe side effects. For example, long-term administration of Disease-Modifying Anti-Rheumatic Drugs such as Methotrexate (MTX), Sulfasalazine and Leflunomide can cause severe side effects like hepatic cirrhosis, myelosuppression, hypersensitivity, and pneumonitis. Besides long-term usage of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for pain and swelling management in RA can cause gastrointestinal bleeding, edema at the site of inflammation and various other side effects. By formulating drugs as nanoparticle, targeted delivery of drugs can be obtained and

drug is also protected from degradation in the body which increases circulation time in the body. So, low amount of dosage is needed for attainment of therapeutic efficacy and results in reduced toxicity thereby improving quality of life of patients and ensuring patient compliance.[31-35] The example of some drugs which have been developed as nanomedicines for RA and are currently undergoing clinical trials is mentioned in Table 3.

Table 3: Nanomedicines for Management of Rheumatoid Arthritis.

Drug name (trade name)	Type of therapy	Type of nanoparticle	Status	Reference
Dexamethasone	Glucocorticoid	Liposome	Preclinical	[36]
Methotrexate	DMARD	Dendrimer	Preclinical	
Piroxicam	NSAID	Liposome	Preclinical	
Certolizumab pegol (Cimzia)	Biological agent	PEGylated antibody	Marketed	[37]

Tuberculosis

The mortality rate in tuberculosis is increasing in the world because of the emergence of Multidrug-Resistant Tuberculosis (MDR-TB). It is a contagious disease caused by the microorganism, *Mycobacterium tuberculosis*, which mainly affects the lungs but spreads to the other parts of the body.[38] Usually tuberculosis is treated with first-line drugs such as a combination therapy with Isoniazid, Rifampin, Pyrazinamide, and Ethambutol. These drugs are administered orally and treatment continues for several months. Second-line drugs are used when the bacterial strain becomes resistant to first-line drugs which usually occur in MDR-TB. Second-line drugs include aminoglycosides such as Amikacin and Kanamycin, polypeptides such as Capreomycin, Viomycin, and Enviomycin, fluoroquinolones such as Ciprofloxacin, Levofloxacin, and Moxifloxacin, and thioamides such as Ethionamide, Prothionamide, and Cycloserine.[39-40] The treatment with second-line drugs takes longer than the one with first-line drugs and various side effects are observed due to long-term dosage administration. Besides, after administration of antituberculosis drugs, most of them do not reach the target site of infection and are rapidly eliminated from the body which limits their effectiveness.[40] So, if the drugs are formulated as nanoparticles, targeted action can be achieved due to greater uptake of the nanoparticles at the infected sites. Besides, sustained and controlled release of drugs from nanoparticles can be achieved which reduces overall treatment period of antituberculosis drugs. However, most of these drugs are in development stage and it is not far when drugs formulated as nanoparticles for tuberculosis treatment will

become available in clinics. Examples of some drugs which are in clinical trial phase are mentioned in Table 4.

Table 4: Anti-tuberculosis Drugs in Clinical Trial.

Drug name	Type of therapy	Phase	Reference
Rifapentine	First-line drug	Phase 2	[40]
Gatifloxacin	Second-line drug	Phase 3	
Moxifloxacin	Second-line drug	Phase 3	

Diabetes Mellitus

Diabetes mellitus or Type II Diabetes is one of the major and most prevalent autoimmune diseases worldwide affecting millions of people and their lifestyles with the increase in number day by day. It is a group of metabolic disorders where there is little or complete lack of insulin secretion, or have resistance to insulin.[41-43] Treatment options for Diabetes Mellitus include administration of oral medications and insulin injections. Oral medications such as Metformin, Gliclazide, Glipizide and Glimepiride result in various side effects with limited efficacy at the targeted site, narrow therapeutic window and long term treatment is needed leading to complex dosage regimens and patient non-compliance.[43] These limitations can be overcome if the drugs become available as nanoparticles. Another treatment option is with insulin injections. However, this treatment regimen requires administration by subcutaneous route which results in localized pain, patient incompliance due to repeated injection at the same site and over dosage may result in hypoglycemia along with various side effects.[43] So, the concept of nanotechnology is now adopted to make insulin available as nanoparticles to be administered by oral route which is the most convenient route with good patient compliance for administration in long term treatment thus overcoming the limitations of subcutaneous route of insulin administration. Besides, insulin being formulated as nanoparticles is protected from enzymatic degradation in the gastrointestinal tract after oral delivery and targeted action is achieved. However, the development of insulin as nanoparticles is currently in development phase and is expected to become available in the near future.[45-46] Examples of insulin nanoparticles which are in clinical trial phase are mentioned in Table 5.

Table 5: Insulin Nanoparticles in Clinical Trial

Name	Product	Company	Status	Reference
IN-105	Conjugated insulin	Biocon/ Bristol‑Myers Squibb	Phase II	[46][47]
CobOral™ Insulin	Coated insulin‑loaded nanoparticles	Access pharmaceuticals, Inc	Preclinical	
APH‑0907	Nanoencapsulated insulin/ biodegradable polymer nanospheres	Aphios Corporation	Preclinical	
HDV-Insulin	Hepatic-directed vesicle-insulin (nanocarrier)	Diasome Pharmaceuticals, Inc	Phase III	
JPM Oral Insulin	Liquid delivery system with insulin-chitosan nanoparticles	Jordanian Pharmaceutical manufacturing Co. PLC	Phase I	
Nodlin	Insulin with bioadhesive nanoencapsulation (nod tech)	Nod Pharmaceuticals, Inc./ Shanghai Biolaxy, Inc.	Phase II	
L-490	Polymeric nanoparticles of insulin	Merck (Darmstadt, Germany)	Phase I	[4]

CONCLUSION

It is important to adapt to new technologies as the challenges we face become more severe in nature. Likewise, in order to combat the newer more virulent strains of organisms making diseases incurable, innovative technology is required in the healthcare system. Nanotechnology can be the solution to the diseases currently creating havoc among mankind by being untreatable. With the site specific drug delivery and customization as per patient requirement opportunities presented by nanomedicine, it can be the key to overcoming the threats posed by diseases with high mortality rates.

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