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Nanotechnology in the Treatment of Infectious Diseases: A Review

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Abstract

The recent development of nanotechnology gradually become the trend of the world which has also revolutionized the pharmaceutical fields. Nanotechnology is the method used to produce nanoscale particles which can be applied in various aspects such as diagnostics and treatments. Meantime, an infectious disease also becomes a major cause of morbidity and mortality in humans nowadays. The small size of infectious disease agents has been a great concern in some of the diagnostics, preventions, and treatments are hard to achieve a desirable effect. In this way, nanotechnology becomes the key to the improvement of the pharmaceutical application's performance for infectious diseases. Vaccination is one of the prevention methods to control the spread of infectious diseases. However, some vaccines lead to serious complications due to the difficulty of accessing and damaging infectious disease agents. By utilizing nanotechnology, vaccines delivered via lipid nanoparticles and viral-vectored vaccines are developed to improve the safety profile and the immune response of the vaccination. Besides prevention, nanotechnology also has been used in the drug delivery system and therapeutic drugs for infectious diseases. A nanoparticle-based drug delivery system can enhance the treatment outcome from various aspects such as the biocompatibility of the drug, the stability of the drug, and the capability of the drug in different drug delivery systems.

Keywords: *Nanotechnology, Drug delivery System, Infectious diseases, Therapeutic drugs*.

1. INTRODUCTION

A nanoparticle is the particle with approximately 1 to 100 nanometer dimensional range. Nanotechnology is defined as a technology that is used to produce nanoscale materials for different fields such as materials engineering, energy, biotechnology, physics, and pharmacy. The development of nano-technology in pharmaceutical fields may improve the treatment outcome by improving the bioavailability, stability, solubility, and therapeutic activity of a nanoparticle therapy. This is due to the size reduction of nanoparticles as compared to larger scale drugs. By taking this advantage, the applications of nanotechnology have been widely studied in recent years, such as the application of nanotechnology in drug delivery systems, diagnostics, and tissue engineering [1].

Bacteria, viruses, fungi, and parasites are the agents that cause infectious diseases. For instance, recently, pandemic Coronavirus disease 2019 (Covid-19) has been a worldwide major concern, it is also known as an infectious disease. Coronavirus is very small in which its diameter is just around 60nm-140nm.

Hence, the incorporation of nanoparticles on surface coating, sanitizers, masks, and air filters have been emphasized to provide more effective protection as well as higher accuracy and sensitivity diagnostic system or even therapeutic application. Nano-technology is not only playing a crucial role in fighting against the pandemic Covid-19 but also other infectious diseases [2]. The major site for virus reservoir which is hard to be treated by normal drug delivery system is in the blood-brain barrier (BBB). However, with the special characteristics of nanoparticle, treatment for the virus on this site can be done. For example, ease of the entry of the drug particles across the negatively charged cellular membrane by its tunable surface charge [3].

Generally, the efficiency of a drug delivery system is mainly determined by the size of the drug particles. First, with smaller particle size, drug's toxicity, distribution, bioavailability, diffusivity, and absorption are more desirable than large drug particle size. Also, a nanoparticle can provide sustained delivery of medication as it can pass through the BBB. Thus, with the nanoparticle-based drug delivery system for the drug which is used in some diseases that are hard to treat, the desired treatment outcome can be achieved [4]. Therefore, these special characteristics of the nanoparticle can enhance the therapeutic effect by improving the drug delivery system toward the target site, releasing drug particles, and the bioavailability of drugs in infectious diseases.

Modulation of immune response done by nanoparticle therapy has been a promising treatment used nowadays, especially in severe diseases such as HIV-1 infections and cancer. In vaccine development, nanoparticles are greatly useful in improving the efficacy of vaccines against certain diseases. The vaccine is a prophylactic preparation that consists of weakened or dead microbial substances that are able to stimulate the body's immune response which leads to antibody production to fight against the microbial substances [5]. The nano-particles medicine preparation technique has been used in the development of vaccines and these vaccines are called nano vaccines. The nanoparticles are served as vehicles to encapsulate the pathogens in the delivery of vaccines such as in the form of metallic nanoparticle, liposomes, dendrimers, carbon nanotubes, micelles, and buckminsterfullerene. Nanoparticles have efficiently improved the delivery of the vaccine by protecting the encapsulated antigen and maintaining sustained release that can induce immune responses [6].

Traditional vaccines mainly consist of dead or inactive microorganisms which often cause unwanted adverse effects to the patients as these traditional vaccines involve the whole body. However, nano vaccines are able to stimulate immune responses by carrying the microorganism to the specific infected sides [7]. Most of the traditional vaccine consists of alum which is used as an adjuvant in order to improve the activation of immune responses. Yet, the adjuvant, alum often causes irritation which is inconvenient when taken by the patients [8]. Apart from this. the nanoparticle techniques are useful in improving the compounds' hydrophobic solubility in the solution which is more convenient to administer parenterally. Antigens encapsulated in the nanoparticles are relatively convenient in delivery and protection. Antigens in nanovaccine are found more stable and are not prone to degradation. Nanovaccine also requires a lesser dosage compared to the traditional vaccine. The nanoparticles can serve as the depot by remain on the surface of the injection site to release the antigens gradually. As a result, the time of vaccine expose to the immune cells is increased [7].

Furthermore, nanoparticles have very small size which is similar to the size of the cells. Hence, the nanoparticles can

diffuse into the cells through endocytosis process. The uptake or absorption of the antigen by the antigen presenting cells is increased, thus the nanovaccine has higher potency compared to the traditional vaccine. The nanovaccine particles are also found that they are able to cross-present the antigen through major histo-compatibility complex class 1 which eventually activate both humoral and cellular immune system. Nanovaccines are said to have better efficiency compared to those traditional vaccines. Besides, smaller size of the nanovaccine particles enable them to move to the lymph node easily without the assistance of the peripheral dendritic cells. Most of the traditional vaccines require injection to achieve their desired therapeutic effects. However, the nanovaccines only can be administered through nasal route. Hence the nanovaccines are relatively safe and low cost compared to the typical vaccines [7]. The storage of nanovaccines are simple. It does not require refrigeration because it function actively for a month at the temperature of 25ºC and 6 weeks at the temperature of 40ºC [8].

Even though nanovaccines are useful in the treatment of various diseases, but there are some disadvantages of nanovaccines. The manufacturing process of nanoparticles uses difficult techniques which has been a challenge of nano-vaccines production. The disadvantages of the nanovaccines also depends of their stability. It is found that liposomes storage of nanovaccine may lead to aggregation and structural destabilization. This has been a great challenge to maintain a cost-effective production of nanovaccines [9]. Apart from that, nanoparticles can target various tissues and organs due to their smaller size in nature. However, this becomes one of the disadvantages as it causes a lot of unwanted adverse effects. For instance, when the nanovaccine is administered through the oral route, it may affect the gastrointestinal system which may consequently cause diarrhea and gastrointestinal upset. Furthermore, the small size of nanovaccine is also able to cross the blood-brain barriers which may cause brain damages. The nanoparticle in the vaccines is able to accumulate in the cells as well. This has been a concern of the toxicity profile of nanovaccine especially exposed for a long period [7].

2. NANOTECHNOLOGY IN THE TREATMENT OF INFECTIOUS DISEASES

2.1. Drug Delivery System of Nano-particles in the Treatment of Infectious Diseases

Nanotechnology is becoming the new approach to counteract the disadvantages of the conventional drugs in the market. Nanomedicine is the usage of particles which is in nanometer range into therapeutic drugs and there are 100 nanomedicine applications and products approved by Food and Drug Administration (FDA) which shows that nanotechnology is playing a vital role in the pharmaceutical field [10]. The main reason nanotechnology is getting more and more popular in pharmaceutical fields is due to conventional drugs having a lot of limitations where the drug will reach a peak concentration after administration and then decreases, the toxicity of drug residue in the patient's body as well as lower drug solubility. Nanotechnology will be the key to solving the limitations faced by conventional drugs as nanotechnology is only nanometer in size whereas nanodrugs are formulated by attaching the therapeutic agent to the nanocarriers. This enables the nano drug to pass through the phospholipid bilayer and reach the targeted tissue more precisely. This will also decrease the concentration of the therapeutic agent used due to higher bioavailability as well as solubility. The cost of nano drugs will be lower than conventional drugs but also provide a higher efficacy [11].

Nano-scale drug delivery system (nano-DDS) systems have high solubility due to extra hydrophilic groups in

chemical structure, sensitivity to heat, capability for controlled release of encapsulated drugs, and high surface area-to-volume ratios. The above properties allow researchers to overcome increased drug resistance issues in infectious diseases. Nano-DDS improves numerous drug performances by minimizing ordinary drug size. Nano-DDS enhances the drug's pharmacokinetic profile for better absorption in the body. Nano-DDS drugs retain in the body for a longer period and deliver drugs to desired receptors, and controlled release with a predictable and reproducible rate.

Nano particles (NPs) can delay the release of drugs by releasing drugs later after administration lengthening immune responses against susceptible infectious particles. This delayed release of drug molecules with the formulation of NPs may be either time-based or based on environmental conditions such as temperature and pH. Positively charged NPs can deliver drugs across the blood-brain barrier (BBB), since endothelial cells are made up of proteins which are negatively charged. NPs attracted to the tight junction and uptake through the endocytosis mechanism [12]. NPs made of polyesters such as polylactide-co-glycolides (PLGA) and polylactic acids (PLA) have been utilized for antigen encapsulation and delivery. In short, NPs are efficient drug delivery systems which widely distributed throughout body for the treatment of various infectious diseases.

Nanogels is a 3-dimensional structure with cross-linking chemical bonds. Nanogels are hydrophilic. Thus, it can absorb a lot of water to retain its physical appearance without dissolving. Nanogels control drug release with the changes in the surrounding temperature. Nanogels with surface charge can improve antifungal and antibacterial activity [13]. Moreover, nanogels loaded with drugs can be lyophilized into a powder form. This can be more convenient in transporting and reconstituting for further usage.

Liposomes are 20 to 30 nm vesicles that are made from phospholipid bilayers around a fluid center [14]. It has been used in the treatment of HIV/AIDS. Indinavir (Protease inhibitor of anti-HIV agent) in liposomes resulted in more efficient delivery of the drug to lymphoid tissues further decreasing HIV viral load and increased CD4 T cells. The AZT plasma concentration has been reported higher with AZT liposome compared to AZT solution. Liposome can incorporate drugs at high density, which decrease drug accumulation in body when high doses are administered. Therefore, risk of drug toxicity may reduce, and frequency of drug administration required also reduced.

Dendrimers are a polymer with defined molecular weight which improve the solubility of hydrophobic drugs by ionic interactions following improve their efficacy. Targeting of the drug efavirenz (NNRTIs of anti-HIV agent) to leucocyte using a mannose-targeting poly (propyleneimine) dendrimer increased the cellular uptake of efavirenz up to 12-fold [15].

Carbon nanotubes have varying diameter and layers of graphite. When nanotubes carrying siRNA specific for C-X-C chemokine receptor type4 (CXCR4) were targeted to CD4 cells, the expression of CXCR4 receptor proteins were reduced in a large amount [16]. Thus, fusion of HIV cells toward CD4+ T cells cannot occur, and pathogenicity of AIDS can be avoided.

2.2. Nanotechnology in the Treatment of Viral Infections

Viral infection is cause by virus which is a non-living organism but use the host cell to replicate and infect another healthy host cell. Virus normally consist of a protein coat on the outermost layer and the core of genetic material is either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). The main challenges face by antiviral treatment are the emergence of multidrug-resistant

strains due to mutation, short half-life of antiviral drug, low bioavailability as well as low permeability. All these factors contribute to a bigger challenge in formulating new antiviral therapies as well as clinical usage of the existing antiviral therapies [17] (Table. 1). With the emerging of nanotechnology, there are several nanomedicines either is being approved or soon to be approved.

Table 1. *Limitation of conventional antiviral drugs and advantages of nanoformulations [17].*

Limitation of conventional antiviral drug	**Advantages of nanoformulation**
Lower bioavailability	Nanometer in size will increase the surface to ratio volume and increase in bioavailability
Higher toxic effect	Decrease concentration of drug needed which led to lower toxicity of drug
Lower compliance by patient	Higher compliance due to reduce dose frequency
Inability to deal with critical disease	Unique characteristics are incorporated which increases the therapeutic efficacy of drug
Shorter half-life of drug	Longer half-life of nanoformualtion
Increasing drug resistance	Can be overcome using coating or filtration

2.3. Nanotechnology in the Treatment of HIV Infections

Human Immunodeficiency Virus (HIV) is a virus that will attack the host cell and it has no practical cure. Highly active antiretroviral therapy (HAART) is one of the effective strategies to treat HIV but not a functional cure also the targeted HIV will be in latency where it will not be detected by the host immune system and there will be higher risk of rebound. Hence, the current antiretroviral drug (ARV) is combined with a nanosystem which will reduce the dosage frequency and also the toxicity. For example, Zalcitabine is loaded into the liposomes which are microscopic vesicles where an inner aqueous core and an outer phospholipid bilayer. The main advantage of using liposomes as a carrier is the human body will not recognise the liposome as a foreign body. Due to the anionic charge on the liposome, it is found that there is an increase intracellular uptake of the Zalcitabine loaded liposome. Based on the murine acquired immunodeficiency syndrome model, liposome is stable regardless of the drug loaded, particle size and chemical stability of the drug.

2.4. Nanotechnology in the Treatment of Bacterial Infections

Bacteria are microscopic living things which are unicellular with shapes like balls, rods or spirals. Their molecular component is distinct from the human cells from genetic material to biosynthetic routes. The pathogenic bacteria will reproduce and produce toxin which will damage the site of infection. Antibiotic is the conventional drug used to treat bacterial infections but nowadays the antimicrobial resistance is increased and is the main setback to treat bacterial infections. Bacteria will exchange the genetic information via horizontal gene transfer which is transduction, conjugation and transformation. Hence, if mutation occurs to be resistance to the antibiotic might lead to a single microbe to acquire a drug resistance gene from different bacteria and causing multiple drug resistance such as superbug. Moreover, the usage of time-dependent drugs for a long period but with poor compliance will also cause the bacteria to develop antibiotic resistance (ABR). Nowadays, nanotechnology is the vital key to the challenges faced by conventional antibiotic.

For example, aminoglycoside is a class of antibiotic which is used to treat wide range of bacterial infections such as Staphylococci and *Mycobacterium*

tuberculosis. It works by binding to the 30s subunit of bacterial ribosome and block the access of amino acyl-tRNA to the mRNA-ribosome complex at the receptor site, hence inhibiting the protein synthesis of the bacteria. The resistance to aminoglycoside occur to due modification of the binding site at the 30s bacteria ribosome. The resistance gene code enzyme will covalently modify the OH or NH_2 groups which in turn decreases the affinity of aminoglycoside to bind to the 30s ribosome and leas to lower efficacy of the drug [18]. Hence, nanoparticle encapsulation is incorporated with the gentamicin which is an aminoglycoside and nitric oxide (NO) is used to overcome the resistance encountered. Poly-oligo methyl ether methacrylate nanoparticle is used to encapsule the NO and gentamicin will being a controlled release of both agent which also bring a synergistic effect as the NO is also one of the compounds that is famous for its antibacterial properties. With this encapsulation, The NO will have longer half-life and higher water solubility and the resistance to gentamicin will be overcome.

2.5. Nanotechnology in the Treatment of Fungal Infections

Fungal infection is the infection caused by fungi that commonly live in the air, water, soil, and plants as well as in the human body. They can be helpful as well as being a pathogen to the human body and cause infections to occur. The most common symptom of fungal infections is skin irritation and itching at the scalp, feet and even in vagina. The main treatment for fungal infections is antifungal drugs like Amphotericin B which bind to the ergosterol in the plasma membrane and thus lead to leakage of the cell and causes cell death. Ketoconazole is also one of the antifungal drugs which will inhibit the demethylation of lanosterol to ergosterol and hence lead to inhibition of cell growth. Antifungal drugs are working well until the emergence of resistance from the superficial mycoses as well as in yeast infections. Hence, nanotechnology is the man key to help in overcoming the emerging resistant towards the antifungal drugs [19].

2.6. Silver Nanoparticles

Fungi such as *T. mentagrophytes, C. albicans, M. canis* and many more will causes fungal infections. Silver compound is one of the antimicrobial compounds that is used even in ancient times, but it is also effective against fungal infections that is used even in ancient times. Silver compound is incorporated with nanoparticle (AgNPs). The mechanism of action of the silver compound is to bind to the sulfur-containing protein of the cell membrane and penetrate the cell membrane. Hence it will disrupt the mitochondria by producing reactive oxygen species (ROS) and hydroxyl radical formation causes cell death and kills the pathogen. Polyvinyl pyrrolidine (PVP) is used to coat the silver nanoparticles and it is effective against a wide range of fungal infections. The coating is to protect the nanoparticle hence the resistance toward the nanoparticle will be avoided [19] (Table. 2). The synthesized silver nanoparticle with flower extract of *Senna siamea* has a strong bactericidal effect against *Staphylococcus aureus* and *Escherichia coli* [20]. The antimicrobial examination of the aqueous leaf extract of *Curcuma caesia* plant silver nanoparticles show great antibacterial action because of high zones of hindrance against test microscopic organisms [21]. Silver nanoparticles from dehydrated leaf extract of *Leucaena leucocephala* (Lam-AgNPs) to evaluate its antibacterial activity against harmful bacteria [22].

Table 2. *Drug Nanoformulation and its uses and advantages.*

Nano formulation	Uses	Advantages
Indinavir is loaded into the liposomes	Treatment of HIV/AIDS	Human body will not recognize the liposome as a foreign body
Zalcitabine is loaded into the liposomes		
Gentamicin incorporated in nanoparticle encapsulation	Treat infections caused by Staphylococci and Mycobacterium tuberculosis	Controlled release of the drug encapsulated
NO incorporated in nanoparticle encapsulation	Antibacterial Property	
Silver compound is coated with Poly vinyl pyrrolidine (PVP)	Treatment of fungal infections	Decrease resistance towards the silver compound

CONCLUSION

In a nutshell, nanotechnology has become a major role in most of the fields of medical sciences which used for different treatment in different diseases. The interactions between the nanoparticles and immune cells are mainly contributed by the special characteristics of the nanoparticles such as the small sizes of nanoparticles and hydrophobicity. These parameters make a big influence in the absorption of nanoparticles in the body. Although nanotechnology is not popular yet in the medical sciences field. But there are few research are being conducted to develop drugs for treatment of diseases other than infectious diseases. Hence, the nanotechnology should be greatly utilized in the field of medical sciences to bring better therapeutic effects and improve the quality of life.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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