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REVIEW

Nanobiotechnology: Cradle for revolution in drug carrier systems

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Abstract: The role of nanobiotechnology in the treatment of diseases is limitless. In this review we tried to focus main aspects of nanotechnology in drug carrier systems for treatment and diagnosis of various diseases such as cancer, pulmonary diseases, infectious diseases, vaccine development, diabetes mellitus and the role of nanotechnology on our economy and its positive social impacts on our community. We discussed here about the different "Biotechnano Strategies" to develop new avenues and ultimately improve the treatment of multiple diseases.

Keywords: Nanochemical products, infectious diseases, vaccines.

INTRODUCTION

Nanotechnology permits the creation of molecular structures, engineered or man-made nanochemical products that have the diameter in nanometer range, so combined with biotechnology that is usually termed as Nano-Biotechnology, which gives support and base to the several practical applications such as, pharmaceuticals, surgery, oncology (Moo-Young 2011). Development of microchip technology using nanotechnology has been advanced to determine the gene function and structures, cell membrane, chromosome and scanning probe microscope for the structural info and sample multiplication cell free protein synthesis and picochamber arrays for Polymerase Chain Reaction (done with microfibricated devices). Nanotechnology also tried to overwhelm the problems encountering with peptides and proteins and also to the drug molecules and other strong potential nominee is the nucleic acid, can be used in therapy. Nucleic acid degrades in biological media vigorously and hardly crosses the biological barriers thus can be widely used as targeted material for the disease site (Couvreur & Vauthier 2006). Example of use of nanotechnology for different purposes is given in fig. 1.

Cancer

Cancer is a disease due to which about 25 million people suffered and approximately 13% of all deaths occur due to cancer worldwide (Tang & Hewlett 2010). Deaths can be controlled and life span can be increased, if the disease has been diagnosed at early stage. Some available techniques are not much reliable because they do not discriminate between healthy persons and cancer patients. As an example, computed tomography screening impact is unsure for lung and prostate cancer (Patz, 2001). Colonoscopy and mammography are reliable for colorectal and breast cancer respectively, but colonoscopy is unpleasant to patients and X-rays are used in mammography which causes mutation (Peng *et al.* 2010).

The most common treatments for cancer are Chemotherapy, Radiations therapy and Surgery but these therapies do not help in the early diagnosis, produce toxicity and low drug concentration at tumor (Jain 2010).

Nanooncology deals with the cancer management. Due to nanobiotechnology based materials (Liposome, nanoparticles, polymerized micelles, etc) diagnosis, drug delivery and treatment of cancer at molecular level has been extended (Qadir, 2017). Figure 2 describes the role of nanotechnology in cancer management (Jain 2010).

Nanotechnology in cancer diagnosis

Early detection of cancer can be achieved using different nanoparticles e.g. Gold nanoparticles and Quantum dots.

Gold nanoparticles

Presence of cancer cells can be detected when the monoclonal antibodies (mAb) are attached to gold nanorods or GNPs. The specific cancer cells are recognized by these antibodies and the resulting signals give information whether the cancer cells are present or not (Heating can be done to destroy cancer cells). Binding affinity of this combination (GNPs coated antibodies) to cancerous cells is 600% greater than non-cancerous cells. In this method, results can be seen immediately, do not require any laser or high powered microscope and can be

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seen by inexpensive optical microscope. Besides, GNPs are non-toxic to human cells.

Quantum dots

Excitation spectra of quantum dots are broad from ultraviolet region to red. A nanoparticle probe can be created by combining quantum dots and magnetic iron oxides nanoparticles, it provides images of tumor and molecules which are involved in cancer (Choi *et al.* 2006).

A reliable nanotechnology assay is MS-qFRET. It detects and quantifies DNA methylation by using Polymerase Chain Reaction (Bailey *et al.* 2009).

Nanotechnology in Cancer imaging

Recent developments in nanobiotechnology have revolutionized the cancer diagnosis and treatment. Diagnosis of cancer at nanoscale level has been achieved via fluorescent nanoparticles, Quantum dots, Organic dye-doped nanoparticles. At cellular and animal level, up conversion nanoparticles are developed due to which sensitive optical imaging of cancer can be achieved. Some novel multifunctional nanoparticles are also developed which can act simultaneously as diagnostic agents, clinical agents in clinical therapies and play major role in cancer therapy. These molecules show different potentials due to conjugation with several molecules at a time such as targeting moieties, imaging probes and therapeutic agents (Jain 2010).

In Magnetic resonance imaging (MRI), iron oxide nanocrystals have also been used. Some highly lymphotropic supermagnetic nanoparticles have greater approach to lymph nodes via interstitial lymphatic fluid transport that detect lymph node metastasis in prostate cancer patients (Sengupta & Sasisekharan 2007).

Ultrasonic Tumor imaging: In mice it is observed that targeted delivery of drug and imaging can be achieved by using ultrasound for doxorubicin (DOX) drug from nanobubbles at tumor site. Micelles containing DOX drug become nanobubbles at physiologic temperature of tumor, these nanobubbles join to form micro bubbles. When these micro bubbles are exposed to ultrasound they produce sound which create tumor image and at the same time sound energy of ultrasound breaks the bubbles and the DOX drug is delivered at tumor site (Jain 2010).

Nanotechnology and drug delivery

Drug delivery and targeting is the foremost and vital point in cancer nanobiotechnology (Steinmetz 2010).
Nanoparticle systems deliver drugs to cancer cells by two strategies; passive targeting and active targeting.

Passive targeting

Extravasations of nanoparticles occurred at the site of disease where microvasculature is leaky is called passive targeting. In passive targeting or passive drug delivery system the vasculature properties of tumor has been utilized. Due to angiogenesis, vasculature of abnormal tumor results in leaky vessels (Sengupta & Sasisekharan 2007) that allows the accumulation of nanoparticles in tumor's interstitial spaces (Wang *et al.* 2009).

Active targeting

Cancer cell not only have leak vasculature but also represent over pressed epitopes and receptors so in active targeting these receptors are targeted by nanomedicines. Active targeting of drug is carried out by the conjugation of targeting moieties (antibodies associated to tumor) to nanoparticles (Sengupta & Sasisekharan 2007). This target moiety binds to the receptor present on tumor cell, NPs loaded with drug enters the cell and provides high intracellular concentration (Wang *et al.* 2009).

Targeted delivery of Biological therapies for cancer

During some therapies, Nucleic acids, Plasmid DNA and single interference RNA are delivered along biological drugs to destroy tumor cells. If these are programmed with nanosystems targeted delivery can be achieved (Dickerson *et al.* 2010).

Single interference RNA is delivered to human breast cancer by using nanodrug that contain supermagnetic iron oxide nanoparticles, nanodrug binds to exact receptors present on tumorous cells, consequences in lessen growth rate of tumor (Dickerson *et al.* 2010).

Nanogels consisting of core/shell hydrogel nanoparticles operated with peptides shows targeted delivery of siRNA to ovarian cancer cells and nanogel also increases the effectiveness of therapeutic drugs for ovarian cancer (Dickerson *et al.* 2010).

Cancer treatment

Nanotechnology is widely used for thermal ablation of cancer to overcome some problems which occur by using other techniques such as by Chemotherapy: Damage of normal cells along tumor cells, incomplete destruction of tumor cells and toxicity etc.

In old methods of thermal ablation zone in which cancer cells are localized show minimum visualization and there was an overlap between healthy and abnormal area which have to be treated and all these complications have been overcome due to nanotechnology (Gilstrap *et al.* 2011).

Different nanoparticles are used for thermal ablation. Gold nanoshells, minuscule gold coated beads are called nanoshells. Antibodies can be immobilized on nanoshells that can recognize the cancer cells. These shells with targeting therapeutic agents moieties, attached to cancerous cells and the medicine is released at the tumor site by heating this complex using near infrared radiations

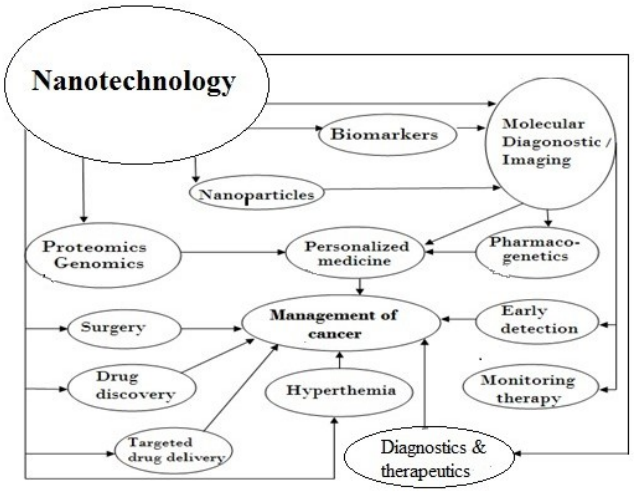

Fig. 1: Nanobiotechnology dealing with cancer management

or photo thermal therapy (Xiao *et al.* 2009). Single walled Carbon nanotubes antibodies, containing single walled carbon nanotubes, attached to cancer cells. Strong Raman signals have been observed by this complex (HER2-IgY-SWNTs) attachment to breast cancer cells which act as a probe and by using near infrared irradiatins only cancer cells are destroyed and not the normal, healthy, receptor free cells (Xiao *et al.* 2009).

Polymeric Nanoparticles

There are two major categories of polymers that are used for preparation of nanoparticles as given in table 1.

Biodegradibility, biocompatibility and functionalization are general requirements for these polymers (Tong & Cheng 2007). The polymeric nanoparticle made up of two parts, hydrophobic core in which anticancer drug is coated and hydrophilic shell due to which nanoparticle stabilizes itself in aqueous environment. Chemical conjugation and physical entrapment are two methods by which the drug can be loaded into polymeric nanoparticle. Core of nanoparticle and drug has hydrophobic interaction due to which drug is entrapped in the core of nanoparticle (Cho *et al.* 2008; Sharma 2014).

Table 1: Natural and synthetic polymers used for preparation of nanoparticles.

Natural polymers	Synthetic polymers
1. Chitosan	1. N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA)
2. Dextran	2. Polyethylene glycol (PEG)
3. Gelatin	3. Polycarprolactone (PCL)
4. Heparin	4. Polyglutamic acid (PGA)
5. Albumin	5. Polylactic acid (PLA)
6. Collagen	
7. Gelatin	

Pulumonary diseases

Physiological classification of pulmonary diseases is as restrictive and obstructive. In obstructive diseases, flow rate into and out of the lung face hindrance. In restrictive diseases, physiological volume of the lung is decreased. Till now, respiratory diseases caused by airway inflammation, are treated by oral or injectable corticosteroids. Generally COPD and asthma are treated by the use of corticosteroids. However, chronic use of corticosteroids has many side effects. Respiratory infections caused by viruses such as no antiviral compound for influenza. An antiviral compound ribavirin is used but it caused hemolytic anemia. Oral or injectable antibiotics are used to treat bacterial respiratory infections. But these drugs are given with combination and high doses are used for long duration. The antibiotics also have poor bioavailability (Swai *et al.* 2009).

Role of Nanomedicine

For drug delivery, lung is an attractive target organ because of non-penetrative administration through aerosols; first pass metabolism avoidance, direct delivery to the action site for pulmonary disease treatment and the presence of large surface area for action of local drug and systemic drug absorption. Nanomedicine (nanocarrier-based system) has following advantages in drug delivery to respiratory system:-

1. Uniform distribution of drug to the alveoli.
2. Enhanced solubility of drug is achieved than its own aqueous solubility.
3. Dosing frequency is reduced by sustained release of drug.
4. Macromolecules are suitably delivered.
5. Side effects are decreased.
6. Patient compliance improved and
7. Cells have potential of drug internalization (Mansour *et al.* 2009).

In airway disease, nano delivery applications included delivery of DNA at target site, siRNA and drugs or peptides. These are delivered for control of chronic pathophysiology of conformational and obstructive disorders. These drugs delivered to epithelium of respiratory system and hematopoietic progenitor cells. Nano delivery has many physiological barriers such as alveolar fluid and mucus for nasal and reticuloendothelial system for systemic delivery (Roy & Vij 2010).

Anatomical and physiological obstacles of pulmonary system limited the treatment of airways. Nanodelivery system avoids these obstacles. For the removal of foreign substances, such as bacteria and particles to the pharynx, mucosiliary separation gives the transport of them in the conducting airways. At the distal end of lung in the lumen of the alveoli, alveolar macrophages are present and known as professional phagocytes. So the alveolar

clearance is done by alveolar macrophages. Removal of these roads is avoided by the use of nanomedicine will be an important challenge. By the use of nanodelivery systems, protein drugs are protected from the protease present in mucus and surfactant, particularly in infected or swollen lung. One important aspect of nanodelivery system is that it has susceptibility to be taken up by pulmonary epithelial cells, as modern treatment strategies goal to put expression vectors, genes, antibodies, siRNA into the cells to restrict local production of proteins involved in respiratory diseases. Due to fluids of extracellular lining, the epithelium of air way has high resistance to transfection so nanodelivery system is important tool to get penetration.

Tight junctions are present in the epithelium of conducting airways so paracellular crossing of foreign substances is prevented. Nanoparticles have ability to translocate via epithelium in animal studies and smaller nanoparticles are more efficient to provide treatment strategies of sub mucosa. Alveolar epithelium has high surface area and small air blood distance so the lower pulmonary system treated by intravenous dosage of pulmonary drugs and nanodelivery system increased their pulmonary transfer.

Possibilities to improve treatments of upper airways by nanodelivery systems are:

1. drug degradation is protected by the enzymes of fluid of epithelial lining,
2. clearance by macrophages is avoided due to nanometer size,
3. efficiency of transfection is improved due to promoted crossing of the lining fluid and endocytosis of nanodelivery system,
4. treatment of submucosa by transcytosis of nanodelivery system,
5. Endothelium crossing provides systemic treatment by nanodelivery system as well as intravenous administration of pulmonary drugs (Boland *et al.* 2011).

Nanoparticles used in respiratory system

Nanoparticles used in pulmonary delivery are micelles, liposome, polymers, solid lipid, dendrimers and submicron emulsion. These particles are delivered to respiratory tracts through aerosols, metered dose inhaler systems, powders such as dry powder inhalers and solutions such as nebulizers (Mansour *et al.* 2009; Smola *et al.* 2008).

Inhalation drugs of nanocarrier system

For local or systemic delivery of respiratory system different drugs are available. In these drugs, small molecules like protein, peptide drug and genes are included.

Inhalation devices and nanocarriers

The inhalation devices are of three types; nebulizers, pressurized metered dose inhaler and dry powder inhaler. In the form of colloidal dispersion, nanocarriers delivered to the lung by nebulizers and in solid form by the use of pressurized metered dose inhaler and dry powder inhaler. Nanocarriers have small size and strong particle-particle interaction so in colloidal dispersion, particle agglomeration and settling occurred.

Polymeric Nanoparticles

Polymeric particles are made up of biodegradable and biocompatible polymers. Poly carpolactone, poly lactic acid and poly lactic-co-glycolic acid are examples of polymers used in polymeric particles. Anti asthmatic drug, antituberculosis drugs, pulmonary hypertension drugs and anticancer drugs are delivered by polymeric nanocarriers. Gene delivery to the lungs is also done by cationic polymers (Stark *et al.* 2007).

Self-Assembled Systems

Micellar solutions, vesicles and liquid crystal dispersions are self-assembled colloidal systems. These dispersions contained small particles of around 100-400 nm diameters and act as nano-carriers in respiratory drug delivery. In the core of micelle, hydrophobic drugs are trapped. Their transported concentration is more than their water intrinsic solubility. A hydrophilic shell is surrounding the micelle which protects the contents. In an aqueous environment self assembly of amphiphilic macromolecules to nano structures is named as polymeric micelles. Drugs which are water insoluble, DNA and proteins are encapsulated by these micelles and by active or passive way delivered to their site of action (Smola *et al.* 2008).

For intravenous administration of drugs, polymeric micelles are used as drug carrier. Production of polymeric micelles is easy and their circulation time is long. They can be functionalized by targeting ligands. Hydrophobic agents are successfully incorporated into polymeric micelles (Yang *et al.* 2010).

Liposomes are widely examined systems that are used for controlled delivery of drug to the lungs. Liposomes are attractive for drug delivery because these are made from compounds endogenous to the lungs, such as components of lung surfactants. Liposome delivered to the lung in liquid state and aerosol delivery is achieved by the use of nebulizers. Dry powders formulations of liposomes are also used to circumvent these tissues. Cationic liposomes are used for gene delivery to lung. Cationic liposomes have self-assembly with DNA material because of cationic-anionic electrostatic interactions (Joshi & Misra 2001).

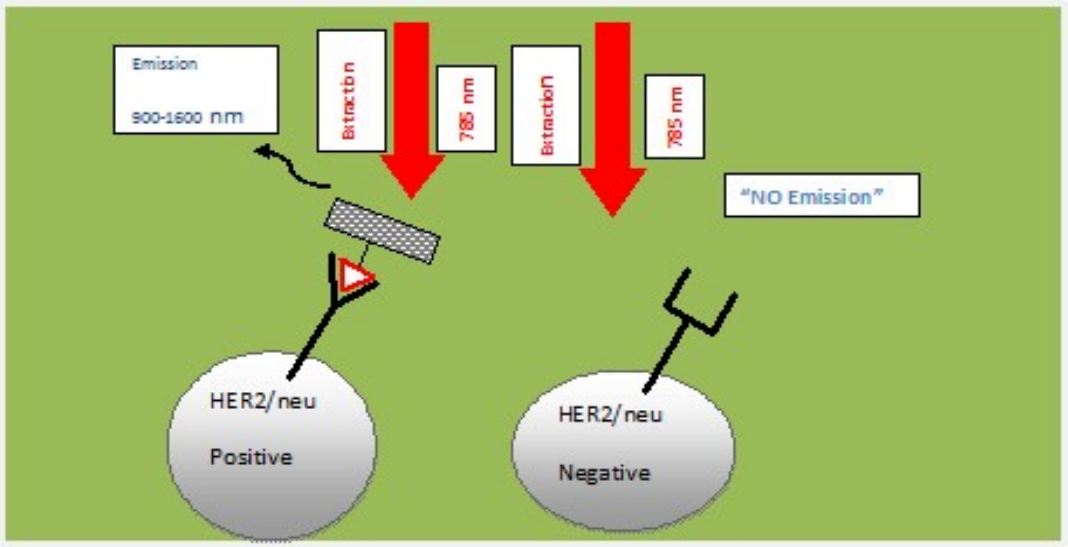

Fig. 2: Single Walled Carbon Nanotubes along HER2 antibody and NIR radiations.

Table 2: Nanomaterial used in the treatment of microbial diseases

Nanoparticles	Antimicrobial action	Reference
Silver nanoparticles	Silver ion released and disruption of transport chain and cell membrane, Damage the DNA.	(Ehsan *et al.* 2012; Pal *et al.* 2007)
Zinc oxide nanoparticles	Release of zinc ions, nanoparticles accumulated ineracellularly and damaged cell membrane and produced hydrogen peroxide	(Huang *et al.* 2008)
Titanium oxide Nanoparticles	Reactive oxygen species produced, cell wall and cell membrane damaged.	(Maness *et al.* 1999)
Gold nanoparticles	Interaction with cell membrane, electrostatic attraction strongly.	(Chamundeeswari *et al.* 2010)
Fullerenes	Cell membrane integrity damaged, activity of neutrophil infiltration increased	(Lyon *et al.* 2005)
Carbon nanotubes	Oxidation of lipids, proteins and cell membrane, cell membrane disrupted by reactive oxygen species	(Blecher *et al.* 2011)
Nanoemulsion	Disruption of spore coat and cell membrane	(Blecher *et al.* 2011)

Solid Lipid Nanoparticles (SLNs)

Solid lipids, surfactants and water are used to make solid lipid nano-particles. The drug released form solid lipid nanoparticles has following advantages; release profile is controlled, prolonged release is possible and *in vivo* degradation is faster than polymeric nanoparticles. Besides, SLNs have more tolerability than polymeric nanoparticles. Aqueous suspensions and dry powder formulations of SLNs are used for pulmonary inhalation of drugs by the nebulizers and dry powder inhalers.

Gene delivery is also introduced to lungs by SLNs. This is done by the use of SLN gene vectors mediate gene expression by aerosol application (MuÈller *et al.* 2000).

Microemulsions/Submicronemulsions

For the pulmonary systems, very few microemulsions are available. But these microemulsions have many advantages over other nanoparticles. They are easy to manufacture and maximum drug is incorporated (Smola *et al.,* 2008).

Nanoparticles based on Dendrimer

Dendrimers are hyper-branch polymers. Their architecture is layered. Dendrimers are used to deliver DNA drugs into the cell nucleus. They are also used for gene and antisense therapy and for nonviral gene transfer agents. Dendrimers can also act as carrier of macromolecule systemic delivery (Rudolph *et al.* 2000).

siRNA delivery by use of Nanosystems in Respiratory Disease

RNA interference is an experimental and potential mean to fight disease. A hindrance is occurred to deliver the short interfering RNA molecules in the target cells of airway. So nanotechnology is used to overcome this hindrance. A method is established by a collaborative research project of Alnylam Inc and group of MIT. In this

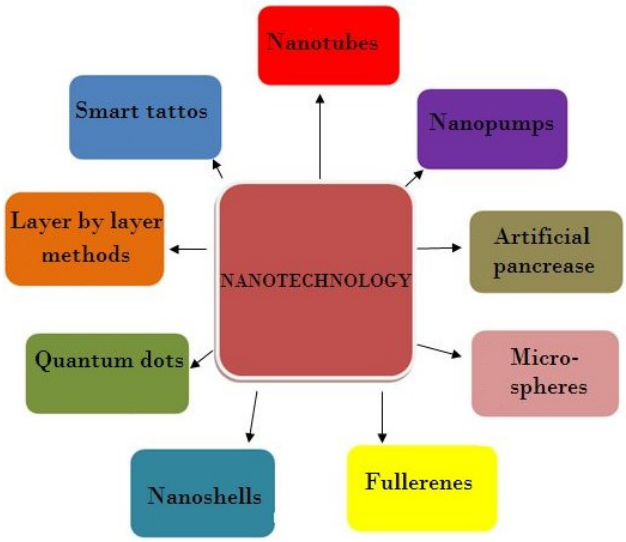

Fig. 3: Summary of role of nanotechnology in management of diabetes

method, thousands of different lipids like molecules are quickly synthesized and then the ability of these molecules to deliver the siRNA to cells is screened. The deliveries of these molecules are ten times more efficient to deliver siRNA for treatment of respiratory disease than those existing methods which delivered siRNA without encapsulation, directly to the lungs. Recently nasal drops have nanoparticulate vectors are developed by Dr. Mohapatra. These drops have ability to delivered siRNA molecules (Roy & Vij 2010).

Infectious diseases

The problem of resistance and tolerance to the existing drugs has created a decreased efficacy of these drugs. This problem has been tried to be overcome by the use of polymers (Khalid *et al*., 2009; Hussain *et al*., 2011; Irfan *et al*., 2016a; Irfan *et al*., 2016b) or through nanotechnology (Naz *et al*., 2012; Ehsan *et al*., 2012), synthesis of new drugs, either by the use of proteomics, or synthesis from lactic acid bacteria (Masood *et al*., 2011), or marine microorganisms (Javed *et al*., 2011). Other techniques are being tried to search out constituents for their possible pharmacological value particularly for their analgesic (Hussain *et al*., 2017a & b), hepatoprotective (Ahmad *et al*., 2012), cytotoxic, antibiotic (Amin *et al*., 2012; Mannan *al*., 2016), antibacterial, spasmolytic, bronchodilator, antioxidant (Janbaz *et al*., 2012) and anti-cancer properties (Bashir and Qadir, 2017). However, biotechnology has opened a new era for control of diseases including infectious ones.

Diagnosis of infectious diseases

Conventional diagnostic methods for the detection of microbial diseases required sufficient time for sample preparation and detection, although these methods are reproducible (Kaittanis *et al.* 2010). Nanomaterials have unique catalytic, magnetic and luminescent properties that enable sensitive, fast and cost effective detection. Nanoparticles also help to determine susceptibility and resistance of anti-bacterial drugs (Jain 2007). Nanoparticles are conjugated with antibody that amplifies the signal for bioanalysis and enumeration of highly pathogenic microbes such as E. coli O157:H7, resulting in very fast detection of single microbe within 20 minutes (Look *et al.,* 2010). For the detection of urinary tract infection, a very rapid method has been developed by the conjugation of gold nano wire arrays with linker arm attached to specific E. coli antibodies (de la Escosura Muniz & Merkoci 2011).

Antibiotic resistant bacteria such as *Methicillin-resistant Staphylococcus aureus* can be differentiated from non-resistant strain by the use of nanoparticles with specific Raman spectroscopic fingerprints in which single nucleotide polymorphism is detected in microarray based system (Li *et al.* 2009). Detection of infection by magnetic nanoparticles is also very sensitive and quick strategy. *Mycobacterium avium* paratuberculosis is identified easily by use of superamagnetic iron oxide nanoprobes and it also help in rapid quantification of mycobacterium in milk and blood with high sensitivity. Quantum dots are used for the analysis of complex samples for histology, cytology and pathology due to their broad absorption spectra. Quantum dot nanotechnology also used in double and triple immune staining of bacterial cells. Nanotechnology is also used in opaque culturing of blood and milk for pharmaceutical assays without any sample preparation (Huh & Kwon 2011).

Treatment of infectious diseases

Nanoparticles with metals and metal oxides made reactive oxygen species under Ultra violet light. They play an important role in formulation and dressing of antimicrobial agents. Silver, copper, magnesium, zinc and titanium are examples of metals used in nanotechnology (Blecher *et al.* 2011). The mode of action of these metals is summarized in table 2. Nanosized zinc and silver are particularly more effective against microbial infections. Titanium and zinc dioxide have high reactivity and used in the bactericidal substances that makes the filters and coating of catheters (Huang *et al.* 2008).

Antibiotics that incorporated in polymeric nanoparticles are more efficient for antimicrobial activity than non-polymerized forms. The preparations of antibiotic conjugated polyacylate network in aqueous media and incorporation of water insoluble drug directly into polymeric network is one step process and required no post modification of nanoparticles. Gold coated nanoparticles also used in the treatment of microbial infections. Carbon nanotubes are used for antimicrobial nanotherapy to detect even single microbe level by the use of photo thermal approach (Zharov *et al.,* 2007). A

wide range of nanoparticles are used for drug delivery. Lipophilic and water soluble both type of antibiotics are incorporated on the surface and inside of nanoparticles. All pharmacokinetic requirements of antibiotics such as increased solubility, controlled release and targeted delivery are attained by the use of suitable nanocarriers.

Vaccines

Nanotechnology and Vaccines

In this new era of science, Nanotechnology provides new methods for the treatment of diseases through vaccination. In the vaccination process, we use nanoparticles to deliver the vaccines. These tiny particles help molecules to reach at specific cell and prevent drug molecules from degradation. Nanoparticles or nanocarriers carry molecules to those specific cells which are difficult to reach and these nanocarriers can be designed specifically to carry molecules to the specific intracellular compartments.

Nanoparticles are equal to the size of viruses and bacteria, so immune system easily recognizes them. The surface properties, size, charge and chemical composition of nanocarrier can be formulated so that its uptake is enhanced by mononuclear phagocytic system and stimulation of antigen presenting cells and immune presentation of antigens (Rice-Ficht *et al.* 2010).

Polymeric nanoparticles are used for the delivery of DNA and protein based vaccines. Polymeric nanoparticles deliver the vaccine but they do not evoke immune response on their own (Chadwick *et al.* 2010; Plummer & Manchester 2011). Poly(lactide-co-glycolide) (PLGA) particles are taken by macrophages and other antigen representing cell efficiently *in vitro* and *in vivo* but they do not evoke proinflammatory cytokine response significantly which is indication of macrophages activation, rather having stimulation ability like the saline. The synthetic polymers not only evoke immunostimulation but also increased immunization through delivery of antigen across mucosal barrier (Rajananthanan *et al.* 1999). Poly methyl methacrylate (PMMA) nanoparticles also show immunostimulatory characteristics. Adjuvants of PMMA nanoparticles trigger a 100 fold enhanced antibody titer response to HIV2 live virus vaccine in murine models. Carboxyfullerene nanoparticles raise immunity by neutrophil stimulation to destroy bacteria in a mouse model infected by streptococcus pyrogenes (Diwan *et al.* 2003).

Many infectious diseases may be aid by “Nanoemulsion vaccines”. Oil-based emulsion is putted into the nose and it creates a powerful immune system against the infectious disease. This emulsion is made up of soybean oil, alcohol, water and detergents consist of very small carries. These carriers are smaller than 400 nm. The tiny particles or nano-carriers joined with all the infection causing micro-organism to initiate the immune system of the body. Smallpox is one of those infectious diseases which can be aid by this nanoemulsion vaccinating technique.

Nanosized spherical micelles are called immune-stimulating complexes (ISCOMs). These complexes function like carriers and immunostimulatory adjuvants because of their saponin derived components such as Quil A. Quil A taken from the Quillaja tree. Antigen presenting cells efficiently taken up the ISCOMs carriers due to the specific nature. ISCOMs activate and up regulate expression of MHC I and II on antigen representing cells even in absence of antigen and initiate adaptive immune response (Chadwick *et al.* 2010). Incorporation of numerous antigens in ISCOMs have been done and shown to induce protective immune response against hepatitis B, *Helicobacter pylori*, Cornybacterium, Influenza and Herpes virus (Sun *et al.* 2009). Chitosan also used as nanocarrier and delivered vaccines across mucosal membrane (Bacon *et al.* 2000).

Tuberculosis is caused by bacteria Mycobacterium tuberculosis and most scourge disease that affects humans. Treatment of tuberculosis is much more complicated through chemotherapy because multi drugs regimens are used to overcome the disease for long period of time. In nanotechnology the nanoparticles are used to diagnose, treat and prevent from disease. For diagnostic purpose a diagnostic kit is used which can be handled easily and economically. In the treatment of TB, the drugs are delivered through nanoparticle drug carriers .The micro carriers are used for the continuous anti TB drug delivery in the body. These micro carriers may be micro spheres or liposomes. A needle-free treatment is now developed for the treatment of TB which is called “arousal vaccine”. This is most stable at room temperature. Some other vaccines are also introduced for TB cure but they need needle injections, whereas this new vaccine (arousal vaccine) is much safer than other vaccines developed by nanotechnology (Mathuria, 2009).

Nanotechnology also play role in the vaccination of cancer. The vaccination of cancer is much more different in humans. There are three main treatments for cancer; chemotherapy, radiotherapy and surgery. But now a new therapy is used for the treatment is “Targeted therapy”. In targeted therapy, the nanoparticles and nanostructures are used which directly attack at the tumor cell and deliver drug to destroy it without having any effect on normal cells. Two types of vaccines are developed and approved by US Food and Drug Administration, one vaccine is used for the treatment of cervical cancer which is caused by human papillomavirus (Nandedkar, 2009).

Diabetes mellitus

Metabolic diseases are treated by administrating proteins and peptides. Diabetes is one of the very common and

sometimes very severe metabolic diseases that cause high level of blood glucose. Insulin produced from pancreatic islets helps glucose to produce energy; however improper production of insulin causes diabetes. It leads to diseases, such as chronic renal failure, cardiovascular disease, nerve damage, micro vascular damage, retinal damage and premature death. Injections of insulin are based on efficient monitoring of glucose level in blood, and specialized diet and exercise regimen. Normal level is difficultly attained by routes other than injections (Couvreur & Vauthier 2006).

The role of nanomedicine and nanotechnology in treatment of diabetes is still in early stages. Many efforts have been made in the field of nanotechnology by the use of different nanomaterials to cure diabetes at different stages of the disease. However, a very few methods have been applied in the clinical use. Overall, nanotechnology made two major improvements; monitoring of glucose level and insulin delivery that are related to diabetes treatment. Recent advances in the management of diabetes by the use of nanotechnology are summarized in fig. 3.

Monitoring of blood glucose level

Recent method for monitoring of Blood glucose level is finger prick method in which capillary tube is easily filled and glucose level is self-monitored. In this method, finger is pricked again and again which cause many problems. Scientists are paying more attention to develop an accurate, cost effective and consistent method for the management of glucose level in blood (Rahiman & Tantry 2012). Various nanotechnology based methods have been developed for monitoring of glucose such as quantum dots, smart tattoos, layer by layer and carbon nanotubes.

Smart tattoos

Smart tattoos are efficient method of in vivo glucose monitoring. In smart tattoos, nanosensors are used which are fluorescence based and respond to glucose. The nanosensors are fixed in skin and the device is operated from outside the body, so monitoring can be performed noninvasively. Nanosensors use the fluorescence to check the concentration of analyte. This method is more reliable than conventional method of electrochemical electrode implantation and do not damage the tissue. Boronic acid derivatives and bacterial binding proteins (l-glucose/galactose-binding proteins (GBPs)) and enzymes such as hexokinase can be engineered as nanosensors. These are artificially prepared biological glucose receptors that transduce glucose molecules into variations in fluorescence (Pickup *et al.* 2008).

Layer by layer method

In layer by layer method, the negatively and positively charged polymers are in arrangement of electrostatic sporadic layers. These polymers are organized as multilayer films with controllable biocompatibility and flexible pores. For six bilayers, the standard thickness is 10 nm (Zhao & Ju 2006). These bilayers eventually fixed in subcutaneous tissue like smart tattoos (Ariga *et al.* 2007). Glucose is entered from interstitial fluid which is permitted by semipermiable capsules that contain and shield the sensor materials (Ariga *et al.* 2007).

The technique for preparing micro vesicle by the layer by layer method is the chronological assimilation of polyelectrolytes surrounding the crystals of glucose oxidase enzyme like glucose oxidase onto a sacrificial template. Then stepwise addition of charged polypeptides like poly-l-glutamate or poly-l-lysine is done. Before the formation of concave microcapsule enclosing circle, the substance is dissolved in ethylenediaminetetraacetic acid (McShane & Ritter 2010).

Carbon nanotubes

Carbon nanotubes can be of single or multi-walled configuration. A microphysiometer is built of multiwalled carbon nanotubes, which consists of many flat sheets of carbon atoms rolled and stacked into mini sized tubes. Insulin level is continuously detected by the sensor in the tubes by verification of transfer of electron production when oxidation of insulin molecules occurred in the presence of glucose. When insulin secretion increased, current in sensor is also increased. So in such way insulin level is monitored in real time (Zhao & Ju 2006).

Quantum dots

Quantum dots are nanocrystals with size ranges from 2-10 nm. These nanocrystals are made-up of cadmium selenide and covered with a shell like zinc sulfide that increase their optical properties and solubility (Cordes *et al.* 2006). Quantum dots can be used in imaging by fluorescent probe labeling of molecules (Li *et al.* 2009).

Insulin delivery by the use of nanotechnology

Delivery of insulin still is a challenge in the treatment of diabetes. Many researchers have done efforts to use oral insulin due to its easy usage. However bioavailability of oral insulin is limited because of its different concentrations when it passes through gastrointestinal tract (Pillai & Panchagnula 2001). This is because of low permeability of insulin across the intestinal biological membranes. Insulin delivery remains a challenge in the management of diabetes (Iwanaga *et al.* 1997).

Production of insulin by microspheres

Most efficient strategy for the oral delivery of insulin is the use of microspheres. Microspheres are used because they can act as both permeation enhancer and protease inhibitors. Microspheres shielded encapsulated insulin from breakdown by enzymes in physiological environment and therefore act as protease inhibitors.

Microspheres also increase penetration capacity because they can provide efficient way across the epithelial layer (Caliceti *et al.* 2000).

Magnetic nanoprobes and nanoshells

Instead of using injections of insulin regularly, magnetic nanoprobes and nanoshells are more useful in the treatment of diabetes (Ehsan *et al.* 2012). Diabetic patients can use an infrared laser of ballpoint pen-sized device and warm the skin at the site where nanoshells polymer is inserted. When nanoshells are heated, the heat activates the polymer to release a pulse of insulin. The nanoshells-polymer system can be embedded in the body for several months. This procedure is easy and cannot cause pain as in the case of injections (Freitas 2005).

Nanopumps

Nanopumps are different equipment with various important applications in the medical field. A nanopump is a mini size volumetric pump that consists of a pair of check valves that are placed into a micro electrical mechanical systems chip. The chip contains three layers which are interconnected. A silicon-on-insulator plate is a small machined pump structure with two pyrex plates that have holes. The insulin is injected at a stable rate by the pump into the body and blood glucose level is maintained (Ramchandani & Heptulla 2012). Debiotech's nanopump is first time used for delivery of insulin. This pump is made up of an electronic component which is reusable and insulin reservoir with pump which is disposable (Anhalt & Bohannon 2010). This nanopump can hold a large volume of insulin (up to 450 units) than other nanopumps which are smaller in size (Ramchandani & Heptulla 2012).

Artificial pancreases

The traditional proposal of an artificial endocrine pancreas is based-on an electrochemical apparatus which is wearable, consisting of a glucose sensor embed in the body and attached to insulin infusion pump through a computer. Mini size silicon boxes that contain pancreatic cells isolated from animals are used to control blood glucose levels. The boxes are enclosed by a substance that has a proper size nanopore, approximately 20 nm in diameter. The nanopore size allows the passage of only insulin and glucose and do not permit the entry of large molecules such as those involve in functions of immune system. The boxes are fixed under the skin of patient (Chick *et al.* 1977). Recently, researchers are making efforts to develop a nanorobot consists of insulin in its inner side and with sensors that can show blood glucose level on the surface of apparatus. When the sensors sense that glucose level is increasing the insulin is released accordingly (Rao & Gan 2014). In the future, the artificial pancreas will provide a permanent solution to the diabetic patients.

CONCLUSION

Nanotechnology is being used as drug carrier systems for treatment and diagnosis of various diseases such as cancer, pulmonary diseases, infectious diseases, vaccine development, diabetes mellitus; and the role of nanotechnology on our economy and its positive social impacts on our community. Nanotechnology expected to reach in mass applications in the product and processes which is guided by the social needs driven governance. Emphasis to increase the commercialization and innovation for the social returns of nanotechnology in job creation or economic development which measure to ensure public participation and safety. Nanotechnology governance has become institutionalized in manufacturing, education, research and medicine for the social benefits. This technology provides new approaches for education, learning, and research development.

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