Research Article

Changing Pharma Scenario from Novel to Nanodrug Delivery System

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ABSTRACT

Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in the size range of 1 to 100nm. The overall goal of nanotechnology is the same as that of medicine: to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects. It is attracting increasing attention in the biomedical community, owing to unique prospects for targeted delivery in imaging, gene therapy, and drug delivery. Nanotechnology seeks to increase the therapeutic index of drugs both by improving their administration and by increasing the exposure of diseased tissues to therapeutics. The nano-sized objects, e.g.,"nanoparticles", take on novel properties and functions that differ markedly from those seen from items made of identical materials. The small size, customized surface, improved solubility, and multi-functionality of nanoparticles will continue to open many doors and create new biomedical applications. Indeed, the novel properties of nanoparticles offer the ability to interact with complex cellular functions in new ways. This rapidly growing field requires cross-disciplinary research and provides opportunities to design and develop multifunctional devices that can target, diagnose, and treat devastating diseases such as cancer. Nanotechnology is a multidisciplinary field that covers a vast and diverse array of devices derived from engineering, physics, chemistry, and biology. The burgeoning new field of nanotechnology, opened up by rapid advances in science and technology, creates myriad new opportunities for advancing medical science and disease treatment in human health care. Applications of nanotechnology to medicine and physiology imply materials and devices designed to interact with the body at sub cellular (i.e., molecular) scales with a high degree of specificity. This can be potentially translated into targeted cellular and tissue-specific clinical applications designed to achieve maximal therapeutic efficacy with minimal side effects. It is the engineering of functional systems at the molecular scale. The increasing demands of understanding how modern medicines work at the molecular level, the shift towards predictive, preventive and personalised health care and challenges from nanotechnology and stem cell technology have added to the need for pharmacists to remain the experts in medicines. Nanotechnology is on its way to make a big impact in Biotech, Pharmaceutical and Medical diagnostics sciences. Now a days, all novel work is in the direction of developing a nanoscale drug delivery system for better targeted approach and lesser side effects. Therefore, in present scenario all novel drug delivery system are actually nano drug delivery system.

Keywords: Nanotechnology, Drug Delivery, Nanoparticles, Pharmaceutical.

INTRODUCTION

Nanotechnology has become a popular term representing the main efforts of the current science and technology. Nanotechnology is unique in that it represents not just one specific area, but a vast variety of disciplines ranging from basic material science to personal care applications. Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale (one-billionth of a meter). One nanometer (nm) is equal to one-billionth of a meter, or about the width of 6 carbon atoms or 10 water molecules. A human hair is approximately 80,000 nm wide, and a red blood cell is approximately 7000 nm wide. Atoms are smaller than 1 nm, whereas many molecules including some proteins range between 1 nm and larger. In the past few years nanotechnology has grown by leaps and bounds, and this multidisciplinary scientific

field is undergoing explosive development. It can prove to be a boon for human health care, because nanoscience and nanotechnologies have a huge potential to bring benefits in areas as diverse as drug development, water decontamination, information and communication technologies and the production of stronger, lighter materials. Human health-care nanotechnology research can definitely result in immense health benefits [1]. The genesis of nanotechnology can be traced to the promise of revolutionary advances across medicine, communications, genomics, and robotics. A complete list of the potential applications of nanotechnology is too vast and diverse to discuss in detail, but without doubt, one of the greatest values of nanotechnology will be in the development of new and effective medical treatments. This review focuses on the potential of nanotechnology in drug delivery, including the development of nanoparticles for drug and characteristics of nanoparticles. These technologies will extend the limits of current molecular diagnostics and permit accurate diagnosis as well as the development of personalized medicine[2,3].

Nanotechnology and Drug Delivery

Many of the current “nano” drug delivery systems, however, are remnants of conventional drug delivery systems that happen to be in the nanometer range, such as liposomes, polymeric micelles, nanoparticles, dendrimers, and nanocrystals. Liposomes and polymer micelles were first prepared in 1960’s, and nanoparticles and dendrimers in 1970’s. Colloidal gold particles in nanometer sizes were first prepared by Michael Faraday more than 150 years ago, but were never referred to or associated with nanoparticles or nanotechnology until recently. About three decades ago, correspondence to colloidal gold particles were conjugated with antibody for target specific staining, known as immune gold staining. Such an application may be considered as a precursor of recent explosive applications of gold particles in nanotechnology. Conventional liposomes, polymeric micelles, and nanoparticles are now called “nanovehicles,” and this, strictly speaking, is correct only in the size scale. To appreciate the true meaning of nanotechnology in drug delivery, it may be beneficial to classify drug delivery systems based on the time period representing before and after the nanotechnology revolution. Nanoparticles can mimic or alter biological processes (e.g., infection, tissue engineering, de novo synthesis, etc.). These devices include, but are not limited to, functionalized carbon nanotubes, nanomachines (e.g., constructed from interchangeable DNA parts and DNA scaffolds), nanofibers, self-assembling polymeric nano constructs, nano membranes, and nano-sized silicon chips for drug, protein, nucleic acid, or peptide delivery and release, biosensors and laboratory diagnostics. Nanocapsules are vesicular systems in which a drug is confined to a cavity surrounded by a polymer membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed[4,5]. Typically, the drug of interest is dissolved, entrapped, adsorbed, attached and/or encapsulated into or onto a nano-matrix. The efficiency of drug delivery to various parts of the body is directly affected by particle size. Nanostructure mediated drug delivery, a key technology for the realization of nanomedicine has the potential to enhance drug bioavailability, improve the timed release of drug molecules, and enable precision drug targeting. Nanoscale drug delivery systems can be implemented within pulmonary therapies, as gene delivery vectors, and in stabilization of drug molecules that would otherwise degrade too rapidly. Additional benefits of using targeted nanoscale drug carriers are reduced drug toxicity and more efficient drug distribution. Advantages of nanostructure-mediated drug delivery include the ability to deliver drug molecules directly into cells and the capacity to target tumors within healthy tissue[6].

Nanotechnology-based drug delivery systems

Hydrogels

Hydrogel nanoparticles are based on proprietary technology that uses hydrophobic polysaccharides for encapsulation and delivery of drug, therapeutic protein, or vaccine antigen. A novel system using cholesterol pullulan shows great promise. In this, four cholesterol molecules gather to form a self-aggregating hydrophobic core with pullulan outside. The resulting cholesterol nanoparticles stabilize entrapped proteins by forming this hybrid complex. These particles stimulate the immune system and are readily taken up by dendritic cells. Alternatively, larger hydrogels can encapsulate and release monoclonal antibodies[7].

Micelles

Block-copolymer micelles are spherical super-molecular assemblies of amphiphilic copolymer. The core of micelles can accommodate hydrophobic drugs, and the

shell is a hydrophilic brush-like corona that makes the micelle water soluble, thereby allowing delivery of the poorly soluble contents. Camptothecin (CPT) is a topoisomerase I inhibitor that is effective against cancer[7].

Liposomes

Liposomes were first developed about 40 years ago. They are small artificial vesicles (50–100nm) developed from phospholipids such as phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine and phosphatidylserine, which have been used in biology, biochemistry, medicine, food and cosmetics. The characteristics of liposomes are determined by the choice of lipid, their composition, method of preparation, size and surface charge. Liposomes have been applied as drug carriers due to their ability to prevent degradation of drugs, reduce side effects and target drugs to site of action. However, limitations of liposomes include low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. However, surface modification may confer stability and structure integrity against harsh bio-environment after oral or parenteral administration. Surface modification can be achieved by attaching polymers such as poly(methacrylic acid-co-stearyl methacrylate) and polyethylene glycol units to improve the circulation time of liposomes in the blood; and by conjugation to antibodies or ligands such as lectins for target specific drug delivery and stability. Applications of liposomes include transdermal drug delivery to enhance skin permeation of drugs with high molecular weight and poor water solubility; a carrier for delivery of drugs, such as gentamicin, in order to reduce toxicity; possible drug delivery to the lungs by nebulisation; ocular drug delivery and in the treatment of parasitic infections. Other vesicular structures include transferosomes, ethosomes, niosomes and marinosomes which are used mainly for transdermal delivery[8,9]. Transferosomes are developed by incorporation of surfactant molecules (edge activators) such as sodium chlorate into liposomes while ethosomes are liposomes that are high in ethanol (up to 45%). Niosomes are vesicles developed from non-ionic surfactants and marinosomes are liposomes produced from a natural marine lipid extract containing a high poly (unsaturated) fatty acid (PUFA) ratio [7].

Nanosystems

Novel nanosystems can be pre-programmed to alter their structure and properties during the drug delivery process, allowing for more effective extra- and intra-cellular delivery of encapsulated drug. This is achieved by the incorporation of molecular sensors that respond to physical or biological stimuli, including changes in pH, redox potential, or enzymes. Tumor-targeting principles include systemic passive targeting and active receptor targeting. Physical forces (e.g., electric or magnetic fields, ultrasound, hyperthermia, or light) may contribute to focusing and triggering activation of nano systems. Biological drugs delivered with programmed nanosystems also include plasmid DNA, siRNA, and other therapeutic nucleic acids[7].

Nanocells

Indiscriminate drug distribution and severe toxicity of systemic administration of chemotherapeutic agents can be overcome through encapsulation and cancer cell targeting of chemotherapeutics in 400 nm nanocells, which can be packaged with significant concentrations of chemotherapeutics of different charge, hydrophobicity, and solubility[10].Targeting of nanocells via bispecific antibodies to receptors on cancer cell membranes results in endocytosis, intracellular degradation, and drug release. Doses of drugs delivered via nanocells are ~1000 times less than the dose of the free drug required for equivalent tumor regression. It produces significant tumor growth inhibition and regression in mouse xenografts and lymphoma in dogs, despite administration of minute amounts of drug and antibody. Indeed, reduced dosage is a critical factor for limiting systemic toxicity[11, 12].

Dendrimers

Dendrimers are nanostructures produced from macromolecules such as polyamidoamine (PAMAM), polypropyleneimine and polyaryl ether; and are highly branched with an inner core. The particle size range is between 1 to 100nm although their sizes are mostly less than 10nm. Recent developments in polymer and dendrimer chemistry have provided a new class of molecules called dendronized polymers, which are linear polymers that bear dendrons at each repeat unit. Their behavior differs from that of linear polymers and provides drug delivery advantages because of their enhanced circulation time. Another approach is to synthesize or conjugate the drug to the dendrimers so that incorporating a degradable link can be further used to control

the release of the drug. Dendrimers are being investigated for both drug and gene delivery, as carriers for penicillin, and for use in anticancer therapy. Dendrimers used in drug delivery studies typically incorporate one or more of the following polymers: polyamidoamine (PAMAM), melamine, poly(L-glutamic acid) (PG), polyethyleneimine (PEI) , poly(propylene imine), and poly(ethylene glycol) (PEG) . Chitin and chitosan have also been incorporated with dendrimers. Their globular structures and the presence of internal cavities enable drugs to be encapsulated within the macromolecule interior. They have been reported to provide controlled release from the inner core. However, drugs are incorporated both in the interior as well as attached on the surface. Due to their versatility, both hydrophilic and hydrophobic drugs can be incorporated into dendrimers. Some of the drug deliver applications include therapeutic and diagnostic utilization for cancer treatment; enhancement of drug solubility and permeability (dendrimer-drug conjugates); and intracellular delivery[7].

Solid lipid nanocarriers

Solid lipid nanoparticles (SLN) are nanostructures made from solid lipids such as glyceryl behenate (Compritol), stearic triglyceride (tristearin), cetyl palmitate and glycerol tripalmitate (tripalmitin) with a size range of 50 and 1000 nm. The lipids employedin SLN are well tolerated by the body; large scale production will be cost effective and simple by using high pressure homogenization. Some of the features of SLN include good tolerability, site-specific targeting, stability (stabilized by surfactants or polymers), controlled drug release and protection of liable drugs from degradation[34]. However, SLN are known for insufficient drug loading, drug expulsion after polymorphic transition on storage and relative high water content of the dispersions[13]. SLN has been studied and developed for parenteral, dermal, ocular, oral, pulmonary and rectal routes of administration34-39. To overcome the limitations of SLN, nanostructured lipid carriers (NLC) were introduced. NLC is composed of solid lipids and a certain amount of liquid lipids with improved drug loading and increased stability on storage thereby reducing drug expulsion[13,14]. NLCs have been explored for dermal delivery in cosmetics and dermatological preparations[15,16]. Lipid drug conjugate (LDC) nanoparticles were introduced to overcome the limitation of types of drugs incorporated in the solid lipid matrix. Lipophilic drugs are usually incorporated in SLN but due to partitioning effects during production, only highly potent hydrophilic drugs are effective

Silicon-based structures

Silicon-based structures can be fabricated by photolithography, etching, a deposition techniques commonly used in the manufacture of semiconductors and micro electromechanical systems (MEMS). The most commonly investigated silicon-based materials for drug delivery are porous silicon and silica, or silicon dioxide. Architectures include calcified nanopores, platinum-containing nanopores, porous nanoparticles, and nanoneedles. The density and diameter of the nanopores can be accurately controlled to achieve a constant drug delivery rate through the pores. Porous hollow silica nanoparticles (PHSNP) are fabricated in a suspension containing sacrificial nanoscale templates such as calcium carbonate. Silica precursors, such as sodium silicate, are added into the suspension, which is then dried and calcinated creating a core of the template material coated with a porous silica shell. The template material is then dissolved in a wet etch bath, leaving behind the porou silica shell. Creation of drug carriers involves the mixing of the PHSNPs with the drug molecule and subsequently drying the mixture to coalesce the drug molecules to the surface of the silica nanoparticles Examples of therapies being investigated for use with silicon-based delivery systems include porous silicon embedded with platinum as an antitumor agent, calcified porous silicon designed as an artificial growth factor, silicon nanopores for antibody delivery and porous silica nanoparticles containing antibiotics, enzymes , and DNA[17].

Fullerenes

An important feature of fullerene molecules is that they have numerous points of attachment, allowing for precise grafting of active chemical groups in three-dimensional orientations. This attribute, the hallmark of rational drug design, allows positional control in matching fullerene compounds to biological targets. Together with other attributes, namely the size of the fullerene molecules, the redox potential and the relative inertness in biological systems, it is possible to tailor requisite pharmacokinetic characteristics to fullerene-based compounds and to optimize their therapeutic effect. Fullerene antioxidants bind and inactivate multiple, circulating, intracellular free radicals. This binding gives them unusual power to stop free-radical injury and to halt the progression of diseases caused by excess free-radical

production. Fullerenes provide an effective defense against all of the principal, damaging forms of reactive oxygen species. C60 fullerene has 30 conjugated carbon–carbon double bonds; all of them can react with a radical species. In addition, the capture of radicals by fullerenes is too fast to measure and is referred to as being 'diffusion controlled'. This means the fullerene forms a bond with a radical every time it encounters one. Numerous studies demonstrate that fullerene antioxidants work much better as therapeutics than other natural and synthetic antioxidants do, at least for CNS-degenerative diseases. In oxidative injury or disease, fullerene antioxidants enter cells and modulate free-radical levels, thereby substantially reducing or preventing permanent cell injury and cell death. Fullerenes have potential applications in the treatment of diseases where oxidative stress plays a role in the pathogenesis (e.g. neurodegenerative diseases). Another possible application of fullerenes is in nuclear medicine as an alternative to chelating compounds that prevent the direct binding of toxic metal ions to serum components. This could increase the therapeutic potency of radiation treatments and decrease their adverse effects because fullerenes are resistant to biochemical degradation within the body[7].

Polymersomes

These are hollow shell nanoparticles, have unique properties that allow delivery of distinct drugs. Loading, delivery and cytosolic uptake of drug mixtures from degradable polymersomes were shown to exploit the thick membrane of these block copolymer vesicles, their aqueous lumen, and pH-triggered release within endolysosomes. Polymersomes break down in the acidic environments for targeted release of these drugs within tumor cell endosomes. While cell membranes and liposomes are created from a double layer of phospholipids, a polymersome is comprised of two layers of synthetic polymers. The individual polymers are considerably larger than individual phospholipids but have many of the same chemical features. Polymersomes have been used to encapsulate paclitaxel and DOX for passive delivery to tumor-bearing mice[18].

Quantum dots

Single-particle quantum dots conjugated to tumor-targeting antihuman epidermal growth factor receptor 2 (HER2) MAb have been used to locate tumors using high-speed confocal microscopy. Following injection of quantum dot-MAb conjugate, six distinct stop-and-go steps were identified in the process as the particles travelled from the injection site to the tumor where they bound HER2. These blood-borne conjugates extravasated into the tumor, bound HER2 on cell membranes, entered the tumor cells and migrated to the perinuclear region. The image analysis of the delivery processes of single particles in vivo provided valuable information on MAb-conjugated therapeutic particles, which will be useful in increasing their anticancer therapeutic efficacy. However, the therapeutic utility of quantum dots remains undetermined.

Polymeric nanoparticles

Polymeric nanoparticles are colloidal solid particles with a size range of 10 to 1000nm and they can be spherical, branched or shell structures. The first fabrication of nanoparticles was about 35 years ago as carriers for vaccines and cancer chemotherapeutics. They are developed from non-biodegradable and biodegradable polymers. Their small sizes enable them to penetrate capillaries and to be taken up by cells, thereby increasing the accumulation of drugs at target sites. Drugs are incorporated into nanoparticles by dissolution, entrapment, adsorption, attachment or by encapsulation, and the nanoparticles provide sustained release of the drugs for longer periods, e.g., days and weeks. To target drugs to site of action, the drug can be conjugated to a tissue or cell specific ligand or coupled to macromolecules that reach the target organs. To target an anticancer agent to the liver, polymeric conjugate nanoparticles which comprised biotin and diamine-terminated poly (ethylene glycol) with a galactose moiety from lactobionic acid were prepared[20]. Some other applications of nanoparticles include possible recognition of vascular endothelial dysfunction; oral delivery of insulin; brain drug targeting for neurodegenerative disorders such as Alzheimer's disease; topical administration to enhance penetration and distribution in and across the skin barrier; and pH-sensitive nanoparticles to improve oral bioavailability of drugs such as cyclosporine A. Some polymers used in the fabrication of nanoparticles include chitosan, alginate, albumin, gelatin, polyacrylates, polycaprolactones, poly (D, L-lactide-co-glycolide) and poly (D, L-lactide) However, there are concerns about polymeric nanoparticles including cytotoxicity of by-products (although some, such as polyanhydrides, degrade into products that are biocompatible[21, 22].

Nanocapsules

Nanocapsules are spherical hollow structures in which the drug is confined in the cavity and is surrounded by a polymer membrane. They were developed over 30 years ago. Sizes between 50 and 300nm are preferred for drug delivery and they may be filled with oil which can dissolve lipophilic drugs. They have low density, high loading capacity and are taken up by the mononuclear phagocyte system, and accumulate at target organs such as liver and spleen. Nanocapsules can be employed as confined reaction vessels, protective shell for cells or enzymes, transfection vectors in gene therapy, dye dispersants, carriers in heterogenous catalysis, imaging and drug carriers. They are known to improve the oral bioavailability of protein and peptides which include insulin, elcatonin and salmon calcitonin. Encapsulation of drugs such as ibuprofen within nanocapsules protects liable drugs from degradation, reduces systemic toxicity, provide controlled release and mask unpleasant taste. Due to their high stability and low permeability, drugs may not be loaded into the capsules after formulation and also the release of the drug at target site may be difficult. To improve on their permeability, they are made responsive to physiological factors such as pH[7].

Nanoemulsions

Nanoemulsions are emulsions with droplet size below 1µ but usually between 20 and 200nm. Unlike microemulsions which are white in colour due to their light scattering ability, nanoemulsions whose nanosize is often smaller than visible wavelength, are transparent. Nanoemulsions are biodegradable, biocompatible, easy to produce and used as carriers for lipophilic drugs which are prone to hydrolysis. They are employed as a sustained release delivery system for depot formation via subcutaneous injection. They enhance gastrointestinal absorption and reduce inter- and intra-subject variability for various drugs. Due to their very large interfacial area, they exhibit excellent drug release profile. Nanoemulsions have been studied and developed for parenteral, oral, ocular, pulmonary and dermal deliveries. Stability against sedimentation is attained based on the nano size of the droplets because the sedimentation rate due to gravity is less than Brownian movement and diffusion. Unlike microemulsions, nanoemulsions are metastable and can be destabilized by Ostwald ripening whereby the small droplets dissolve and their mass is taken up by the large droplets and depletion induced flocculation due to addition of thickening polymers. When this happens, the nanoemulsion becomes opaque and creaming will occur. However, addition of a small amount of second oil with low solubility into the aqueous phase and addition of a second surfactant may reduce Ostwald ripening. Also, a number of factors during production should be controlled. These factors include selecting an appropriate composition, controlling the order of addition of components, applying the shear in a manner that will effectively rupture the droplets, and ensuring that the dispersed phase molecules are insoluble in the continuous phase so that Ostwald ripening does not occur rapidly[7].

Metallic nanoparticles

Metallic nanoparticles include iron oxide, gold, silver, gadolinium and nickel which have been studied for targeted cellular delivery. Gold exhibits favourable optical and chemical properties at nanoscale for biomedical imaging and therapeutic applications. It can be manipulated to obtain the desired size in the range of 0.8 to 200nm[23, 24]. The surface can be modified with different functional groups for gene transfection, modified into gene delivery vector by conjugation and also modified to target proteins and peptides to the cell nucleus. Gadolinium has been studied for enhanced tumour targeted delivery by modification of the nanoparticles with folate, thiamine and poly (ethylene glycol)[25,26]. Modification with folate was reported to enhance the recognition, internalization and retention of gadolinium nanoparticles in tumour cells. Metallic nanoparticles have large surface area thereby incorporating a high drug dose. However, the toxicity of metallic nanoparticles is of concern[27,28,29].

Characteristics important for drug delivery using nanoparticles

Particle size

The fastest and most routine method of determining nanoparticles size is by photon-correlation spectroscopy or dynamic light scattering. Photon-correlation spectroscopy requires the viscosity of the medium to be known and determines the diameter of the particle by Brownian motion and light scattering properties. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM). Particle size and size distribution are the most important characteristics of nanoparticles. They determine the in vivo distribution, biological fate, toxicity, and targeting ability of these

delivery systems. In addition, they can influence drug loading, drug release and stability of nanoparticles. Nanoparticles can cross the blood–brain barrier (BBB) following the opening of endothelium tight junctions by hyper-osmotic mannitol, which may provide sustained delivery of therapeutic agents for difficult-to-treat diseases like brain tumors . Tween 80-coated nanoparticles have been shown to cross the BBB as well. Drug release is also affected by particle size. Smaller particles have a larger surface area-to-volume ratio; therefore, most of the drug associated with small particles would be at or near the particle surface, leading to faster drug release. In contrast, larger particles have large cores, which allow more drug to be encapsulated per particle and give slower release[8]. Thus, control of particle size provides a means of tuning drug release rates[30].

Surface properties of nanoparticles

The association of a drug to conventional carriers leads to modification of the drug biodistribution profile, as it is mainly delivered to the mononuclear phagocyte system (MPS) such as liver, spleen, lungs and bone marrow. Nanoparticles can be recognized by the host immune system when intravenously administered and cleared by phagocytes from the circulation[31]. Apart from the size of nanoparticles, nanoparticle hydrophobicity determines the level of blood components (e.g., opsonins) that bind this surface. Hence, hydrophobicity influences the in vivo fate of nanoparticles[31,32]. Indeed, once in the blood stream, surface non-modified nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by the MPS. To increase the likelihood of success in drug targeting, it is necessary to minimize the opsonization and prolong the circulation of nanoparticles in vivo. This can be achieved by coating nanoparticles with hydrophilic polymers/surfactants or formulating nanoparticles with biodegradable copolymers with hydrophilic characteristics, e.g., polyethylene glycol (PEG), polyethylene oxide, polyoxamer, poloxamine, and polysorbate 80 (Tween 80). The zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles [33]. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above ±30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles. The zeta potential also can be used to determine whether a charged active material is encapsulated within the center of the nanoparticle or on the surface.

Drug loading

A successful nanodelivery system should have a high drug-loading capacity, thereby reducing the quantity of matrix materials for administration. Drug loading can be accomplished by two methods. The incorporation method requires the drug to be incorporated at the time of nanoparticle formulation. The adsorption/absorption methods call for absorption of the drug after nanoparticle formation; this is achieved by incubating the nano-carrier with a concentrated drug solution. Drug loading and entrapment efficiency depend on drug solubility in the excipient matrix material (solid polymer or liquid dispersion agent), which is related to the matrix composition, molecular weight, drug–polymer interactions, and the presence of end functional groups (i.e., ester or carboxyl) in either the drug or matrix[34, 35]. A polymer of choice for some nanoparticle formulations is PEG, which has little or no effect on drug-loading and interactions[36, 37]. In addition, the macromolecules, drugs or protein encapsulated in nanoparticles show the greatest loading efficiency when they are loaded at or near their isoelectric point (pI). For small molecules, studies show the use of ionic interaction between the drug and matrix materials can be very effective in increasing drug-loading[38].

Drug release

It is important to consider both drug release and polymer biodegradation when developing a nanoparticulate delivery system. In general, the drug release rate depends on: (1) drug solubility; (2) desorption of the surface-bound or adsorbed drug; (3) drug diffusion through the nanoparticle matrix; (4) nanoparticle matrix erosion or degradation; and (5) the combination of erosion and diffusion processes. Hence, solubility, diffusion, and biodegradation of the particle matrix govern the release process. In the case of nanospheres, where the drug is uniformly distributed, drug release occurs by diffusion or erosion of the matrix. If the diffusion of the drug is faster than matrix erosion, then the mechanism of release is largely controlled by a diffusion process. The rapid, initial release, or ‘burst’, is mainly attributed to weakly bound or adsorbed drug to the relatively large surface of nanoparticles[39]. It is evident that the method of incorporation has an effect on the release profile. If the drug is loaded by the

incorporation method, then the system has a relatively small burst effect and sustained release characteristics. If the nanoparticle is coated by polymer, the release is then controlled by diffusion of the drug from the polymeric membrane. Membrane coating acts as a drug release barrier; therefore, drug solubility and diffusion in or across the polymer membrane becomes a determining factor in drug release. Furthermore, the release rate also can be affected by ionic interactions between the drug and auxiliary ingredients. When the entrapped drug interacts with auxiliary ingredients, a less water soluble complex can form, which can slow the drug release — having almost no burst release effect[38]. Whereas if the addition of auxiliary ingredients, e.g., ethylene oxide–propylene oxide block copolymer (PEO-PPO) to chitosan, reduces the interaction of the drug with the matrix material due to competitive electrostatic interaction of PEO-PPO with chitosan, then an increase in drug release could be achieved . Various methods can be used to study the release of drug from the nanoparticle: (1) side-by-side diffusion cells with artificial or biological membranes; (2) dialysis bag diffusion; (3) reverse dialysis bag diffusion; (4) agitation followed by ultracentrifugation/centrifugation; or (5) ultra-filtration. Usually the release study is carried out by controlled agitation followed by centrifugation. Due to the time consuming nature and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred. However, these methods prove difficult to replicate and scale-up for industrial use.

Targeted drug delivery

This can be actively or passively achieved. Active targeting requires the therapeutic agent to be achieved by conjugating the therapeutic agent or carrier system to a tissue or cell-specific ligand[40]. Passive targeting is achieved by incorporating the therapeutic agent into a macromolecule or nanoparticle that passively reaches the target organ. Nanoparticles also can be formulated to deliver drugs across several biological barriers[41]. Anti-neoplastics, anti-viral drugs, and several other types of drugs are markedly hindered because of inability of these molecules to cross the BBB. The application of nanoparticles to deliver across this barrier is extremely promising. It has been reported that nanoparticles can cross the BBB following the opening of tight junctions by hyper-osmotic mannitol, which also may provide sustained delivery of therapeutic agents for difficult-to-treat diseases like brain tumors[20]. Tween 80-coated nanoparticles also have been shown to cross the BBB.

Applications and Advantages of nanoparticle drug carriers

Polymeric nanoparticles made from natural and synthetic polymers have received the majority of attention due to their stability and ease of surface modification[9]. They can be tailor-made to achieve both controlled drug release and disease-specific localization by tuning the polymer characteristics and surface chemistry[42,37]. It has been established that nanocarriers can become concentrated preferentially to tumors, inflammatory sites, and at antigen sampling sites by virtue of the enhanced permeability and retention (EPR) effect of the vasculature. Once accumulated at the target site, hydrophobic biodegradable polymeric nanoparticles can act as a local drug depot depending on the make-up of the carrier, providing a source for a continuous supply of encapsulated therapeutic compound(s) at the disease site, e.g., solid tumors. These systems in general can be used to provide targeted (cellular or tissue) delivery of drugs, improve bioavailability, sustain release of drugs or solubilise drugs for systemic delivery. This process can be adapted to protect therapeutic agents against enzymatic degradation (i.e., nucleases and proteases). Thus, the advantages of using nanoparticles for drug delivery are a result of two main basic properties: small size and use of biodegradable materials. Nanoparticles, because of their small size, can extravasate through the endothelium in inflammatory sites, epithelium (e.g., intestinal tract and liver), tumors, or penetrate microcapillaries. In general, the nanosize of these particles allows for efficient uptake by a variety of cell types and selective drug accumulation at target sites.

Challenges of Nano drug delivery

Although nanotechnology in drug delivery has been successful, as evidenced by some nano drug products in the market, not all approaches have met with the same success. New nanomaterials being developed come with challenges which have to be surmounted. However some of the challenges encountered have been and are still being tackled by modification of the physicochemical characteristics of the nanomaterials to improve on properties such as long circulation in the blood, increased functional surface area, protection of incorporated drug from

degradation, crossing of biological barriers and site-specific targeting. Another challenge of research and development (R&D) of nanomaterials for drug delivery is large scale production. There is always a need to scale up laboratory or pilot technologies for eventual commercialization. A number of nano drug delivery technologies may not be scalable due to the method and process of production and high cost of materials employed. The challenges of scaling up include low concentration of nanomaterials, agglomeration and the chemistry process – it is easier to modify nanomaterials at laboratory scale for improved performance than at large scale. Maintaining the size and composition of nanomaterials at large scale is also a challenge. Despite the number of patents for nano drug delivery technologies, commercialization is still at its early stage. This is partially due to the fact that most of the research studies in nano drug delivery are carried out by researchers in academia. Therefore, for these technologies to get to the market there has to be increased partnership with the pharmaceutical companies. Unfortunately, a number of the major pharmaceutical industries are yet to consider nanotechnology as one of their priorities due to lack of regulatory guidelines and challenges of scaling up. However, it is envisaged that with the expiration of more patents and market loss, more pharmaceutical industries will take up the production of nano drug products in order to compete favourably. Advances in nano drug delivery technology also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nano drug products, which are different from conventional drug products. The United States' Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) have taken the initiative to identify some possible scientific and regulatory challenges. Furthermore, the International Organization for Standardization has set up a technical committee (TC 229) for the field of nanotechnologies to develop standards pertaining to terminology and nomenclature; measurement and characterization; and health, safety and environment amongst other standards. These standards are still under development[43].

Safety issues

With increased R&D work on nano drug delivery, it emerge concerns about the safety of the nanotechnologies in humans. Some of the nanomaterials are biodegradable while some are not; furthermore, the side effects of the by-products present a huge concern. Materials which may be safe at macroscale may not be at nanoscale since there may be change in physicochemical characteristics at nanoscale. These nanomaterials may not clear completely from the body and their accumulation may have several possible effects. Safety and possible impact nano materials should not be considered for the patient population alone but also for the entire manufacturing and disposal processes. Conventional safety measures in a pharmaceutical factory may not be appropriate for the development and fabrication of nanomaterials. Also extra measures are to be taken to protect the environment from increased envisaged negative impacts of nanomaterials. Although reduced cost to the patients is envisaged to be one of the advantages of nanotechnology since fewer materials are expected to go into production as compared to bulk production; it is doubtful if this will be so, as successful commercialization will be expensive. There is also the general public reluctance to embrace nanotechnology based on the unavailability of documented safety guidelines. However, despite these challenges, nano drug delivery is a development that cannot be ignored and so the challenges will be tackled with time[43].

Limitations of use of nanotechnologies for drug discovery

The nanoparticles available are not ideal for all of the requirements of drug discovery and the choice of nanoparticle will depend on the individual needs. QDs can be used for high-throughput cell-based studies with the advantage of multiplexing (i.e. multiple leads can be tested at the same time). There are some limitations still to be resolved for their use in the drug-discovery studies such as toxicity, size variation, agglomeration, potential multiple drug attachment to a single QD and blinking. With a large number of nanotechnologies and nanomaterials, no generalizations can be made about safety and toxicity. *In vitro* diagnostic use does not pose any safety risks to people but there is a concern over the *in vivo* use of nanoparticles, particularly those <50 nm in size, which can enter the cells and there are still many unanswered questions about their fate in the living body. Because of the huge diversity of materials used and the wide range in sizes of nanoparticles, these effects will vary a lot. It is conceivable that particular sizes of some materials might turn out to have toxic effects

and further investigations will be needed. The FDA approval is essential for clinical applications of nanotechnology and substantial regulatory problems could be encountered in the approval of nanotechnology-based products. Pharmaceuticals, biologicals and devices are all regulated differently by the FDA and it is not yet clear how emerging nanotherapeutics will be evaluated[44].

Future of nanotechnology-based drug discovery

An increasing use of nanotechnology by the pharmaceutical and biotechnology industries is anticipated. Apart from innovations based on nanoparticles, several other nanotechnologies are in development for use in life sciences. In the near future, it might be possible to accurately model the structure of an individual cell and to predict its function using computers connected to nanobiotechnology systems. Such a detailed virtual representation of how a cell functions might enable scientists to develop novel drugs with unprecedented speed and precision, without doing any experiments in living animals. Nanotechnology will be applied at all stages of drug development, from formulations for optimal delivery to diagnostic applications in clinical trials. It will fit in with the concepts for the integration of diagnostics and therapeutics to develop personalized medicine[44,45,46].

CONCLUSIONS

The increasing awareness and R&D in the area of nano drug delivery would continue to change the whole concept of medicines including aspects such as product characteristics, bioavailability, pharmacokinetics, stability, drug use, and toxicity in human as well as animal and plant diseases. This in itself poses enormous challenges to the formulation scientist who has to keep abreast of rapid developments in this field. A whole segment of R & D has opened up, posing great challenges to equipment manufacturers, material scientists, pharmaceutical researchers, and regulatory agencies[47,48]. It is anticipated that better understanding and application of nanotechnology for effective drug delivery would ultimately enhance efficacy of treatment and patient drug use compliance. Nano delivery systems hold great potential to overcome some of the obstacles to efficiently target a number of diverse cell types. This represents an exciting possibility to overcome problems of drug resistance in target cells and to facilitate the movement of drugs across barriers (e.g., BBB). The challenge, however, remains the precise characterization of molecular targets and ensuring that these molecules only affect targeted organs. Furthermore, it is important to understand the fate of the drugs once delivered to the nucleus and other sensitive cell organelles[49,50].

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