Review Article

NANOTECHNOLOGY FOR BIOMEDICAL APPLICATION

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ABSTRACT

In this new era of nanotechnology attempts are to be made for making use of nanoparticles as carriers for a wide range of drugs for therapeutic applications and diagnosis because of their versatility and wide range of properties in tissue targeting and controlling drug release. Nanomedicines are helping in challenges to face the delivery of modern, as well as conventional drugs. In particular, this class of carrier holds tremendous promise in the areas of biomedical nanotechnology, bio nanotechnology and nanomedicines. Here we review formulation aspects, characteristics and their effect on drug delivery of nanoparticulate formulation.

Keywords: Nanoparticles, polymeric nanoparticles, targeting, drug delivery, drug release.

INTRODUCTION

Nanotechnology is a field of applied science and technology which controls matter on molecular level in scales within the 1-100nm and the preparation of devices in the range. Nanotechnology frequently applied in fibre and textiles, agriculture, electronics, forensic science, space and medical therapeutics namely in disease detection, controlled drug delivery, as biosensors in tissue engineering and so on[1–14]. This nanoparticle–drug formulation reduces the patient expenses and risks of toxicity[15, 16]. Nanoencapsulation of medicinal drugs (nanomedicines) increases drug efficacy, specificity, tolerability and therapeutic index of corresponding drugs [17–22].

Need for developing nanoparticles: The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents so as to achieve the site-specific action of the drug at the rationale rate and dose. Polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties [23-24].

Advantages: Some of the advantages of using nanoparticles as a drug delivery system are as follows;

1. Ease of manipulation of the particle size and surface characteristics of nanoparticles so as to achieve both passive and active drug targeting after parenteral administration.
2. The nanoparticle surface can be modified to alter biodistribution of drugs with subsequent clearance of the drug so as to achieve maximum therapeutic efficacy with minimal side effects of the drug.
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.
4. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
5. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
6. Liposomes and polymer based nano particulates are generally biodegradable, do not accumulate in the body and so are possibly risk free.
7. Small sized nanoparticles can penetrate through smaller capillaries, which could allow efficient drug accumulation at the target sites.
8. Various routes of administration are available including oral, nasal, parenteral, intra-ocular etc.[1, 25]

Limitations: In spite of these advantages nanoparticles do have Limitations like,

1. Altered physical properties which lead to particle – particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms due to smaller size and larger surface area.
2. Smaller the particles size greater the surface area and this property makes nanoparticles very reactive in the cellular environment.
3. Small particles size results in limited drug loading and burst release. These practical problems have to be sorted out before nanoparticles can be used clinically or made commercially available[2].

Toxicity: These tiny particles can easily get the entry inside the body through the skin, lungs or intestinal tract, depositing in several organs and may cause severe adverse biological reactions by altering the physiochemical properties of tissue. Non-biodegradable particles when used for drug delivery may show accumulation on the site of the drug delivery, leading to chronic inflammatory

reactions. Most of the nanoparticulate toxicity reactions are observed due to inhalation of particulate matter leading to lung and cardiovascular diseases.

TYPES OF NANOPARTICLES

Polymeric nanoparticles are colloidal structures composed of synthetic or semi synthetic polymers. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsule can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. The general synthesis and encapsulation of polymer are represented in fig.1. Polymers such as polysaccharide Chitosan-Polylactic acid, Polylactic acid co-glycolic acid, Poly-caprolactone, Chitosan nanoparticles have been used [7].

Solid lipid nanoparticles (SLN) have been proposed as a new type of colloidal drug carrier system suitable for intravenous administration. The system consists of spherical solid lipid particles in the nanometres range, which is dispersed in water or in surfactant solution.

Figure 1: Types of polymeric nanoparticles: According to the structural organization biodegradable nanoparticles are classified as Nanocapsules and nanospheres. The drug molecules are either entrapped inside or adsorbed on the surface.

The hydrophobic chains of phospholipids are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics[27]. Liposomes are nanoparticles comprising lipid bilayers membrane surrounding an aqueous interior. The amphiphilic molecules used for the preparation of these molecules have similarities between the biologic membranes and so been used for improving efficacy and safety of new drugs.

Liposomes: are classified into three categories depending on their size and lamellariety (number of bilayers).

Classification:

1. Small unilamellar vesicles or oligolamellar,

2. Large unilamellar vesicles and

3. Multilamelar vesicles.

Recently stealth liposomes have developed. They have the ability to evade the interception by the immune system and therefore longer half-life [28-30].

Recently, water-soluble polymer hybrid constructs have been developed. Polymer conjugation to proteins reduces immunogenicity, prolongs plasma half-life and enhances protein stability. Polymer-drug conjugation promotes tumour targeting through the enhanced permeability and retention effect and, at the cellular level following endocytic capture allows lysosomotropic drug delivery [31]. Ceramic nanoparticles are inorganic systems, with porous characteristics that have recently emerged as drug vehicles. Biocompatible ceramic nanoparticles like Silica, Titania and Alumina can be used in cancer therapy. Metallic particles such as iron oxide nanoparticles (15-60 nm) generally comprise a class of super paramagnetic agents that can be coated with dextran, phospholipids, or other compounds to inhibit aggregation and enhance stability. The particles are used as passive or active targeting agents [32]. Gold shell nanoparticles, other metal-based agents, are a novel category of spherical nanoparticles consisting of a dielectric core covered by a thin metallic shell, which is typically gold. These particles possess highly favorable optical and chemical properties for biomedical imaging and therapeSgiagb(n)18(i)0(a)293.36 Tm 5-5

biodegradability, biocompatibility and toxicity; (e) desired drug release profile; and (f) Antigenicity of the final product[26]. Nanoparticles have been prepared most frequently by three methods: [38].

A) Dispersion of preformed polymers

1. Solvent evaporation method
2. Spontaneous emulsification or solvent diffusion method

B) Polymerization of monomers

1. Coacervation or ionic gelation method

C) Ionic gelation or coacervation of hydrophilic polymers

D) Supercritical fluid technology

However, other methods such as supercritical fluid technology[39] and particle replication in non-wetting templates (PRINT)[40] have also been described in the literature for production of nanoparticles.

A) Dispersion of preformed polymers: Is the most common technique used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA); poly (D, L-glycolide), PLG; poly (D, L-lactide-co-glycolide) (PLGA) and poly (cyanoacrylates) (PCA), [41,42].

1. **Solvent evaporation method:** Organic solvents such as dichloromethane, chloroform or ethyl acetate are used to dissolve the polymer which is also used as the solvent for dissolving the hydrophobic drug. The drug dissolved or dispersed in polymer solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form oil in water emulsion. Once stable emulsion is formed, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. For preparation of the small uniform sized particle size, High-speed homogenizer or ultrasonication may be employed [43].

2. **Spontaneous emulsification or solvent diffusion method:** This is a modification of solvent evaporation method[44]. This technique involves the use of water miscible solvent along with a small amount of the water immiscible organic solvent as an oil phase. An interfacial turbulence is generated between the two phases due to spontaneous diffusion of immiscible solvents leading to the formation of small particles. By increasing the concentration of water miscible solvent decrease in the particle size can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. For hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase.

B) Polymerization method: In this method, monomers are polymerized to form nanoparticles in an aqueous solution in which drug may be dissolved. Drug may also be incorporated by adsorption onto the nanoparticles after polymerization completed. The nanoparticle suspension is then purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles[45, 46].

C) Coacervation or ionic gelation method: The method involves a mixture of two aqueous phases, of which one is the polymer Chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate. In this method, positively charged amino group of Chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometre. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature[48, 49].

Supercritical fluid technology: Conventional methods such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods require the use of enormous amounts of organic solvents which are hazardous to the environment as well as to human beings. Therefore, the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro- and nanoparticles. Supercritical fluids are environmentally safe [51]. A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure. Supercritical CO_2 (SC CO_2) is the most widely used supercritical fluid because of its mild critical conditions (T_c = 31.1 °C, P_c = 73.8 bars), nontoxicity, non-flammability and low price. The most common processing techniques involving supercritical fluids are supercritical anti-solvent (SAS) and rapid expansion of critical solution (RESS). The process of SAS employs a liquid solvent, e.g. methanol, which is completely miscible with the supercritical fluid (SC CO_2), to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting the formation of nanoparticles. The solvent power of supercritical fluids dramatically decreases and the solute eventually precipitates. This technique is clean because the precipitate is basically solvent free. RESS and its modified process have been used for the product of polymeric nanoparticles[52, 53]. Supercritical fluid technology technique, although environmentally friendly and suitable for mass production, requires specially designed equipment and is more expensive.

Characteristics of Nanoparticles and their effect on Drug Delivery

Polymeric nanoparticles have been characterized by their morphology and polymer composition in the core and corona. The unique sizes of nanoparticles are amenable to surface functionalization or modification to achieve desired characteristics. This was achieved by various methods to form the corona to increase drug retention time in blood, reduction of nonspecific distribution and target tissues or specific cell surface antigens with targeting ligands (peptide, aptamer, antibody and small molecule)[39].

Particle size and particle size distribution: Particle size and size distribution are the most important characteristics determining the fate of nanoparticle systems including distribution, biological fate, toxicity and the targeting ability of nanoparticle systems *in vivo*. Drug loading, drug release and stability of nanoparticles are also influenced by particle size and size distribution. Many studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over micro particles as a drug delivery system[54]. Generally nanoparticles have relatively higher intracellular uptake compared to micro particles and available to a wider range of biological targets due to their small size and relative mobility. Researchers have reported that 100 nm nanoparticles had a 2.5 fold greater uptake than 1 µm micro particles and 6 fold greater uptake than 10 µm micro particles in a Caco-2 cell line [55]. It was also reported that nanoparticles can cross the blood-brain barrier following the opening of tight junctions by hyper osmotic mannitol, which may provide sustained delivery of therapeutic agents for difficult-to-treat diseases like brain tumours[57]. Tween 80 coated nanoparticles have been shown to cross the blood-brain barrier[58]. Some cell lines are capable of up taking of only submicron nanoparticles efficiently than larger size micro particles [59]. Drug release is affected by particle size. Smaller particles have larger surface area, therefore, most of the drug associated would be at or near the particle surface, leading to fast drug release. Whereas, larger particles have large cores which allow more drug to be encapsulated and slowly diffuse out [60]. Smaller particles also have greater risk of aggregation of particles during storage and transportation of nanoparticle dispersion. It is always a challenge to formulate nanoparticles with the smallest size possible but maximum stability. Polymer degradation can also be affected by the particle size[61]. Currently, the fastest and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM), field flow fractionation method and size exclusion chromatography. X-ray photoelectron spectroscopy (ESCA) can be used to determine the chemical composition of the nanoparticle surface. This technique is a very useful tool for the development of surface modified nanoparticles providing a direct evidence of the presence of the components that are believed to be on the nanoparticle surface[62].

Surface properties of nanoparticles: intravenously administered nanoparticles are easily recognized by the body immune systems and are then cleared by phagocytes from the circulation. The hydrophilicity of the nanoparticle surface can be evaluated by hydrophobic interaction chromatography[62]. This technique, based on affinity chromatography, allows a very rapid discrimination between hydrophilic and hydrophobic nanoparticles. Apart from the size of nanoparticles, their surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (opsonins). This in turn influences the *in vivo* fate of nanoparticles[63, 64]. Binding of these opsonins onto the surface of nanoparticles called opsonisation acts as a bridge between nanoparticles and phagocytes. The association of a drug to conventional carriers leads to modification of the drug biodistribution profile, as it is mainly delivered to the mononuclear phagocytes system (MPS) such as liver, spleen, lungs and bone marrow. In the blood stream, conventional nanoparticles (surface non-modified) are rapidly opsonised cleared by the macrophages of MPS rich organs[66]. For the drug targeting by nanoparticles, it is necessary to minimize the opsonisation and to prolong the circulation of nanoparticles *in vivo*. This can be achieved by (a) surface coating of nanoparticles with hydrophilic polymers/surfactants; (b) formulation of nanoparticles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, poloxamer, poloxamine and polysorbate 80 (Tween 80) [66].

Zeta potential: The zeta potential of a nanoparticle is used to characterise the surface charge property of nanoparticles[68]. It reflects the electrical potential of particles and is affected by the surface composition of the nanoparticles, the presence or the absence of adsorbed compounds and the composition of the dispersing phase, mainly the ionic strength and the pH. 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.

Drug loading and drug release mechanisms

A successful ideal nanoparticulate system is the one which have a high drug-loading capacity by which reduce the quantity of matrix materials for administration. The solid-state drug solubility in polymer depends on the polymer composition. Molecular weight, the drug polymer interaction and the presence of end functional groups (ester or carboxyl) are the factors which determines drug loading and entrapment efficiency[68, 69, 70]. The protein molecule shows greatest loading efficiency when it is loaded at or near its isoelectric point at which it has minimum solubility and maximum adsorption [71]. The type of binding and the binding rate (mg drug/mg nanoparticle) can be determined by the adsorption isotherm. Linear sorption isotherms characterize solid solutions and Langmuir or S-type isotherms characterize surface

adsorption. From the amount of drug bound, the encapsulation efficiency (EE) of the drug can be calculated by using the formula:

EE = Amount of drug bound /Total amount of drug used for nano particle production

Because nanoparticles are colloidal systems, precise determination of the drug content is a major problem. Therefore, the most reliable way to separate the nanoparticles from the solution containing unbound drug is ultracentrifugation or gel filtration.

The drug release mechanisms are equally important as the drug loading because of the proposed application in sustained drug delivery. A good understanding of Drug release to develop a successful nanoparticulate system, both drug release and polymer biodegradation are important consideration factors. In the case of nanospheres, where the drug is uniformly distributed, the release occurs by diffusion or erosion of the matrix under sink conditions. If the diffusion of the drug is faster than matrix erosion, 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 large surface of nanoparticles [72]. It is evident that the method of incorporation has an effect on release profile. If the drug is loaded by incorporation method, the system has a relatively small burst effect and better sustained release characteristics [73]. If the nanoparticle is coated by polymer, the release is then controlled by diffusion of the drug from the core across the polymeric membrane. The membrane coating acts as a barrier to release, therefore, the solubility and diffusivity of drug in polymer membrane becomes determining factor in drug release. Furthermore release rate can also be affected by ionic interaction between the drug and addition of auxillary ingredients. When the drug is involved in interaction with auxillary ingredients to form a less water soluble complex, then the drug release can be very slow with almost no burst release effect [74].

Methods of evaluation for release of drugs

Various methods which can be used to study the *in vitro* release of the drug from nanoparticles are:

(i) side-by-side diffusion cells with artificial or biological membranes

(ii) dialysis bag diffusion technique

(iii) reverse dialysis bag technique

(iv) agitation followed by ultracentrifugation/ centrifugation

(v) Ultra-filtration or centrifugal ultra-filtration techniques.

Commonly release study is carried out by controlled agitation and centrifugation. As the method is time consuming and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred. The mechanism of drug release is needed. There are five possible mechanisms for drug release: (a) desorption of drug bound to the surface, (b) diffusion through the nanoparticle matrix, (c) diffusion through the polymer wall of nanocapsule, (d) nanoparticles matrix erosion, or (e) a combined erosion–diffusion process [75]. The kinetic analysis of drug release from nanoparticles can be described by a biexponential function

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

Where C is the concentration of drug remaining in the nanoparticles at time t, A and B are system characteristic constants (A is used for diffusion control system and B for erosion control system)and are rate constants that can be obtained from semi logarithmic plots[75]. In general drug release rate depends upon solubility, diffusion and biodegradation of the matrix materials.

APPLICATIONS

a) Nanoparticle as drug delivery systems

The use of pharmacological agents is frequently limited by drug resistance at the target level owing to physiological barriers cellular mechanism is encountered. In addition, many drugs have a poor solubility, low bioavailability and they can be quickly cleared in the body by the reticuloendothelial system. Furthermore, the efficacy of different drugs, such as chemotherapeutical agents, is often limited by dose- dependent side effects.

Gastrointestinal tract: Other portals for entry are GI and Skin It is known that the kinetics of particle uptake in GI tract depends on diffusion and accessibility through mucus initial contact with enterocytes, cellular trafficking and post-translocation events. The smaller the particle diameter is, the faster they could diffuse through GI secretion to reach the colonic enterocytes Following uptake by GI tract nanoparticles can translocate to the blood stream and distribute all over the body. Targeting strategies to improve the interaction of nanoparticles with adsorptive sites (enterocytes and M-cells of Peyer's patches) in the GI tract utilizes specific binding to ligands or receptors and nonspecific adsorptive mechanism. The surface of enterocytes and M cells shows cell-specific carbohydrates, which can serve as binding sites to nanoparticle drug carriers with appropriate ligands. Certain glycoproteins and lectins bind selectively to this type of surface structure by specific receptor-mediated mechanism.

Brain: The brain is probably one of the least accessible organs for the delivery of drugs due to the presence of the blood–brain barrier (BBB) that controls the transport of endogenous and exogenous compounds, thus providing the neuroprotective function. Drugs normally unable to cross the BBB could be delivered to the brain after binding to the surface-modified poly (butyl cyanoacrylate) (PBCA) nanoparticles [78].

Tumor cell targeting: Anticancer drugs, which usually have large volume of distribution, are toxic to both normal and

cancer cells. Therefore, precise drug release into highly specified target involves miniaturizing the delivery systems to become much smaller than their targets. With the use of nanotechnology, targeting drug molecules to the site of action is becoming a reality resulting in a personalized medicine, which reduces the effect of the drug on other sites while maximizing the therapeutic effect. This goal is mainly achieved by the small size of these particles, which can penetrate across different barriers through small capillaries into individual cells. In addition, nanoparticles can be prepared to entrap, encapsulate, or bind molecules improving the solubility, stability and absorption of several drugs, as well as avoiding the reticuloendothelial system, thus protecting the drug from premature inactivation during its transport. In fact, it has been shown that nanoparticles have the ability to carry various therapeutic agents including DNA, proteins, peptides and low molecular weight compounds. Among all of them, liposome and polymer-based nanoparticulates are the most widely used nanoparticles as drug delivery systems, as these compounds are generally biodegradable, do not accumulate in the body and they are possibly risk-free. For instance, several anticancer drugs, including paclitaxel, 5-fluorouracil, doxorubicin, have been successfully formulated using polymers and liposomes as drug delivery systems.

Respiratory tract: One of the most common entry passage for nanoparticles is respiratory tract. Nanoparticles could avoid normal phagocytic defenses therein respiratory tract and gain access to systemic circulation and may reach to CNS. Aerosol therapy using nanoparticles as drug carrier is gaining importance for delivering therapeutic compounds. The lung is an attractive target for drug delivery due to non-invasive administration via inhalation aerosols, avoidance of first-pass metabolism, direct delivery to the site of action for the treatment of respiratory diseases and the availability of a huge surface area for local drug action and systemic absorption of drug. Colloidal carriers (i.e., nanocarrier systems) in pulmonary drug delivery offer many advantages such as the potential to achieve relatively uniform distribution of drug dose among the alveoli, achievement of improved solubility of the drug from its own aqueous solubility, a sustained drug release which consequently reduces dosing frequency, improves patient compliance, decreases incidence of side effects and the potential of drug internalization by cells [76].

b) For gene delivery: The key ingredient of polynucleotide vaccines, DNA, can be produced cheaply and has much better storage and handling properties than the ingredients of the majority of protein-based vaccines. However, there are several issues related to the delivery of polynucleotides which limit their application. These issues include efficient delivery of the polynucleotide to the target cell population and its localization to the nucleus of these cells and ensuring that the integrity of the polynucleotide is maintained during delivery to the target site. Nanoparticles loaded with plasmid DNA could also serve as an efficient sustained release gene delivery system due to their rapid escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment[77]. Following the intracellular uptake and endolysosomal escape, nanoparticles could release DNA at a sustained rate resulting in sustained gene expression. This gene delivery strategy could be applied to facilitate bone healing by using PLGA nanoparticles containing therapeutic genes such as bone morphogenic protein[78].

c) For Diagnosis and Bioimaging: A number of molecular imaging techniques are available, such as optical imaging (OI), magnetic resonance imaging (MRI), ultrasound imaging (USI), positron emission tomography (PET) and others have been reported for imaging of in vitro and in vivo biological specimens[79,80.] The current development of luminescent and magnetic nanoparticles advances bio imaging technologies [81]. Two different types of nanoparticles have been widely used for imaging: luminescent nanoprobes for OI and magnetic nanoparticles for MRI. There are also dual-mode nanoparticles for simultaneous imaging by OI and MRI [82.] Nanobiotech scientists have successfully produced microchips that are coated with human molecules. The chip is designed to emit an electrical impulse signal when the molecules detect signs of a disease. Special sensor nanobots can be inserted into the body under the skin where they check blood contents and warn of any possible diseases. They can also be used to monitor the sugar level in the blood. Advantages of using such nanobots are that they are very cheap and easy to produce [83].

Gold nanoparticles are being used for detection of cancer. Gold nanoparticles have been used as ultrasensitive fluorescent probes to detect cancer biomarkers in human blood. The method is very sensitive and could also be employed in direct detection of viral or bacterial DNA. Gold nanoparticles are promising probes for biomedical applications because they can be easily prepared and, unlike other fluorescent probes such as quantum dots or organic dyes, don't burn out after long exposure to light [84].

d) Tissue repair: Tissue repair using iron oxide nanoparticles is accomplished either through welding, apposing two tissue surfaces then heating the tissues sufficiently to join them, or through soldering, where protein or synthetic polymer-coated nanoparticles are placed between two tissue surfaces to enhance joining of the tissues. Temperatures greater than 50°C are known to induce tissue union induced by the denaturation of proteins and the subsequent entanglement of adjacent protein chains[85-87]. This is believed to be Nanoparticles that strongly absorb light corresponding to the output of a laser are also useful for tissue-repairing procedures. Specifically, gold- or silica-coated iron oxide nanoparticles have been designed to strongly absorb light [88, 89]. The nanoparticles are coated onto the surfaces of two pieces of tissue at the site where joining was desired. This technique affords methods to minimize tissue damage by using the least harmful wavelengths of light and/or lower powered light sources. Stem cells are the body's master

cells and have a unique ability to renew them and give rise to other specialized cell types. These cells, therefore, have the potential to be used for transplantation purposes, for example, to replace degenerated cells or repairing of a damaged tissue, providing signals so that the stem cells can yield the appropriate cell types for the development of a tissue[90]. In addition, various proteins, growth factors, etc., could be bound to these nanoparticles that might be delivered at the damaged tissue, where it would play a role in tissue development. Magnetic nanoparticles can also be used to target the stem cells and activate at required sites of injury and repair in diseases such as diabetes, cancer, heart disease, Alzheimer's and Parkinson's disease[91]. Biodegradable nanoparticle-based vaccines, for oral vaccination, are also in development and may allow targeting of antigens to specific dendritic cell receptors.

CONCLUSION

Nanoparticles present a highly attractive platform for a diverse array of biological applications. The surface and core properties of these systems can be engineered for individual and multimodal applications, including tissue engineering, therapeutic delivery, biosensing and bioimaging. Nanoparticles have already been used for a wide range of applications both in vitro and in vivo. Full realization of their potential, however, requires addressing a number of open issues, including acute and long-term health effects of nanomaterials as well as scalability, reproducibility, manufacturing methods and reliable methods for characterization of these materials.

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