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Review Article

NANOSCALE DRUG DELIVERY TECHNOLOGIES: INTRODUCTION AND RECENT DEVELOPMENTS

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ABSTRACT
Nanoscale drug delivery systems are now proposed as an alternative to classical formulations for drug administration, delivery and targeting. For the past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Nanoscale technologies are beginning to change the foundations of disease diagnosis, treatment and prevention. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. Here, we review various approaches of nanoscale drug delivery system in delivery of drug molecules and therapeutic genes. The article also reveals the concept of DNA nanotechnology as well as nanospore sequencing from nanomedicine.
Keywords: Nanoscale drug delivery, nanodrug, nanoparticles, nanoscience.

INTRODUCTION

The development of a wide spectrum of nanoscale technologies is beginning to change the foundations of disease diagnosis, treatment and prevention[1]. These technologies involve utilization of man-made products no larger than 1–1000 nm (i.e., a few atoms to smaller than a single cell). A dictionary definition (Nano nano-pref. 1: Extremely small nanoid. 2: One-billionth (10^{-9} m) nanometer) elucidates the scale of this field and allows us to define that nanoscale particles are in the 10^{-9} m dimension range, consistent with the magnitude of most synthetic nanoparticles to date. For a real perspective, the width of a DNA molecule is 2.5 nm; cell membranes are 6–10 nm thick; and most proteins are between 5 and 20 nm in diameter. Therefore, most conventional molecular research is already proceeding in nanoscale dimensions[2].

Nanoscale Drug Delivery System

A nanodrug delivery system consists of a core, a particle or emulsion, prepared by chemical methods to function as a carrier. Functional groups are added to the core. Such groups may include therapeutic molecules and ligands for targeting specific locations[3]. Nanodrug delivery system develops particles or molecules of nanoscale size to improve drug bioavailability. Many approaches to nanomedicine have been developed that enable the association of a variety of drugs to these nanocarriers, ranging from classical small drug to large DNA fragments and their successful development is almost inevitable and their subsequent incorporation into valuable medical diagnostics or clinical therapeutics is highly likely and may occur very soon[4]. The materials and structures currently being investigated at the nanoscale for drug delivery are shown in Table 1[5]. This review summarizes the currently available approaches of nanoscale drug delivery system are as follows;

Table 1: Nanoscale Drug Delivery Technologies

Drug Delivery Technology	Materials	Nanostructure Forms
Biologic	Lipids, Peptides, Nucleic acids Polysaccharides, Viruses	Vesicles, Nanotubes, Rings, Nanoparticles
Polymeric	Poly(lactic acid), Poly(glycolic acid), Poly(alkylcyanoacrylate) Poly(3-hydroxybutanoic acid) Poly(organophosphazene) Poly(ethylene glycol) Poly(caprolactone) Poly(ethylene oxide) Poly(amidoamine) Poly(L-glutamic acid) Poly(ethylene imine) Poly(propylene imine)	Vesicles, Spheres, Micelles, Nanoparticles, Dendrimers
Silicon based	Silicon, Silicon dioxide	Porous, Nanoparticles, Nanoneedles
Carbon based	Carbon	Nanotubes, Fullerenes
Metallic	Gold, Silver Palladium, Platinum	Nanoparticles, Nanoshells

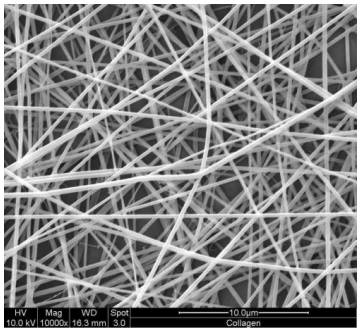

Figure 1: Structure of Nanofibers

Nanofibers as Biomaterials

By applying molecular self-assembly, nanofibers of various structures and chemistries can be formed (Figure 1). Nanofibers may be designed to present high densities of bioactive molecules such as those which promote cell adhesion and growth. For example amphiphiles that present the pentapeptide epitope IKVAV, an amino acid sequence of laminin that promotes neurite adhesion, self-assemble in aqueous media, or when injected directly into a tissue, to form fibers with a diameter of 5–10 nm. Indeed, these scaffolds were shown to induce rapid differentiation of cells to neurons, while discouraging the development of astrocytes. This presumably suggests that synthetic materials may have the ability to modulate selective gene expression. The development of nanofibers has enhanced the scope for fabricating scaffolds that can potentially mimic the architecture of natural human tissue at the nanometer scale. The high surface area to volume ratio of the nanofibers combined with their microporous structure favors cell adhesion, proliferation, migration and differentiation, all of which are highly desired properties for tissue engineering applications[6].

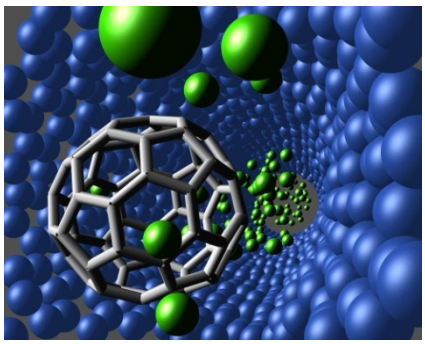

Figure 2: Carbon Nanotubes

Carbon Nanotubes

A carbon nanotube belongs to the family of fullerenes and consists of graphite sheets rolled up into a tubular form (Figure 2). These structures can be obtained either as single- (characterized by the presence of a single grapheme sheet) or multi-walled (formed from several concentric grapheme sheets) nanotubes. The diameter and the length of single-walled nanotubes may vary between 0.5–3.0 nm and 20–1000 nm, respectively. The corresponding dimensions for multi-walled nanotubes are 1.5–100 nm and 1–50 µm, respectively. Carbon nanotubes can be made water soluble by surface fictionalization. Molecular and ionic migration through carbon nanotubes can occur, thus offering opportunities for fabrication of molecular sensors and electronic nucleic acid sequencing. Carbon nanotubes can apparently cross the cell membrane as nanoneedles without perturbing or disrupting the membrane and localize into cytosol and mitochondria. However, the mechanisms are poorly understood[5,7].

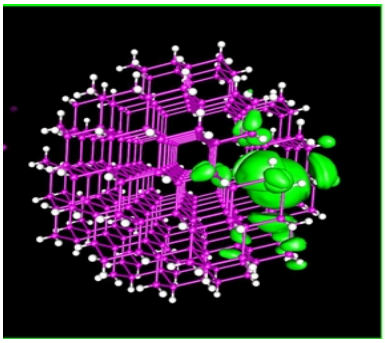

Figure 3: Quantum Dots

Quantum Dots

These are nano-scale crystalline structures made from a variety of different compounds, such as cadmium selenide, that can transform the colour of light and have been around since the 1980s. Quantum dots absorb white light and then re-emit it a couple of nanoseconds later at a specific wavelength. By varying the size and composition of quantum dots, the emission wavelength can be tuned from blue to near infrared. For example, 2 nm quantum dots luminescence bright green, while 5 nm quantum dots luminescence red. Quantum dots have greater flexibility, when compared to other fluorescent materials and this makes them suitable for use in building nano-scale computing applications where light is used to process information. These structures offer new capabilities for multicolor optical coding in gene expression studies (Figure 3), high throughput screening and *in vivo* imaging[6].

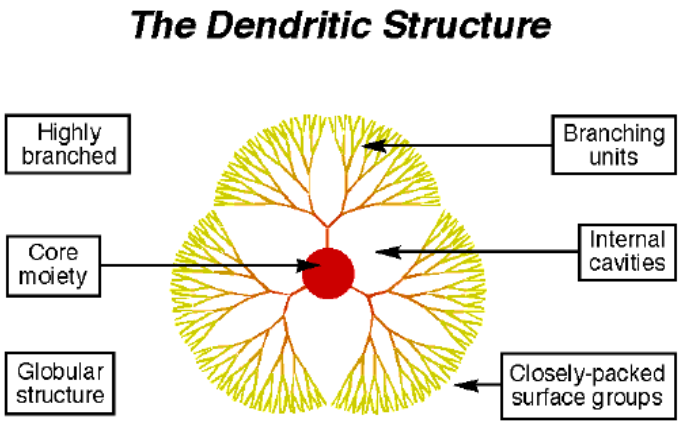

Figure 4: The Dendritic Structure

Dendrimers

These are highly branched macromolecules with controlled near monodisperse three-dimensional architecture emanating from a central core (Figure 4). Polymer growth starts from a central core molecule and growth occurs in an outward direction by a series of polymerization reactions. Hence, precise control over size can be achieved by the extent of polymerization, starting from a few nanometers. Cavities in the core structure and folding of the branches create cages and channels. The surface groups of dendrimers are amenable to modification and can be tailored for specific applications.

Therapeutic and diagnostic agents are usually attached to surface groups on dendrimers by chemical modification[8].

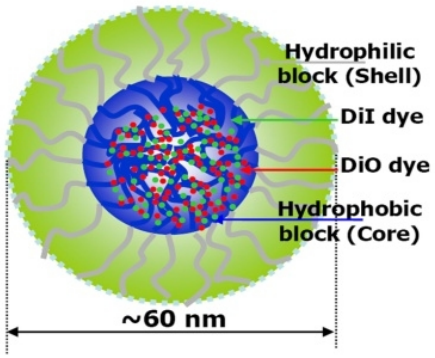

Figure 5: Structure of Micelles

Polymeric Micelles

Micelles are formed in solution as aggregates in which the component molecules (e.g., amphiphilic AB-type or ABA-type block copolymers, where A and B are hydrophobic and hydrophilic components, respectively) are generally arranged in a spheroidal structure with hydrophobic cores shielded from the water by a mantle of hydrophilic groups (Figure 5). These dynamic systems, which are usually below 50 nm in diameter, are used for the systemic delivery of water-insoluble drugs. Drugs or contrast agents may be trapped physically within the hydrophobic cores or can be linked covalently to component molecules of the micelle[9].

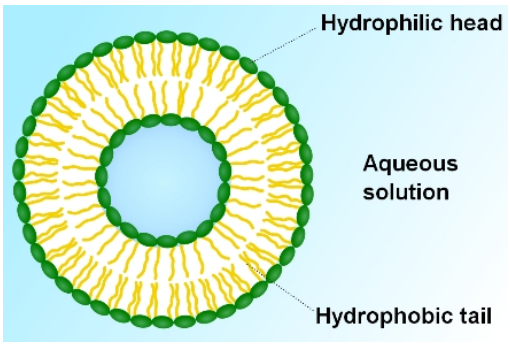

Figure 6: Liposomal Structure

Liposomes

These are closed vesicles that form on hydration of dry phospholipids above their transition temperature. Liposomes are classified into three basic types based on their size and number of bilayers. Multilamellar vesicles consist of several lipid bilayers separated from one another by aqueous spaces. These entities are heterogeneous in size, often ranging from a few hundreds to thousands of nanometers in diameter. On the other hand, both small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) consist of a single bilayer surrounding the entrapped aqueous space. SUVs are less than 100 nm in size whereas LUVs have diameters larger than 100 nm. Drug molecules can be either entrapped in the aqueous space or intercalated into the lipid bilayer of liposomes, depending on the physicochemical characteristics of the drug. The liposome surface is amenable to modification with targeting ligands and polymers[10].

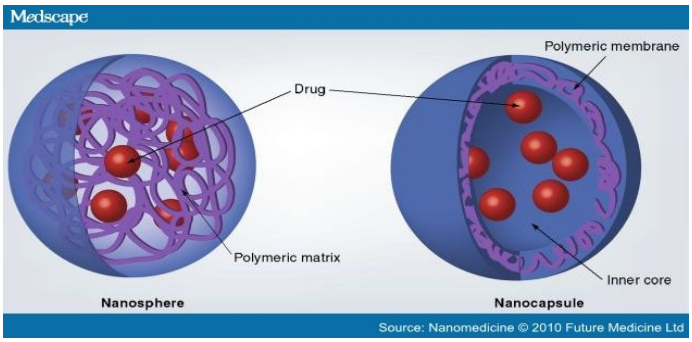

Figure 7: Modified Nanospheres

Nanospheres

These are spherical objects, ranging from tens to hundreds of nanometers in size, consisting of synthetic or natural polymers (collagen, albumin). The drug of interest is dissolved, entrapped, attached or encapsulated throughout or within the polymeric matrix. Depending on the method of preparation, the release characteristic of the incorporated drug can be controlled. As with liposomes, technology also allows precision surface modification of nanospheres with polymeric and biological materials for specific applications or targeting to the desired locations in the body[9].

Fullerenes

Fullerenes, the so called "miracle molecules" of nanotechnology (buckyballs and carbon nanotubes are included in this class of carbon molecules), are hollow cages of sixty carbon atoms less than a couple of nanometers wide.

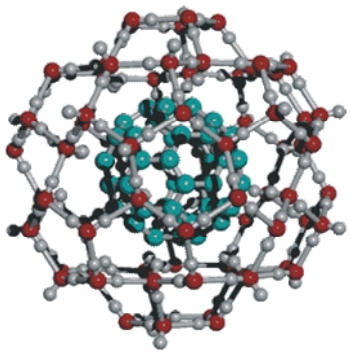

Figure 8: Structure of Fullerenes

Because they are hollow, Pharma companies are exploring filling the fullerenes with drug compounds and then functionalizing them to bind in different parts of the body[11,12].

Nanoshells

Nanoshells (gold-coated nanoparticles) are layered colloidal with non-conducting nanoparticles core covered by ultra thin metal shells. These comprise of 110 nm\diameter silica core covered by 8 to 10 nm thick gold shells. The nanoshells are 20 times smaller than RBC's. Nanoshells rely on the plasmon mediated conversion of electrical energy into light. They have the ability to be tunable optically and have emission/absorption properties that range from the UV to the infrared. Nanoshells are attractive because they offer imaging and potential therapeutic properties similar to those of quantum dots without the potential for heavy metal toxicity.

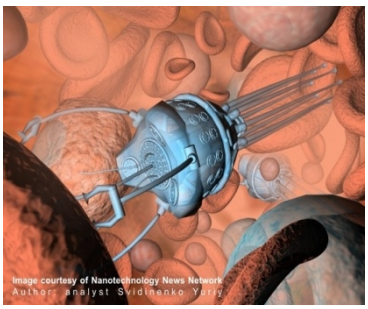

Figure 9: Nanorobots in Medicine

Nanorobots

The somewhat speculative claims about the possibility of using nanorobots in medicine, advocates say, would totally change the world of medicine once it is realized. Nanomedicine would make use of these nanorobots (e.g., Computational Genes), introduced into the body, to repair or detect damages and infections. According to Robert Freitas of the Institute for Molecular Manufacturing, a typical blood borne medical nanorobot would be between 0.5-3 micrometers in size, because that is the maximum size possible due to capillary passage requirement. Carbon could be the primary element used to build these nanorobots due to the inherent strength and other characteristics of some forms of carbon (diamond/fullerene composites) and nanorobots would be fabricated in desktop nanofactories specialized for this purpose. Nanodevices could be observed at work inside the body using MRI, especially if their components were manufactured using mostly 13C atoms rather than the natural 12C isotope of carbon, since 13C has a nonzero nuclear magnetic moment. Medical nanodevices would first be injected into a human body and would then go to work in a specific organ or tissue mass. The doctor will monitor the progress and make certain that the nanodevices have gotten to the correct target treatment region. The doctor will also be able to scan a section of the body and actually see the nanodevices congregated neatly around their target (a tumour mass, etc.) so that he or she can be sure that the procedure was successful[13].

DNA Nanocapsules

DNA nanocapsules smuggle strands of viral DNA into cells shows in Figure 10. Once the capsule breaks down, the DNA hijacks the cells machinery to produce compounds that would be expected in a virus attack, thus alerting and training the immune system to recognize them**.**

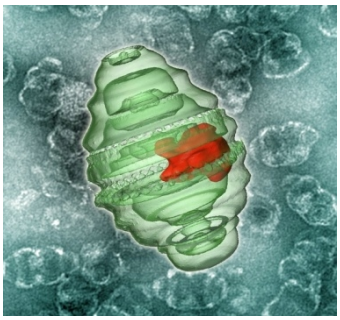

Figure 10: DNA Nanocapsule Technology

DNA nanocapsule technology could also be used to hijack living cells to produce other compounds such as new proteins or toxins. As a result, they must be carefully monitored as a potential biowarfare technology.

Aquasomes (carbohydrate-ceramic nanoparticles)

These are spherical 60–300 nm particles used for drug and antigen delivery. The particle core is composed of nanocrystalline calcium phosphate or ceramic diamond and is covered by a polyhydroxyl oligomeric film. Drugs and antigens are then adsorbed on to the surface of these particles.

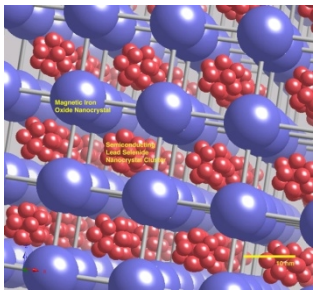

Figure 11: Superparamagnetic Iron Oxide Crystals Embedded in Protons

Superparamagnetic iron oxide crystals

These entities are usually prepared by the alkaline co-precipitation of appropriate ratios of Fe^{2+} and Fe^{3+} salts in water in the presence of a suitable hydrophilic polymer such as dextran or poly (ethylene glycol). This yields an iron core of 4–5 nm in diameter, which is hexagonally shaped and surrounded by dextran or poly (ethylene glycol) molecules. These crystals possess large magnetic moments when brought into a magnetic field, thus producing a localized disturbance in magnetic field homogeneity, but the magnetic memory is lost when the field is removed. Due to such induced magnetic disturbances, there exist a large susceptibility difference between superparamagnetic iron oxide crystals and the nearby protons (Figure 11), causing rapid dephasing of spins and resultant decrease in T2 relaxation times with a loss of local signal intensity. But the effects of these crystals on T1 relaxation times are relatively minor, compared with the T2 effects. These crystals are therefore "negative enhancers".

Ferrofluids

Ferrofluids are colloidal solutions of iron oxide magnetic nanoparticles surrounded by a polymeric layer coated with affinity molecules, such as antibodies, for capturing cells and other biological targets from blood or other fluid and tissue samples. Ferrofluid particles are so small (25–100 nm in radius) that they behave in liquids as a solution rather than suspension. When the coated ferrofluid particles are mixed with a sample containing cells or other analytes, they interact intimately and completely. These properties enable the development of specialized reagents and systems with extremely high sensitivity and efficiency and capture[9].

Silicon-Based Structures (BioSilicon)

Silicon-based structures can be fabricated by photolithography, etching and deposition techniques commonly used in the manufacture of semiconductors and microelectro mechanical 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[14].

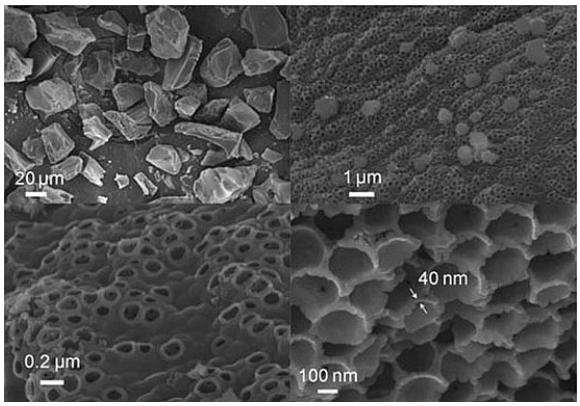

Figure 12: Structure of Porous Hollow Silica Nanoparticles

Porous hollow silica nanoparticles (PHSNP) are fabricated in a suspension containing sacrificial nanoscale templates such as calcium carbonate (Figure 12). 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 porous 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[5].

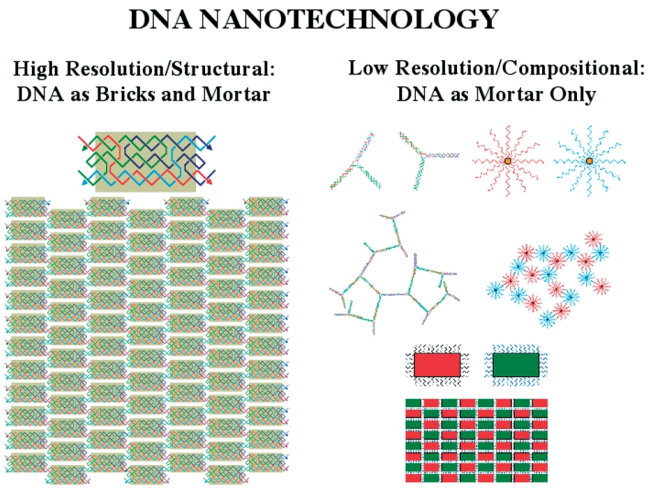

Figure 13: Types of DNA nanotechnology

Nucleic acid lattices (DNA nanotechnology)

{High resolution/structural DNA nanotechnology is shown on the left, where DNA is both the bricks and mortar of an assembly. A TX molecule is shown assembled into a two-dimensional array. Low resolution/compositional DNA nanotechnology is shown on the right with floppy components or applications using DNA as 'smart glue' (top). This type of DNA nanotechnology can also be used to build structures, as shown at the bottom, but the resolution is not as high.}[15] DNA can be programmed to self-assemble into an array of remarkable nanometer-scale structures different from the double helix. Stick cube, a construct shaped like a cube formed from sticks, and truncated DNA octahedron are two examples. For instance, the cube self-assembles from DNA fragments that are designed to adhere to one another. The free ends are connected by ligases, resulting in six closed loops, one for each face of the cube. Due to the helical nature of DNA, each of these loops is twisted around the loops that flank it, thus ensuring that the cube cannot come apart. Such scaffolds and assemblies can hold biological molecules in an ordered array for x-ray crystallography. This approach could be particularly useful for those materials that do not form a regular crystalline structure on their own (e.g., certain cell receptors that function as drug targets). These architectures could also hold molecule-size electronic devices, or be used to engineer materials with precise molecular configurations. Future efforts may lead to the design of DNA devices that can replicate and DNA machines with moving parts as nanomechanical sensors, switches and tweezers.

Polyplexes/Lipopolyplexes

Lipopolyplexes (LPPs) (a ternary complex of cationic liposomes, cationic polymer and DNA) represent a second generation of nonviral gene delivery vectors that can improve gene transfer compared to the first generation cationic-liposome–DNA complexes. In general, these vectors are compact particles that exhibit superior colloidal stability, reduced cytotoxicity and elevated transfection efficiency compared to polyplexes and lipoplexes[16].

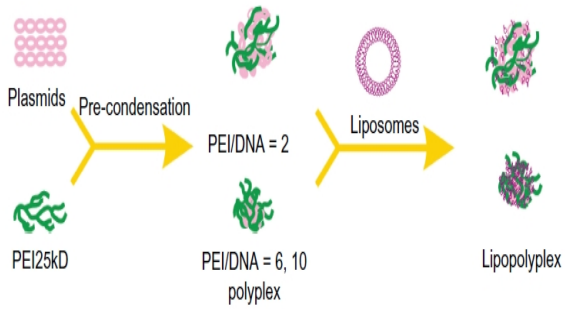

Figure 14: Formation of lipopolyplexes by combining preformed polyplex core with cationic lipids
(Abbreviation: PEI, polyethylenimine.)[17]

These are assemblies, which form spontaneously between nucleic acids and polycations or cationic liposomes (or polycations conjugated to targeting ligands or hydrophilic polymers) and are used in transfection protocols. The shape, size distribution and transfection capability of these complexes depends on their composition and charge ratio of nucleic acid to that of cationic lipid/polymer. Examples of polycations that have been used in gene transfer/therapy protocols include poly-L-lysine, linear- and branched-poly(ethylenimine), poly(amidoamine), poly-ß-amino esters and cationic cyclodextrin.

Nanopore Sequencing

This is an ultra-rapid method of sequencing based on pore nanoengineering and assembly. A small electric potential draws a charged strand of DNA through a pore of 1–2 nm in diameter in α–hemolysin protein complex, which is inserted into a lipid bilayer separating two conductive compartments.

The current and time profile is recorded and these are translated into electronic signatures to identify each base. This method can sequence more than 1000 bases per second. This technology has much potential for the detection of single nucleotide polymorphisms and for gene diagnosis of pathogens[18].

CONCLUSION

Nanoscale drug delivery systems are now proposed as an alternative to classical formulations for drug administration, delivery and targeting. Many approaches to nanoscale drug delivery system have been developed that enable the association of a variety of drugs to these nanocarriers, ranging from classical small drug to large DNA fragments and their successful development is almost inevitable, and their subsequent incorporation into valuable medical diagnostics or clinical therapeutics is highly likely and may occur very soon. This article reviewed various approaches of nanoscale drug delivery system in delivery of drug molecules and therapeutic genes including DNA nanotechnology as well as nanospore sequencing.

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