Chapter 2

Medicated Nanoparticle for Gene Delivery

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Abstract

Delivering the drug to the target site with a desired concentration to provide therapeutic effect is a major problem in the drug delivery system. Effectiveness, poor distribution and lack of selectivity are the drawbacks of the conventional dosage form. Recently Nanotechnology has been given much attention in various fields specifically in the biomedical application. Material includes organic, inorganic, polymeric and lipid-based nanobiomaterials after surface modification; it has been utilized for drug and gene delivery systems. Viral and non-viral vectors are the two types in gene delivery utilizing genetic materials like DNA plasmids, RNA and siRNA. Cellular and extracellular barriers are the two main barriers in gene delivery. The basic mechanism involved in the gene delivery is an introduction of a gene encoding a functional protein altering the expression of an endogenous gene or owning the capacity to cure or prevent the progression of a disease. Nanoparticle surface features like particle shape and surface charge are having major roles in the gene delivery. To provide the site-specific delivery various properties like nature of polymer, particle size, solubility, biocompatibility, biodegradability and nanoparticle surface features are need to be considered. Gene delivery has been utilized for various disease treatments such as cancer, AIDS, and cardiovascular diseases.

Keywords: Gene delivery, DNA, RNA, Nanoparticle

1. Introduction

Drug and gene delivery system include organic, inorganic, polymeric and lipid-based nanobiomaterials. Binding of the nanobiomaterials to the receptors to target cells/tissues can be improved by surface modification. This surface modification may increase solubility, immune compatibility, and cellular uptake.

Various nano drug delivery systems include nanoparticles, nanocapsules, nanotubes, nanogels, and dendrimers. They can be used to deliver both small molecule drugs and various classes of biomacromolecules, such as peptides, proteins, plasmid DNA, and synthetic oligodeoxynucleotides. Antisense oligonucleotide (AS-ODN) and small interfering RNA (siRNA) are shown as promise one in gene delivery and good therapeutic agents, but it can be used directly due to their limitations such as sequence size, length, charge, half-life, or stability in solutions [1].

Various diseases are occurred in human beings due to mutations or deletions in genes lead to metabolic pathway disorder, regulation of cell cycle, protein function and its structure, function of receptor, and cell skeleton [2]. This can be treated effectively through gene delivery system. Gene delivery is a term used when referring to the delivery of genetic material such as DNA plasmids, RNA, and siRNA into target cells either encapsulated inside or conjugated to the NPs to express or suppress the biosynthesis of proteins (also called transfection) to treat or cure many diseases [3–10].

2. Various gene delivery mechanisms

2.1. Plasmid DNA

It is currently the most commonly investigated nucleic acid in gene delivery applications. When the pDNA is entering into the nucleus, the pDNA strand is transcribed, and the coding gene is translated to protein, which is then expressed from the cell.

2.2. RNA interference

It is triggered by double-stranded RNA (dsRNA), activates the anti-viral interferon leads to shutdown of protein synthesis by degradation of messenger RNA (mRNA). Another mechanism involves the use of microRNAs (miRNA), which are small non-coding nucleic acids responsible for post-translational regulation of protein expression.

2.3. Small interfering RNA

Small interfering RNA comprises around 21–23 nucleotides, which can be designed to be better targeted than long dsRNA and can eliminate the activation of the response of the interferon while still inhibiting target gene expression. The gene expression can be able to control/block transected siRNA into mammalian cells; this specific gene block can be used to treat certain infectious diseases and cancers [11–14].

To obtain an efficient vector system and to achieve a high rate of cell transfection, the following two limitations must be integrated in the development of an ideal genetic vector. In the gene transfer methods whether viral, physical, or chemical, these two major limitations must be overcome.

1. The first limitation is a carrier, which is needed to carry the nucleic acids to the target cells without potential risks. Naturally viruses having the ability to recognize and locate the defined target cells due to its body defense mechanisms, such as the reticulo-endothelial system (RES). Whereas the chemical vectors conjugate with targeting molecules to realize the specific location through various techniques.
2. The second limitation is the penetration of the nucleic acids into the cell through the plasma membrane. Viruses can achieve the same through natural mechanisms, whereas the chemical vectors must disturb the plasma membrane (e.g. physical vectors)/or internal vesicular membranes (e.g. the cationic lipids) [15].

3. Gene delivery

In gene delivery, a vector/carrier is essential in order to carry the hydrophilic, negatively charged DNA through the hydrophobic and negatively charged cell membrane. The therapeutic efficiency depends upon the efficient delivery of DNA into the target site. Barriers including cellular like intracellular uptake, endosomal escape, DNA release, and nuclear uptake and extracellular barriers like avoidance of particle clearance mechanisms, targeting to specific tissues and/or cells of interest, and protection of DNA from degradation are present in the system [16–19]. One main hurdle in gene delivery is the delivery of therapeutic polynucleotides crossing the plasma membrane and delivering into the cells of interest. This is the limitation one in the gene delivery for efficient and safe delivery into the cells. A good gene delivery vector should be able to effectively compact and protect DNA, sufficient stability during bypassing the immune system of the host, traverse the plasma membrane (typically through endocytosis), disrupt the endosomal membrane, and deliver the DNA into the nucleus [20–22]. Successful gene transfer requires sufficient stability of DNA during the extracellular delivery phase, transportation through cell membranes, cytoplasm, and eventual disassembly and nuclear delivery.

Gene delivery systems can be divided into two general categories:

1. Viral transduction systems
2. Nonviral transfection systems

Initially, viruses were used for gene delivery. The disadvantages of viral vectors limited their application in gene delivery like due to its size of DNA that they can carry, low loading capacity, large-scale manufacturing, quality control cost, and safety factor such as immunogenicity and potential oncogenicity [23].

Hence, more attention has been paid to develop non-viral vectors as an alternative one for gene delivery [6, 8–10, 24].

Nonviral delivery systems have advantages like easy to prepare, amenable to synthetic manipulations of polymer properties, cell/tissue targeting, less immunogenic and oncogenic, no potential of virus recombination and limitation on the size of a transferred gene, virtually no limitation on the unrestricted plasmid size that can be delivered and the cost of production is relatively low [25]. Moreover, they can be consigned readily to carry genetic materials to target cells by virtue of their size, charge and structurally modifying the vectors [26]. Difference between viral and nonviral gene delivery is based on the various gene transfer and its complementary mechanisms. The mechanism includes in the viral gene delivery is the ability of virus to circulate in the blood, bind to cell surface receptors, gain entry into the cell, avoid lysosomal destruction, survive degradation in the cytosol, and deliver genetic material to the nucleus. In the nonviral gene delivery overcoming biological barriers in the circulation or inside the target cell and transferring the gene vector is based on the molecular weight of the vector, ratio between the vector nitrogens and the DNA phosphates (termed the N:P ratio) and the salt concentration of the buffer solution. [27–30].

Nonviral gene delivery systems are typically composed of plasmid DNA condensed into nanoparticles by a cationic polymer [31].

Nonviral vectors are categories into lipid- and polymer-based one. Whereas the polymeric based nonviral vectors have the advantage over lipid-based one due to its modification property.

The steps involved in the polymeric gene delivery are given below:

- DNA/polymer complexation: Nanosize complex forms when cationic polymer neutralizes charged phosphate with negatively charged cell membrane.
- DNA/polymer complex: Also referred as polyplex, which passes through cell membrane by a nonspecific or receptor-mediated endocytosis.
- Endosome: Complex enters into cytoplasm through endosome.
- Transportation to nucleus.
- It is free to be encoded into a therapeutic protein or to be inserted into the genome [6, 8–10].

4. Targeted drug delivery

It is necessary to ensure that the nanomaterials are carefully delivered only to the infected region of the body without affecting the surrounding healthy tissues.

When drugs or gene-loaded nanoparticles are injected into bodies, they can circulate in the blood vessels by crossing the epithelial barriers before reaching the target site. Escape of nanoparticles from the vascular circulation occurs in either continuous or fenestrated tissues.

Nanoparticles can escape from the bloodstream at continuous vascular endothelium through paracellular pathway, intracellular process or transcellular pathway. It is different; the space between the fenestration sites on the endothelium is between 100 nm and 2 μm, which is longer than in healthy tissues that are normally 2–6 nm. Therefore, nanoparticles can penetrate fenestrations thus increase the drug concentration in target/tumor site which is called "enhanced permeation and retention effect (EPR effect)" [32–34]. Particle shape, surface charge, and feature are playing important roles in intercellular delivery [35, 36]. Quantity and type of polymers, particle size, solubility, biodegradability, and surface properties are having important role in release of bioactive drugs into the target site [37]. Drug entries through transcellular and paracellular pathways are shown in **Figure 1**.

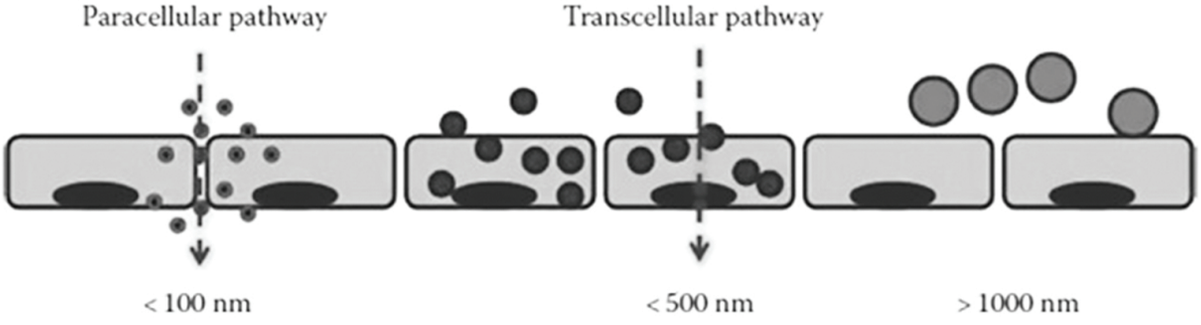

Figure 1. Drug entry through transcellular and paracellular pathways.

Targeted drug delivery is classified into two categories. They are

1. Passive targeting
2. Active targeting

4.1. Passive targeting

Passive targeting involves the cells that are to be targeted migrate toward the drug-carrying vehicles. This system is widely used in the delivery of cells like neutrophils, macrophages, dendritic cells for vaccination purposes. In this system, it is not necessary the drug-carrying vehicles in nanometer regime [38].

4.2. Active targeting

Active targeting involves rational design of nanosytems with suitable surface engineering performed with acceptable chemical linking strategies to specifically target the cell receptors of a target tissue. Furthermore, the targeting operates at two levels; first, the targeting of tissue/system in order to enrich the concentration of the carriers at the infected site [9, 39].

5. Nonviral vector gene delivery

Nonviral vector consists of either natural vectors (plasmid DNA or small nucleic acids, antisense oligonucleotides, small interfering RNAs) or synthetic vectors (liposomes, cationic polymers) [40]. Naked DNA, usually in plasmid form, is the simplest form of non-viral transferring of a gene into a target cell [41–44].

Nonviral vector delivery is categorized as organic (lipid complexes, conjugated polymers, cationic polymers, etc.) and inorganic systems (magnetic nanoparticles, quantum dots, carbon nanotubes, gold nanoparticles (GNPs), etc.) [45].

To achieve the desired therapeutic efficacy, a suitable carrier system is needed. Nanoparticles can be considered as a good carrier for various therapeutic applications due to the following reasons.

- They exist in the same size domain as proteins.
- They have large surface areas and ability to bind to a large number of surface functional groups.
- They possess controllable absorption and release properties and particle size and surface characteristics. [46].

6. Inorganic type nonviral delivery vectors

Inorganic type of nonviral delivery vectors are magnetic nanoparticles, quantum dots, and gold nanoparticles, and so on [31, 47].

6.1. Magnetic nanoparticle

Combination of inorganic nanoparticles with organic materials forms hybrids which possess unique physical, chemical, optical, and electrical properties. These unique properties can be utilized in different applications than large size materials. Recently, magnetic nanoparticles have been utilized as an effective tool in gene delivery because of its submicron size. Hence, much research has been carried out to control the size and shape of the metal nanostructure due to its magnetic, catalytic, electrical, and optical properties. Iron oxides, such as $CoFe_2O_4$, $NiFe_2O_4$, and $MnFe_2O_4$, exhibit superior performance compared to other magnetic materials but highly toxic to cells. The most widely used iron oxide as magnetic cores are magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), possess high magnetic moments and relatively safe. The magnetic nanoparticle core is fairly reactive, prevents corrosion and leaking when applied *in vivo*. In the magnetic nanoparticle gene delivery system, the gene directly binds to the magnetic particle or carrier. In magnetic nanoparticle, a magnetic core is coated by a protective layer either by dispersing in a polymer matrix or encapsulated within a polymer/metallic shell, which can be combined with therapeutic agents (carrier/DNA complexes or other drugs) through covalent or noncovalent bond. Silica, gold, natural polymers, such as dextran, or

synthetic polymers, such as PEI, PLL, PEG, and polyvinyl alcohol (PVA), are commonly used coating materials in magnetic nanoparticle. Introduction of various functional groups (organic linkers) like carboxyl, amines, thiols, and aldehyde can alter the surface properties to suit various therapeutic agents to improve targeted gene delivery. The preferred coating surface for magnetic particles is strongly cationic because of the negatively charged DNA molecules that are to be delivered. Magnetofection is a methodology based on the association of magnetic nanoparticle with gene vectors in order to optimize/enhance gene delivery in the presence of a magnetic field. The magnetic field is applied to move the MNP-gene vector complexes toward the target site. In magnetofection, gene can be delivered in few minutes to the target site, whereas traditional transfection methods can take several hours. Stability of any magnetic nanoparticles depends upon the balance between attractive (van der Waals and dipole-dipole) and repulsive (steric and electrostatic) forces between the particles and the surrounding solvent molecules. Temperature also has an effect in the stability of the magnetic nanoparticle due to energy transfer from the solvent molecules (Brownian motion) to the nanometric particles. Hence, magnetic nanoparticle can be coated with a biocompatible polymer to enhance its stability [30, 31, 48–62].

6.2. Metal nanoparticle (gold nanoparticle)

Owing to nano-dimension size to volume ratio and its stability, inorganic (metal) nanoparticles are being extensively used as promising gene carriers in various biomedical applications. Among the various metal nanoparticle gold nanoparticles (GNPs) are an obvious choice due to its inert, amenability of synthesis, high functionalization, fictionalization ability, higher absorption coefficient, good biocompatibility, less cytotoxic, ease of detection, and potential capability of targeted delivery, hence it is extensively used for various applications including drug and gene delivery. Due to its remarkable stability, large surface area, surface modification, and high biocompatibility, gold nanoparticles can retain the native structure and enzymatic activity of the attached proteins or enzymes in the drug delivery. Gold nanoparticles have large surface area due to which their surfaces are readily available for modification with targeting molecules or specific biomarkers and applicable in biomedical purposes.

Gold nanoparticles have large surface bio conjugation with molecular probes, and they also have many optical properties which are mainly concerned with localized plasmon resonance (PR). Gold nanoparticles can bind with a wide range of organic molecules and have tunable physical and chemical properties. Gold nanoparticles can be synthesized by chemical (seeding growth method), physical (γ-irradiation method, microwave irradiation method), and green methods (natural biomaterial egg shell membrane, sun light irradiation method).

Combination of gold nanoparticles into smart polymer like poly (N-isopropylacrylamine) is an effective process to enhance its properties. Gold nanoparticles exhibit different shapes such as spherical, sub-octahedral, octahedral, decahedral, icosahedral multiple twined, multiple twined, irregular shape, tetrahedral, nanotriangles, nanoprisms, hexagonal platelets, and nanorods, which are shown in **Figure 2**. Among the various shapes triangular-shaped nanoparticles show attractive optical properties compared with the spherical-shaped nanoparticles [30, 58, 63–72].

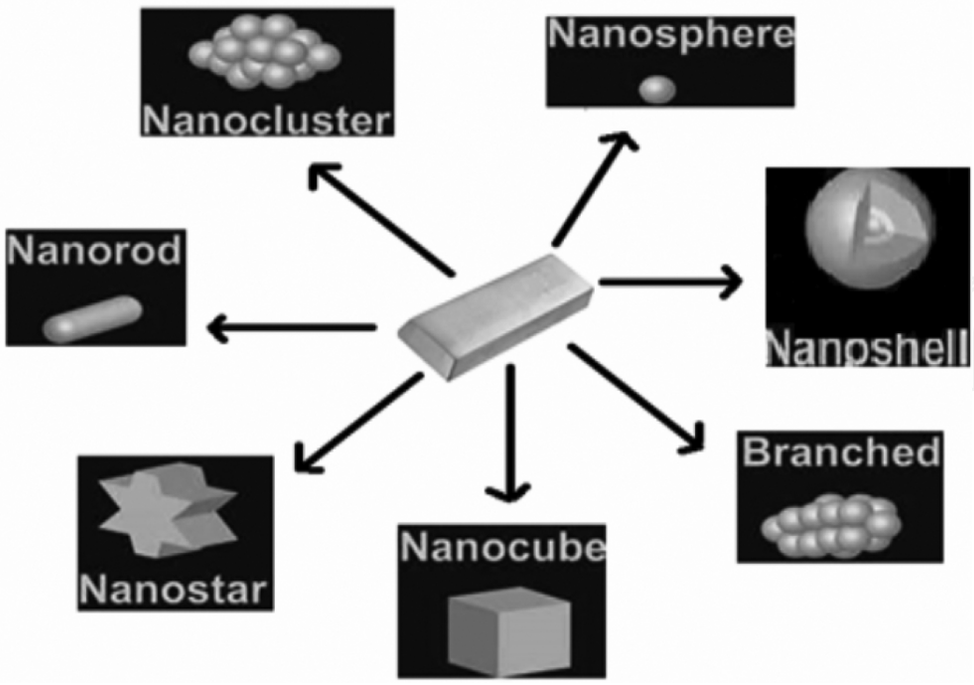

Figure 2. Various shapes of gold nanoparticle.

6.3. Quantum dots

Quantum dots are tiny semiconductor crystals of luminescent nanocrystals with rich surface chemistry and unique optical properties with the size of 1–10 nm made up of compounds from group II to VI and III to V, for example, Ag, Cd, Hg, Ln, P, Pb, Se, Te, Zn, and so on. QDs have distinctive characteristics such as size-tunable light emission, improved signal brightness, resistance against photobleaching, and simultaneous excitation of multiple fluorescence colors.

Depending on their size by laser, the quantum dots glow brightly in different colors, such as Adirondack Green (520nm), Blue (514 nm), Greenish blue (544 nm), Green (559 nm), Yellowish green (571 nm), Yellow (577 nm), Yellowish orange (581 nm), Fort Orange (600nm), Orange (610 nm), and Maple Red-Orange (620nm).

QDs are nearly spherical semiconductor particles with core-shell structure. Colloidal core/shell QDs, such as CdSe/ZnS, CdSe/CdS/ZnS, CdTe/CdSe, and InP/ZnS, are commonly synthesized for biomedical applications, whereas CdSe/ZnS, CdTe/ZnS, and CdSe/CdS/ZnS have been commonly used.

Quantum dots are made up of three parts, that is, core, shell, and cap.

Core is made up of CdSe, which is a semiconductor material. Core is surrounded by shell which is made up of ZnS for improving its optical properties and cap encapsulates the double layer quantum dots by different materials like silica which helps in improving solubility in aqueous buffers. Structure of quantum dot is shown in **Figure 3**.

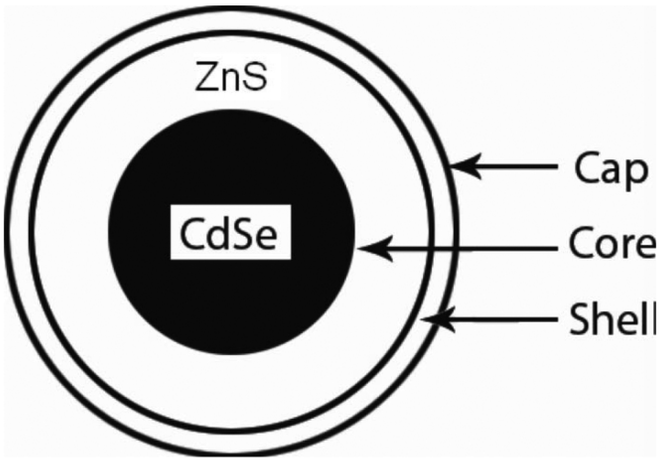

Figure 3. Structure of a quantum dot.

The semiconducting nature and the size-dependent fluorescence of these nanocrystals have been successfully applied for in vitro, in vivo transfection and for diagnosis of various diseases. One of the most important emerging applications of QDs appears to be *traceable* drug delivery, because it has the potential to elucidate the pharmacokinetics and pharmacodynamics of drug candidates and to provide the design principles for drug carrier engineering.

In gene technology, the quantum dot can be conjugated with oligonucleotide sequences (attached via surface carboxylic acid groups) may be targeted to bind with DNA or mRNA. Gene-associated drugs can be loaded within a QD core or attached to the surface of these nanoparticles through direct conjugation or electrostatic complexation by which QDs can protect the gene from degradation by nucleases. This property has been utilized for an assay of single nucleotide polymorphism (SNP). Due to concerns about long-term *in vivo* toxicity and degradation, QDs are currently limited to cell and small animal uses [30, 31, 77–101].

7. Conclusion

Recently nanotechnology-based gene delivery is one of the most attractive therapeutic methods for treatment of various diseases. In drug delivery, size and distribution of particles are critical parameters to target specific organs and tissues. Proteins (derived from their secondary structure) are suitable materials for drug/gene carriers due to their precise molecular sizes. An ideal nanoparticle formulation for a drug or gene carrier system can achieve long circulation time, low immunogenicity, good biocompatibility, and selective targeting.

Gene delivery involves viral and non-viral vectors. Viral vectors are having low loading capacity, large-scale manufacturing, quality control cost, and safety factor such as immunogenicity and potential oncogenicity. From the stability and safety concern, non-viral vectors have more efficiently passing the gene transfection through the biological barriers compared to viral vectors. Organic, inorganic, and various hybrid materials are used for the preparation of nanoparticles. Among these, polymeric nanoparticles have great therapeutic application

due to its wide range of sizes and varieties and can be used in sustained and targeted gene delivery for long periods. Biopolymers used for the preparation of nonviral vectors possess several favorable characteristics, such as high biocompatibility, low toxicity, good biodegradability, and abundant renewable sources, which can be used for efficiency delivery of drug/gene to the target site.

Choosing a suitable design of nanoparticle structure can increase gene transfection efficiency to overcome extracellular and intracellular transfection barriers: the blood stream, the cellular membrane, endosomes, and the nuclear membrane. Nanoparticle in gene delivery depends upon the nature of the polymer charge and its chain length. Furthermore, modifications in the nanoparticle by introducing ligands onto the surface can enhance localization and retention in specific target tissue, local delivery of agents to a large volume of tissues for better clinical application. However, biopolymer-based nanoparticle will become a tool in near future for the precisely targeted delivery of drugs and genes in many therapeutic fields, but toxicological issues and degradation products of nanoparticles are need to be considered before being applied into humans.

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