

Chapter 11

Nano-Based Drug Delivery Tools for Personalized Nanomedicine



Shama Parveen, Neera Yadav, and Monisha Banerjee

11.1 Introduction

Recent chemotherapeutics are not so effective; therefore, the development of new alternative strategies is necessary to fight lethal diseases such as cancer, HIV, hepatitis, etc. Nanotechnology provides the manipulation of compounds at nanorange and has the possibility to increase response, compatibility, and reduce the expense of diagnosis. The generative biomolecules such as DNA or proteins can be analyzed by red-shifted absorbance of gold nanoparticles or alteration in the conductance of nanowires and declination of a nano-cantilever. Different types of nanocarriers, for example, quantum dots and metal oxides have shown adequate benefits over conventional detections, tagging of intracellular, and image of the target site. Nanotechnology has also provided many routes which enable increased detection of target cells. Proteins and DNA are used over a point for care of tool. Chips (protein or gene) can be developed by using nanomaterials which could be attached to convenient nanofluidic tools for better diagnosis of diseases. Nanomaterials have design flexibility and small size and can be modified easily for compatibility to the target site. Interactions of nanosized materials with the biological system will benefit from knowing their effects and development of differently sophisticated nanodevices. Different nanocarriers are being used for delivery of compounds like inorganic nanocarriers (metal nanoparticles, graphene, mesoporous silica, etc.), lipid-based nanovesicles (liposome, nanoemulsion, solid lipid nanocarrier, etc.), polymer-based nanocapsules (dendrimer, ligand decorated nanoparticles, core-shell nanocapsule, etc.), and molecular complexes (protein nanocomplexes, cyclodextrin nanocomplexes, etc.) (Fig. 11.1). The main goal of nanobiotechnology is to use this technique

S. Parveen · N. Yadav · M. Banerjee (✉)
Molecular & Human Genetics Laboratory, Department of Zoology, University of Lucknow,
Lucknow, India

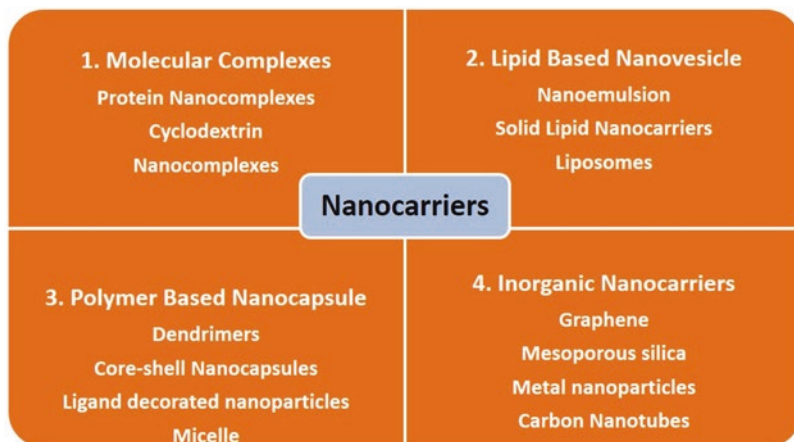


Fig. 11.1 Types of nanocarriers

to study how biological systems work and, in turn, can perk up existing nanotechnologies or create more beneficial nanomaterials.

11.2 Applications of Nanotechnology in Biological Sciences

11.2.1 Drug Delivery in Cancer

11.2.1.1 Gelatin Nanoparticle

A targeted drug-reaching system followed by reformed “decrease in size and hydrophobic/hydrophilic modification” was processed by the addition of gelatin nanoparticles (GNPs) with a drug Doxorubicin-Lactose (Dox-Lac). The effect of GNPs-Dox-Lac nanoformulation lasting in the circulatory system has a more effective accumulation toward the tumor region. Nanocarrier breakdown is stimulated by MMP2 (matrix metalloproteinase) present in tumor cells, and drugs are released to make an easy penetration in tumor tissues and cellular uptake. The pH change will result in dissociation of drug Dox-Lac in tumor cells, and free Dox (Mw 543 Da) will stimulate toxicity. GNPs-Dox-Lac promotes inhibition of tumor growth rate up to 90.4% by less in vivo toxicity, indicating that the activity was improved in the nanoform for hepatocellular carcinoma (HCC) (Liu et al. 2018).

11.2.1.2 PEGylated Liposomes

PEGylated liposome (PEG-LS) formulation mostly is used as a targeted drug delivery tool. The inflexibility and hydrophilicity of liposomal PEG corona membranes limited cellular uptake of the drug (Sadzuka et al. 2003). A new assembly for drug

release was developed on lipid-based self-assembled nanoparticles that are competent for increased cellular uptake, penetration in tissues, and release of drug. Researchers characterized a better bicellar nanoformulation with the addition of a PEGylated phospholipid which presented a remarkable change of physicochemical property in morphology, i.e., the bicelles (disc-shaped) equally distributed into very small (~12 nm) circular micelles. The converted lipid nanoparticles were defined as hyper-cell-permeable micelles (HCPMi). The HCPMi confirmed not only extended stability in serum but also higher cellular and tumoral uptake than the usual PEGylated liposomal system (PEG-LS) (Saw et al. 2017). HCPMi exhibited fast cellular intake and release of cargo in the cytoplasm of cancerous cells. Cancerous cells treated from the drug (docetaxel) loaded with HCPMi compared to the DTX (docetaxel) loaded with PEG-LS showed about fivefold decrease in viability of cells, showing best effectiveness in HCPMi intake and discharge of drug. HCPMi entered deeply into the tumor cells and found more uptake than PEG-LS as shown by in vivo tumor imaging analysis. Studies showed that in vivo treatment with HCPMi (DTX) increased tumoral uptake and remarkable tumor growth inhibition, about 70% tumor weight reduction in an experimental model (Saw et al. 2017).

11.2.1.3 Nanovaccines

Nanoformulation is useful in the development of cancer vaccines. Earlier PLGA (poly lactic-co-glycolic acid) nanoformulations were modified with toll-like receptor 7 agonist, imiquimod. These, immune adjuvant nanoparticles (NP-R) was coated with membranes of cancer cell (NP-R@M). These formulations were further modified by mannose moiety (NP-R@M-M). The resulting nanovaccine exhibited increased cellular uptake through dendritic cells that are antigen-presenting cells, which could be further stimulated for enhanced antitumor immune response by delaying tumor development and thereby act as a preventive vaccine (Yang et al. 2018). Combination of vaccine (NP-R@M-M) by cellular checkpoint-regulator treatment provides us with more effective therapeutic impact to treat established tumors. It would be helpful to design cancer nanovaccines, and the principle may apply to a broad range of tumor types (Yang et al. 2018).

11.2.2 *Phytochemical-Based Nanodrugs*

11.2.2.1 Nanocurcumin

The anticancerous activity of curcumin has been reported in different studies including pancreatic cancer (Vallianou et al. 2015). Curcumin is of immense importance it can not be utilized completely as medicine due to certain drawbacks such as low bioavailability, solubility and stability. For enhancing its therapeutic effect, a polymeric form of nanoparticles shows an ideal delivery method. Moreover, for improving the

potential of a drug, availability at target site, and circulation time in blood, modifications on the surface of nanocarriers by different macromolecules, such as chitosan and polyethylene glycol (PEG), hold tremendous potential. Curcumin loaded PLGA make it more effective by modifying the surface with chitosan and PEG can diminish the restrictions of native curcumin delivery for obtaining a maximum therapeutic response. *In vitro* studies of CNPs in pancreatic cancer showed higher cytotoxicity, increased anti-migratory, and ability to induce apoptosis in comparison to the native form of curcumin. Therefore, results of such studies can provide options for combating pancreatic cancer (Arya et al. 2018).

11.2.2.2 Nano-ginseng

Ginseng plant product having anticancerous activity was used in nanoformulation with ginsenoside Rb1/protopanaxadiol nanoparticles (Rb1/PPD NPs). The range of nanoparticles was about 110 nm with high drug loading capacity and stability in blood circulation, effective both *in vitro* and *in vivo* with better accumulation in tumor tissues and less toxic to normal tissue. The process of producing “nano-ginseng” formulation is easy, measurable, and economical (Dai et al. 2018).

11.2.2.3 Nano-quercetin

Quercetin is a potential chemotherapeutic drug. The drug was encapsulated in soluplus polymeric micelles by using the film dispersion method in order to improve its poor aqueous solubility and stability. In polymeric micelles (Qu-PMs) loaded with quercetin, more encapsulation efficiency and narrow size distribution led to complete drug dispersibility in water. Quercetin was in molecular form within the plasma membrane and was analyzed by X-ray diffraction (XRD) (Dian et al. 2014). Quercetin also formed intermolecular hydrogen bonding with carriers, analyzed by Fourier-transform infrared spectroscopy (FTIR). The stable formulation Qu-PMs exhibited significant sustained-release property. The pharmacokinetic study showed that absorption was also improved when compared with the free form of quercetin. Development of more appropriate formulations such as soluplus polymeric micelles were used for encapsulation of many drugs, i.e., poorly water soluble (Dian et al. 2014).

11.2.2.4 pH-Dependent Nanotools

siRNA-based nanotools in RISC (RNA-induced silencing complex) will undergo many changes in pH before showing their gene silencing mechanism (Nelson et al. 2014). They flood through the circulatory system, protrude into tumor tissue (pH 7.2–6.0), are introduced in the cell organelles such as endosomes with pH 5.0–6.5 and lysosomes (pH 4.0–5.0), and at last evade in the cytoplasmic

environment of the cell. Many pH-based formulations were developed by decreasing the pH. Due to a decrease in pH, ionizable polymers like polyacids, cationic lipid, and poly amino acids can protonate to change solubility and electrostatic interaction or break the acid-cleavable bonds like hydrazine, ketal, ester, and nanocarriers for the release of cargo (Zhang et al. 2018).

11.3 Disease Diagnostics

11.3.1 Magnetic and Electrochemical-Based Nanoparticles

HIV-infected cells have been detected by magnetic nanoparticles (NPs) in vitro (Dodd et al. 2001). Magnetic NPs can be formulated according to target cells. Separation of treated cells from other cells is through a magnetic separation device. The formulation of anti-HIV drug-loaded magnetic nanoparticles is applied with changing magnetic field. Magnetic NPs such as magnetite (Fe_3O_4) have been studied due to their specific characteristics like stability, biocompatibility, and sensitivity toward the magnetic field. Magnetic-based carriers for targeted drug delivery are mostly used due to their less toxicity, biocompatibility, magnetic resonance imaging, and higher magnetic saturation (Mahajan et al. 2012). Magnetic properties of these NPs are dependent on their synthesis. Co-precipitation method was used to synthesize Fe_3O_4 NPs. Size of the particles can be controlled by coating of polyethylene glycol (PEG) at the surface. Evaluation of biocompatibility of these nanoparticles was done by cytotoxic assay and analysis of cell cycle in MCF-7 (human breast cancer cell line) (Kansara et al. 2018).

11.3.2 Gold Nanoparticles

Hepatitis is a viral disease which can cause chronic syndrome and many other diseases. Nanoformulation also performs a good role in diagnosing hepatitis caused by hepatitis B and C viruses. Previous recognition tools did not yield much efficiency and susceptibility. New detection systems were developed by researchers that are based on the electrochemical method, with a test of gold-enhanced nanoformulation conjugation of magnetic beads. This technique is very sensitive and specific for recognition of the DNA sequences of hepatitis B virus (HBV) (Hanaee et al. 2007). Electric potential of immunosensors increases with an increase in the amount of HBV (Tang et al. 2004). The study provides support that immunosensors can be used in the future as a detection system for hepatitis B virus. Gold nanoparticles are a preferred delivery system for immunosensors because of their compatibility with antibodies. Nanosized gold protein chips were created to detect and analyze antibodies of hepatitis B and C at the same time. Formulation of gold nanoparticles

provides evenness and stability. Easier detection of antibodies is a result of stronger signals generated by gold nanoparticles (Duan et al. 2005). Significant amount of data shows that gold nanoparticles make the analysis and detection of hepatitis virus more successful.

Mycobacterium tuberculosis (MTB) bacteria cause the infectious disease tuberculosis that infects respiratory system (Shingadia and Novelli 2003) and considered as the second deadliest disease (WHO 2010). According to WHO report 2010, one third of the global population was infected by MTB, the strain which provides difficulty in detection and treatment. Gold nanoparticles detect MTB strands by DNA and RNA screening. MTB can be detected within few hours by nanoparticle probe (Veigas et al. 2010). Detection of MTB is based on pattern of color change due to aggregation of nanoparticles. The culture of MTB was important to analyze and detect bacterial strains. DNA fragments of MTB are broken down by electrochemical biosensors and are labeled by gold nanoparticles (Wang et al. 2013).

Nanotechnology is emerging as an advanced technique for the treatment of bone inflammation. Acton initiates as metallic nanoparticles offer a good surface for osteoblasts to connect to the bone. Metallic nanoparticles enable the growing of osteoblasts in a specific time interval and are helpful in successful osteo-regeneration. Nanocomposite materials induced specific protein for bone regrowth. Nanoformulated hydroxyapatite, the ceramic component of the bone, shows an increase in production of osteoblast (Tran and Webster 2009). Nanocomposites with carbon nanotubes also exhibit increasing osteoblast formation. Osteointegration process is accomplished in nanotubes by preventing the competition with other types of cells.

11.3.3 Nitric Oxide-Embedded Nanoparticles

Recently, the barrier of skin infection treatment has been overcome by nanotechnology. Nanoformulated therapeutic drugs are able to release the drug over a time period without any damage to the skin (Cevc and Vierl 2010). Nitric oxide-loaded nanoparticles are used in skin treatment, and the drug is released in a controlled time period. Different types of skin diseases were also treated by other formulations based on the same technique (Wang et al. 2008). Nitric oxide-loaded nanoparticles showed an improved response to treatment compared to the use of injectable needles for a skin infection (Englander and Friedman 2010).

11.3.4 Sunscreen

Ultraviolet (UV) radiation is a well-known cause of skin inflammation. The outer most layer, stratum corneum, provides protection to the body against harmful UV radiation. Sunscreens containing nanoparticles are used by humans to protect the

skin from UV damage. Zinc oxide (ZnO)- and titanium dioxide (TiO₂)-based nanoformulations are mostly used in the manufacturing of sunscreens. This nanoformulation reflects the harmful UV-A and UV-B radiations to the atmosphere in the form of heat. ZnO and TiO₂ inhibit UV photons from reaching the skin cells through absorption and reflection mechanism (Popov et al. 2010).

11.3.5 Personalized Nanomedicine

Personalized medicine is a healthcare strategy that involves development of specific treatment at the individual level on the basis of their genetic makeup, phenotype, and environmental conditions (Ge et al. 2014). These days, use of nanomedicines is increasing exponentially and providing a platform for the treatment of every patient or group of patients (cohort) on the basis of a specific requirement in their genome (Zhang et al. 2012). Nanomedicines are used as therapeutic agents for personalized treatment, and their application is considered for a better treatment by pharma companies. Different types of nanomedicines exist, i.e., liposome, polymeric nanoparticles, magnetic-based nanoparticles, and micelles. All show advantages and improve the effect of conventional therapy (Fig. 11.2). These advantages are due to their small size, different nature, protected encapsulated material, controlled release

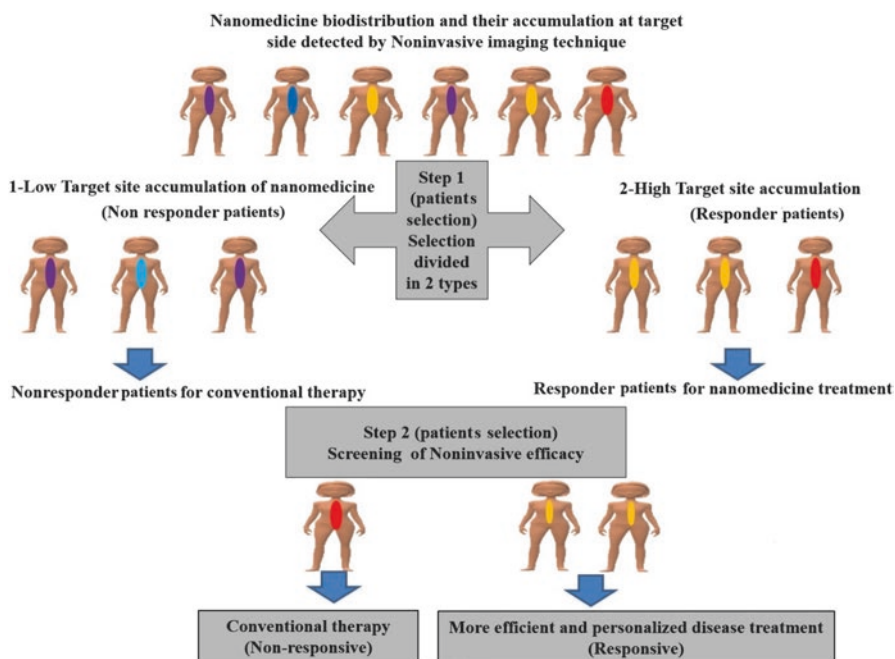


Fig. 11.2 Selection of patients selection after treatment with nanomedicines

for targeted delivery, increased therapeutic effect, and reduced side effects (Fornaguera and García-Celma 2017).

11.3.6 Personalized Nanodevices

Point of care (P-o-C) provides a beneficial platform for personalized medicine. It is useful in early diagnostic and more sensitive toward the detection of biomarkers in treatment monitoring. The infectious diseases can be controlled by a personalized diagnostic method by using P-o-C technologies in developing countries and environment where resource is limited. The liability of disease diagnostic protocols can be improved by using multiplexed assays by analyzing multiple biomarkers. Multiplexing of assays provides the multivariate analysis of huge number of the patient samples at one time (Romeo et al. 2016). In this way improved determination diagnosis of a particular biomarker of the disease can be achieved. The much more diagnostic power of multiplexed point-of-care biosensors is generated which are portable, cheap, and user-friendly devices. The first device of such kind, i.e., multiplexed volumetric bar-chart chip, was reported for analyzing protein biomarker of cancer (Song et al. 2012).

11.3.7 Microfluidic Channels on Bar Charts of Glass Chip

Channels contain covalently attached antibodies on the surface of glass walls with dye and pre-loaded hydrogen peroxide for an enzyme-linked immune sorbent assay (ELISA). The principle of V-chip is based on the measurement of oxygen that is generated on the chip as a result of reaction between hydrogen peroxide and catalase. The concentration of oxygen is directly proportional to the target analyte. The excellence of this inked bar result is based on the concentration of particular ELISA target in every well. Complete unification of the device provides results without any data processing steps. The V-chip method is rooted in the expression of different biomarkers such as including estrogen receptor, human epidermal growth factor receptor 2, and progesterone receptor (Song et al. 2012).

11.3.8 Proteinticles

Proteinticles are engineered nanoscale protein particles which are very helpful in modifying different properties based on size and surface area of many conventional things. The detection of more than one biomarker in serum is also possible through

multiplexed viral detection (Chen et al. 2015). The method of disease detection is imperative in diseases like AIDS and hepatitis. This protocol is based on lateral flow assay (LFA) for protein nanoformulation. Proteinticles have better biodegradability and biocompatibility and are easily accessible to surface modifications (Lee et al. 2015). These nanoformulations are synthesized by using different proteins like gelatin, gliadin, elastin, zein, legumin, soy protein, albumin, and milk protein. Different methods used for the formulation include desolvation, emulsification, electrospray, and coacervation. Characterization parameters of these nanoforms comprise size of particle, morphology of particle, their surface charge, loading of drug, entrapment of drug, and structure of particle and drug release in vitro. Application of administration route of protein nanoparticles through different methods has been examined by renowned researchers (Verma et al. 2018).

11.3.9 Aptamers

The aptamer is an oligonucleotide-based nanoformulation. Advance characteristics of aptamer show high-binding affinity and specificity with target molecules in both intra- and extracellular environment. It works as an agonist or antagonist in a biological system. In recent years, several aptamers are used in the detection of disease, and curative purposes are under development to identify different molecules of HCC (hepatocellular carcinoma). The aptamer has been to increase the effect of conventional chemotherapies and reduces the growth of HCC cells in vitro. Aptamer induces antitumor activity and cell death in vivo. Overall data show that aptamer has reduced toxicity levels, and it may provide safer platform in the field of personalized medicine (Ladju et al. 2018).

11.4 Conclusion

Nanoscale materials allow nanodevices to enter new scientific and technological frontiers in disease diagnosis and treatment. Advance nanoscale characteristics of these devices especially their increased surface to volume ratio afford high-sensitivity and low-response times.

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