Chapter 19
Application of Nanotechnology in Diagnosis, Drug Dissolution, Drug Discovery, and Drug Carrier

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Contents

19.1 Introduction

In healthcare and medicine, diagnosis of a disease is a very critical step. Diagnosis is a multistep process which includes patient's history, examination, and assessment of laboratory reports. Diagnosis should be fast and accurate, having very low chances of false-positive results with a high degree of sensitivity and specificity. Fast and precise diagnosis aid earlier detection of disease and is helpful in better prognosis. Since the invention of stethoscope, scientists have endeavored to develop an advanced method of diagnostics for rapid and accurate diagnosis of diseases.

Nanotechnology (NT) in the field of molecular diagnostics extends the limits to the nanoscale and explores one more dimension of microfluidic/lab-on-a-chip technology. It becomes so fast and easier to sense the presence or activity of certain

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R. Prasad et al. (eds.), *Nanobiotechnology in Bioformulations*, Nanotechnology in the Life Sciences, https://doi.org/10.1007/978-3-030-17061-5_19

compounds through labeling or tagging of certain nanoscale particles. Application of NT in the field of biomedical diagnostics comes under nanodiagnostics (NDs) which provides new insights for point-of-care performance in personalized medicine (Krukemeyer et al. 2015). NDs offers great advantage over the traditional methods of diagnosis such as:

(i) It provides rapid testing protocol and can be performed even in the doctor's chamber and thus provides early start of the treatment and possibly less damage to the patients.
(ii) Being highly sensitive, very small quantity of samples is required.

The very first step in NT-based testing is the detection of signals generated through the binding of labeled/tagged probes to the target biomolecules which produce characteristic signals. The probe may be quantum dots (QDs), nanoshells, and metallic nanoparticles (Challa and Kumar 2007).

Detection of biomarkers in laboratories needs sophisticated automated analyzers, too much time, and high costs which can be substituted by robust, faster, and economical devices. Nanoscale-fabricated structured devices provide diagnostic results available at the patient's bedside, i.e., point-of-care diagnosis (Mascini and Tombelli 2008).

This chapter explores the nanodiagnostics in use or in different phases of development.

19.2 Nanotechnology in Medical Diagnosis

Nanotechnology has revolutionized the era of diagnostics by overcoming the drawbacks like poor sensitivity, specificity, and reproducibility in conventional diagnostic methods like bioassays, biosensors, and imaging (Prasad et al. 2016). Nanotechnology-fabricated structured devices are elegantly small and prepared by the engineering of systems at the atomic or molecular scale. These devices can recognize very low concentrations of disease biomarkers compared with traditional tools. Application of nanotechnology in medical diagnosis includes diagnosis, prevention, and treatment (Rajasundari and Hamurugu 2011; Geho et al. 2006). Nanostructures have been successfully used in in vitro diagnostics which have made the diagnosis rapid, simpler, and more precise than earlier traditional methods. The main goal of nanotechnology is to focus on development of novel biomarkers for disease diagnosis and construction of nanobiosensors using ultrasensitive nanomaterials such as carbon nanotubes, nanoparticles, and so on. The use of nanomaterials in nanodiagnostics significantly improved the method of diagnosis in techniques such as immunohistochemistry (IHC), genotyping, cancer detection, and biomarker detection. A variety of materials are used to construct diagnostic nanodevices by manipulation of matter at the nanoscale.

19.2.1 Nanomaterials and Nanodevices for Medical Diagnosis

Nanomaterials used in medical diagnosis are very small in size and possess high surface to unit volume ratio due to which they show higher chemical reactivity, increased tensile strength, and faster electrical and magnetic responses (Jackson et al. 2017). The usefulness of nanoparticles and their unique properties are due to their size similar to that of biomolecules such as proteins and nucleic acids which makes them suitable for real-time interaction with biomolecules inside the cells. Nanoparticles can be synthesized in a number of ways. The common method of nanoparticle synthesis includes physical, chemical, and biological synthesis (Prasad 2014; Prasad et al. 2016). Generally, nanomaterials are produced by top-down and bottom-up techniques. In the top-down approach with the help of mechanical, chemical, or other form of energy, a bulk material breaks into smaller pieces. The bottom-up technique is based on chemical reactions in which materials are synthesized by allowing the precursor particles to grow in size (Chan and Kwok 2011). Biological synthesis of nanoparticles is ecofriendly and performed by manipulation of microorganisms of biomedical interests (Prasad 2017; Prasad et al. 2016, 2018; Aziz et al. 2015, 2016, 2019; Jackson et al. 2017). Nanomaterials of biomedical interests can be classified according to their structure, chemical composition, and applications. The structural basis of classification includes nanoparticles, quantum dots, nanotubes, dendrimers, and micelle formations (Nasimi and Haidari 2013; Prasad et al. 2017a). Nanomaterials can be either organic or inorganic. Inorganic structures include metal oxide nanoparticles, semimetal oxides, metal nanoparticles whereas carbon structures (nanotubes, graphene, fullerenes) and organic structures include polymer nanoparticles or dendrimers (Choi et al. 2014). The classification of nanomaterials on the basis of chemical composition is not universally acceptable as most of the nanostructures are hybrid in nature or a combination of both inorganic and organic substances as organic substances stabilize the functions of nanomaterials. Some of the nanomaterials useful in the fabrication of nanostructured devices are nanotubes, nanocrystals, nanobots, nanowires.

19.2.1.1 Nanotube

Nanotubes are cylindrical carbon molecule of 0.5–3 nm in diameter and 20–1000 nm in length and are very useful in biomedical science because of their unique properties such as extraordinary strength and high conductance of electrical and thermal energy. The reason for high conductance is the sp^2 hybridization state of carbon, e.g., fullerene, an allotrope of carbon. Carbon nanotubes have been implicated in combination with other gold nanoparticles and silicon nanowires for the detection of oral cancer and lung cancer (Beishon 2013; Shehada et al. 2015).

19.2.1.2 Nanocrystal

They are crystalline substances having at least one dimension less than 1 μm. Electrical and thermodynamic properties of nanocrystal vary with size. In the range of 10 nm, nanocrystals in the space between them show loose microstructures – nanopores. An Ireland-based pharmaceutical company – Elan Pharma International Limited – developed nanocrystals for nanoparticle drug formulation. Nanocrystals of 2–9.5 nm size have been used to improve solubility of poorly soluble drugs and in labeling of breast cancer markers (Kumar and Vijayalakshmi 2006; Roco et al. 2017).

19.2.1.3 Nanobots

Nanobots are also known as nanorobots. They also fall in the category of nanosized materials. They have been employed for early diagnosis of the disease as well as targeted drug delivery, diabetes monitoring, and in other applications of healthcare mostly in cancer. Nanobot dentifrices are one of the types of nanobots (dentifrobots), used in the identification of pathogenic bacteria in the mouth. When used in the form of mouthwash or toothpaste, they spread over the subgingival surfaces and metabolize trapped bacteria or organic matter into odorless vapors (Shetty et al. 2013).

19.2.1.4 Nanowires

Nanowires (NW) are of nm size and made up of carbon nanotubes or silicon. Being smaller in size, slight change in the electrical properties of it due to binding of additional molecule could be detected. Antibodies could be loaded over its surface as detectors. When the antibody binds to target biomolecules, it undergoes conformational changes which can be detected as signals. When several nanowires are loaded with different antibodies over the surface assembled in a single device, they can work as detectors for cancer (silicon nanowires in field effect transistors (SNW-FET)) (Reimhult and Höök 2015; Lyberopoulou et al. 2015; Takahashi et al. 2015).

19.2.1.5 Quantum Dots

As the name indicates, quantum dots are crystals in the form of small dots of 2–9.5 nm in size. They are constituted with inorganic materials having fluorescent properties. When low energy light falls on it, quantum dots emit fluorescent light. The color of the emitted light depends on the size of dot. On excitation, quantum dots of different size when embedded in a given microbead show spectra of distinct pattern of colors. Quantum dots are very sensitive as even in a general excitation they can produce broad spectra and could be used in image-guided surgery, molecular diagnostics, and genotype determination (Rajasundari and Hamurugu 2011).

19.2.1.6 Nanocapacitor

A capacitor is an electrical device which is formed by the combination of two electrode plates and an insulating material sandwiched between the gaps of plates. If the gap between plates is a few nanometers, nanocapacitors are formed. The capacitance can be measured from the area of plate, distance between plates, and the dielectric constant value of the insulating medium. Nanocapacitor-based devices work on the principle that when a target molecule comes in contact with the dielectric material the value of dielectric constant of the medium changes significantly and thus capacitance will be also changed and the change in capacitance could be measured. When using this device, there is no need for prior labeling of the samples. A limitation of this method is that the quantity of sample should be enough to create appropriate change in dielectric constant of the medium. Transparent nanocapacitors are developed by Kang et al. (2003) to monitor dielectric and optical behavior of biomolecules. Silicon nanolithography was used to create 50 nm gaps between the electrodes (Kang et al. 2003) of a nanocapacitor.

19.2.1.7 Nanoparticles

As the name indicates, nanoparticles are the particles of nm in size. They possess at least one of the diameters <100 nm (Buzea et al. 2007). A number of varieties of nanoparticles are available. The difference in varieties of nanoparticles is due to difference in their shapes, materials, and sizes. The nanoparticles occur in different shapes such as dot, sphere, star, prism, and rod. Nanoparticles are synthesized using metals or polymers. Gold nanoparticles (GNPs) are the best example of metallic nanoparticles (Boisselier and Astruc 2009; Fu et al. 2010). GNPs can be detected by Raman scattering, fluorescence, optical absorption, magnetic/atomic force microscopy, and electrical resistance measurements (Marzán 2006).

19.2.1.8 Nanotechnology-Based Chips: "Nanobiochips"

Nanobiochips are the most advanced application of nanobiotechnology. It is also called Lab-on a-chip. The size of the nanobiochip is much smaller than the size of a cell. The chip is made up of biologically active artificial structures. The microarrays are spread in a very small area over the solid surface of chip which enables to perform several biochemical tests simultaneously. Therefore, identification of novel biomarkers can be verified using multiple tests. Nanobiochips are generally used in analytical separations and identification of biomolecules such as nucleic acids and proteins. Implementation of lab-on a-chip on PCR and other in vitro diagnostics shows its substantial impact in the field of biotechnology (Bahadorimehr et al. 2010; Sharma and Hashim 2013). Lab-on a-chip establishes a very simple method of in vitro diagnostics in which a number of cantilever biosensors can be used together on a single array. The device can be developed in the most advanced

manner by the integration of analytical technique and signal extraction system. Surface plasmon resonance (SPR) nanobiochip expresses the interaction of biomolecules in terms of affinity. It is useful in the study of association or dissociation affinity of ligands with its binding partners. The device is very simple, rapid, and advanced than earlier available affinity measurement methods. Very low sample size is required, and there is no need of tracer for labeling. Advanced application of SPR nanobiosensor device has been seen in the field of proteomics, where the sensor is combined with matrix-assisted laser desorption/Ionization time of flight mass spectrometry (MALDI-TOF) MS. This combination is very useful for the interaction study of biomolecules if one molecule is known. If there are varieties of proteins, then it will be very difficult to identify the interacting molecule. However, this technique permits to determine the interaction of molecule from mixture with sensor (Zhang et al. 2005; Marzán 2006).

In future, if a combination is prepared by the integration of nanofluids, nanobiosensors with biochip, the device will be more efficient to identify a number of biomolecules and their concentration. Therefore, nanobiochip offers new opportunities for innovative point-of-care diagnosis.

19.2.1.9 Biosensors and Nanobiosensors

Biosensor is an analytical device which detects the presence or concentration of biological product. It is a combination of a biorecognition element such as enzymes, antibodies, nucleic acids, or whole cell with a physiochemical transducer and an electronic reader device.

Principle of Biosensor

When a biorecognition element binds with a biological analyte, a biological event is performed on the interface and a signal is generated. The generated signal is sensed by transducer and converted into electrical signals which undergo amplification by a detector circuit. The intensity of signal directly denotes the concentration of chemical species (analyte). Signal processing by computer software into meaningful physical parameters describes the process being investigated (Barone et al. 2005; Huang et al. 2009; Lueke and Moussa 2011). With the progress of nanobiotechnology, biosensors have also been modified and fabricated at nanoscale for construction of nanobiosensors. Due to their wider applications, nanobiosensors have created the most important place in nanodiagnostic world. Nanobiosensors are very useful due to its portability, sensitivity, reproducibility, and low sample requirement for the detection of analyte. It is very simple to use and generate results quickly. The main aim of biosensor is to detect any biophysical or biochemical signal associated with the specific disease or disease-causing organism at the level of a single cell or molecule. In molecular diagnostics, integration of nanobiosensor with lab-on-a-chip has great potential for detection of disease-specific metabolites, pathogens, and cancers from a variety of samples. Detection of circulating tumor cells, pathogens, nucleic acids, and proteins not only just

facilitates early diagnosis of disease but also creates new horizon for drug discovery and development. In the field of medical diagnosis, integration of nanobiosensors with other medical instruments creates new dimensions for emerging nanodiagnostics. Examples of nanobiosensors are nanowire-based sensors, cantilever biosensor, and ion channel sensing.

Nanowire-Based Sensors

Nanowires are the key component for the fabrication of nanowire-based sensors. The surface of nanowires is coated by biomolecules such as nucleic acids, proteins, or bacteriophages. Nanowires are fibril-like structures of definite length and diameter 10 nm or less. Surface properties of nanowires can be easily modified virtually by coating biomolecules as biorecognition elements over its surface which make them analyte independent. Nanowires are very sensitive for signal detection as chemical binding events change its conductance in a real time and quantitative fashion.

One-dimensional nanowires such as nanotubes and nanosprings can transport electrons efficiently and undergo the process of optical excitation which makes them appropriate nanomaterial for fabrication of ultrasensitive high-density nanoscale devices. Because of their unique properties, minor perturbations influence the electrical properties of nanowires. Carbon nanotubes are equipped with unique properties such as higher surface to unit volume ratio, high ductility, efficient electron transporter, and electrocatalytic properties. Therefore, carbon nanotubes have been found to be excellent material for the development of enzymatic nanobiosensors. Wang et al. (2003) used carbon nanotubes/Nafion electrodes for the immobilization of enzyme glucose oxidase for the detection of glucose. The combination of carbon nanotube/ Nafion was prepared over the surface of an electrode by dispersing the solubilized form of carbon nanotubes in a solution of Nafion. The constructed nanobiosensor was efficient enough to improve the intensity and quality of signals even at a very low potential with fast response time. In the future, multiplexed nanobiosensors can be developed by using an array of highly ordered nanowires and their combination with multiple biorecognition elements. Small size and robustness make nanowire biosensors very efficient in in vivo as well as in vitro sensing and hold great promises in healthcare diagnostics (Cui et al. 2001; Wang et al. 2003).

Cantilever Biosensors

At nanoscale, micromechanically generated cantilevers are found to be an excellent transducer for the fabrication of cantilever-based nanobiosensors. Bending of cantilevers of more than 100 nm due to sensing interaction on surface is detected by a laser. The high sensitivity of microcantilever-based sensor created a very good platform in label-free and less time detection. Microcantilever biosensors can detect processes in both static and dynamic modes. In the static mode, asymmetric chemical absorption on one surface of cantilever results in bending due to stress in the

chemical adsorption, and the bending can be measured. In the dynamic mode, the frequency of microcantilever is changed due to mass adsorption over its surface, and the shift in resonating frequency can be measured. Cantilever biosensors have been employed widely for wider detection of ions, vapors, antibiotics, and biomolecules such as DNA, proteins, and a number of disease-causing pathogens. The change in mechanical sensitivity of cantilever nanobiosensors is due to change in molecular interactions with surface in static mode and lateral interactions such as steric hindrance, electrostatic forces, structural change within the layer of molecules. In the static mode, high sensitivity to structural changes is very useful to measure binding of biomolecules attached to the surface of microcantilever. Bergar et al. proposed a model in which a cantilever biosensor is combined with an atomic force microscopy (AFM). In this model, the cantilever biosensor with a tip can detect and analyze at nanoscale. Therefore, cantilever biosensing system will be more efficient for pathogen detection, cancer detection, genotyping, and SNPs (Ziegler 2004; Fritz 2008).

It has been observed by several research groups that microcantilevers can act as signal transducers for different domains such as heat, temperature, stress, and electromagnetic field. At present, because of their high flexibility and low sample size requirement without any previous treatment, cantilever-based nanobiosensors are employed in the field of genomics and proteomics extensively.

Ion Channel-Based Sensing

In biological system, ion channels are formed by the interaction of membranous protein molecules of cells. The size of the ion channels may be in the range of nm or lesser. They are filled with water molecules. Ion channels are selectively permeable, i.e., control the in- and outflow of ions. Therefore, they play a very crucial role in the regulation of electrical and biochemical activities of cells. The novel nanobiosensors are developed which are based on the approach that on binding of biorecognition elements such as enzymes, nucleic acids, and proteins to a population of ion channels, their conductance changes. Nanobiosensors fabricated on this approach can be used for most of the receptors, antibodies, and nucleic acids. The device is very flexible and can sense proteins even at a picomolar concentrations. After reducing its dimensions, the sensor which is actually an impedance element can be fitted into a microelectronic circuit as an integral part. The switch of the ion channels contains a gold electrode which is linked to the membrane lipid which harbors gramicidin ion channels attached to antibodies. The structure of the lipid membrane creates a reservoir between the gold electrode and membrane. The movement of ions results in the dimer formation, and conductance is changed. The change in conductance depends on the number of dimer formation. So, it is very simple to calculate the number of dimers formed as a result of change in conductance. The generated signals can be measured using a reader device. The wider application of the device includes detection of blood, media, nucleic acids, proteins, viruses, and compounds of low molecular weight (Krishnamurthy 2010; Holzinger et al. 2014).

19.2.2 Nanobiosensors for Glucose Detection

Globally, diabetes is a major concern. There are a number of advanced versions of insulin, though patients are suffering from worst outcomes of diabetes. In diabetic patients, blood samples are used for the detection of glucose level. In this situation, there is a need for a diagnostic method which is simple, easy to perform, noninvasive, and sensitive enough to meet the requirements of point-of-care diagnosis. Clark and Lyons developed the first glucose biosensor in 1962. The developed sensor was originally an amperometric glucose biosensor. The sensor was able to detect oxygen pressure. A number of biosensors have been developed for the detection of glucose molecules (Cash and Clark 2010).

19.2.2.1 Electrochemical Biosensors for the Detection of Glucose

In electrochemical biosensor, glucose oxidase is the enzyme which breaks glucose into gluconic acid and hydrogen peroxide (H_2O_2). Under the influence of external oxidation potential, H_2O_2 emit protons, O_2, and electrons. The monitoring signal is directly proportional to the concentration of glucose (Taguchi and Ptitsyn 2014). This approach is not very successful as few electrodes damage the cells and sensitivity is restricted to the quantity of active immobilized enzyme. The sensor was improved using entrapment of enzyme in polymers and covalent bonding of several nanostructures with Glucose oxidase enzyme. The quality of generated signal is improved by the integration of carbon nanotubes, graphene, and metallic nanoparticles in the original design of biosensor (Chen et al. 2007).

19.2.2.2 Optical Biosensors for the Detection of Glucose

Optical glucose biosensors are fabricated to nanoscale by using ultrasensitive nanostructures. Fluorescence resonance energy transfer (FRET) is the technique on which the device works. When a radiation of particular energy falls on a photoluminescent material, its molecules become excited to a higher energy state. When these molecules return to their ground state, they emit the radiation of low energy. This phenomenon is known as fluorescence which creates the platform for fabrication of fluorescent glucose biosensors. This sensor is based on the principle that the signal generated by the detection of glucose is converted into correlated fluorescent signal. Nanomaterials are very good transducer for the conversion of signal. FRET is a sensitive analytical technique and nowadays frequently used in fluorescence biosensing systems (Chen et al. 2017).

19.2.2.3 Nanoparticle-Based Biosensors for the Detection of Glucose

Nanoparticles are extensively used for the fabrication of nanobiosensors due to their small size, catalytic property, high unit to volume surface ratio, and high degree of sensitivity. They are frequently used for labeling of biomolecules and adsorption. They improve the performance of electrochemical and enzymatic biosensors by rapid transfer of electrons and make the process fast by shortening distance between enzyme and electrodes. Nanobiosensors based on surface-enhanced Raman spectroscopy (SERS) are widely used for glucose sensing. Direct concentration of glucose was detected for the first time by integration of silver nanoparticles in biosensor design. In many varieties of glucose nanobiosensors, nanoparticles are immobilized on electrodes. Metallic nanoparticles and quantum dots were used for this design. On the surface of single electrode, arrays of electrodes can be created by arranging the nanoparticles in ordered structures. These arrays improve the signal to noise ratio and detection limits (Garcia and Merkoci 2016).

19.3 Nanomaterials and Nanodevices for the Diagnosis of Infectious Diseases

Nowadays, PCR, ELISA, and sequencing are the main techniques used for the detection of disease-causing pathogens. These techniques are expensive and time taking and require large sample size, and there is a need for the expert to perform the PCR and sequencing techniques. Contrary to this, nanodiagnostics are found to be a very useful approach in pathogen detection. The technique is very simple to use, rapid, and cost-effective and provides reproducible results, and there is no need for expert to perform the test. Nanodiagnostics are well suited to meet the requirement of point-of-care diagnosis. Nanotechnology uses nanoparticle-conjugated antibodies as targeted ligands for binding with the molecules expressed on microbial surface such as proteins and lipids. This is the basis for the development of nanotechnology-based immunoassays.

Gold and silver nanoparticles are widely applied in conjugation with affinity ligands for microbial detection. To develop colorimetric assays, nanoparticles have been also used in conjugation with short nucleic acid sequences to bind complementary sequences present in pathogens. Quantum dots and carbon nanotubes have been also used for the DNA detection of bacteria and viruses. Several immunoassays have been developed using nanoparticles such as fluorescent nanoparticles, metallic nanoparticles, and magnetic nanoparticles. High sensitivity and photostability of fluorescent nanoparticles make them suitable for use as a probe to label different biological targets (Thévenot et al. 2001).

Fluorescent nanoparticles have been evolved as a new strategy for real-time diagnosis of the diseases. They are mainly used for imaging and sensing. Quantum dots (QDs) are fluorescent nanostructures of 1–10 nm in size. They fall in the category of semiconductor nanomaterials (NMs).The unique properties of QDs such as

photostability and bright fluorescence can be employed successfully in NDs. The inherent properties of QDs can be easily configured through the change in their size and composition (Peeling and Mabey 2010).

Fluorescent signals of QDs can be amplified by the packing of several QDs inside an individual NP. The arrangement is called quantum dots nano beads (QDNBs). QDNBs were used in a dot-based immunoassay for the detection of HBV. In this assay, surface antigen of HBV (HBsAg) was immobilized on a porous surface of polyvinylidene fluoride (PVDF). QDNB-conjugated antibodies were used as probe. Probes were allowed to incubate with antigen. When a UV light emitted through UV lamp falls on the PVDF surface, combination of conjugated antibody-antigen flourishes in the form of dots. The device is simple to use and sensitive enough to detect picogram concentrations of HBsAg (Li et al. 2018; Yu et al. 2015).

Generally, gold and silver NPs are used in nanodiagnostics. Gold nanoparticles (AuNPs) were the first nanomaterial used in 1996 for DNA detection. AuNPs have the unique property of color change (on excitation through electromagnetic radiation) which makes them a suitable candidate for the fabrication of nanodevices and/or use in NDs (Fuente and Jesus 2006).

Gold nanorods are elongated nanoparticles and received a lot of attention due to their tunable optic properties. Gold nanorods have been used in the diagnosis of human immunodeficiency virus (HIV) with the help of hyper-Rayleigh scattering (HRS) spectroscopy. Oligonucleotide probe of 145 mer was used as a probe to detect 100 picomolar of target DNA with single base mismatch. The detection was based on the change in the intensity of HRS. HRS spectroscopy was also used for the detection of Hepatitis C virus (HCV) using gold nanoparticles. To detect the HCV, gold nanoparticles were conjugated with single-stranded RNA of HCV tagged with Rhodamine 6G. These particles are very sensitive for the detection of up to 80 picomolar concentration of HCV RNA with single base mismatch (Draz and Shafiee 2018; Fazio et al. 2016).

Application of magnetic nanoparticles in nanodiagnostics is based on the fact that when an external magnetic field is applied, separation and detection of magnetic nanoparticles bonded with target is enhanced. Detection of malaria in early stage using conventional approaches such as real-time PCR is very challenging due to the presence of very low concentration of parasite in the blood. The application of magnetic nanoparticles is seen in the early diagnosis of malaria through the magnetic-enriched SERS. In this approach, β-hematin crystals (an equivalent of hemozoin granule biomarker in malaria) were detected through magnetic nanoparticles. In the early diagnosis of malaria, by applying external magnetic field, the detection limit can be improved as low as 5 nM of β-hematin crystals ≈ 30 parasites/μL of blood samples (Yuen and Liu 2012; Kumvongpin et al. 2016; Chen et al. 2017).

In another approach, to improve the sensitivity of assay, microfluidics-integrated nanodevices have been used for the enrichment of pathogens or their DNA. The method of enrichment significantly improved the sensitivity of the assay. Therefore, very low concentration of pathogens could be detected from blood samples using conventional diagnostics (Warkiani et al. 2015).

To prepare an advanced nanodevice-based diagnostic platform, many techniques are integrated with nanotechnology, i.e., integration of microfluidics with lab-on-a-chip. The device is very useful in the diagnosis when a patient is infected with more than one strain/parasite (Cabibbe et al. 2015; Dixon et al. 2016). Lab-on-a-chip in integration with other techniques can be used for the detection of multiple tests simultaneously. It reduces cost, time, and sample size.

To detect the blood-borne infections caused by HBV, HCV, and HIV, a high-throughput and multiplexed nanodevice was developed by the integration of quantum dots and microfluidics. The device can precisely detect multiple infecting agents from serum volume as low as 100 μL. The assay can be performed in less than an hour with the sensitivity more than 50 times from the currently available US Food and Drug Administration (USFDA)-approved platforms (Klostranec and Chan 2006). Another nanodevice based on silica membrane was developed to detect envelop glycoprotein gp120 of HIV. Human cell surface receptor CD4 was coated on the surface of membrane. The system is useful to study the real-time interaction between host cell surface receptor CD4 and gp120 of HIV (Cheng et al. 2012).

Immunofluorescence-based integrated nanodevices have been successfully used in the detection of mycobacteria in the sputum. In this device, a microtip sensor in combination with genus-specific antibodies was used for the concentration of the pathogen using electric field and streaming flow technique. The sensitivity of the assay was equivalent to the PCR, but there was no need for additional steps like culture or amplification because it can be finished in 25 min (Yeo et al. 2009; Kim et al. 2012).

When a charged or uncharged dielectric particle is subjected to a nonuniform electric field, an external force is exerted on the particle. In the presence of an electric field, all particles exhibit dielectrophoretic activity irrespective of their charge. The property of dielectrophoresis was used in combination with capillary action to enrich the extracellular DNA on nanostructured tips. In the first step, dielectrophoresis was applied for attraction of DNA and other molecules near the nanostructured tips followed by enrichment of DNA onto the nanotips through capillary action. The detection limit of this method is nearly 6.7 pg/mL of DNA; however, the approach is not very useful for pathogen detection in small volume of samples (Yeo et al. 2009).

19.3.1 Nanostructures in Cancer Diagnosis

Cancer is a malignant tumor and responsible for high mortality rate worldwide. Lung cancer, liver cancer, colorectal cancer, stomach cancer, and breast cancer are placed in the list of the World Health Organization (WHO) in 2015 as top 5 cancer types responsible for maximum deaths across the world. To control the stage transition from curable benign form to advanced metastasis stage, diagnosis of cancer in early stage is required. Early detection of cancers is very important for the onset of treatment and prevents further disease-associated complications in the patient's body. In short, early detection leads to better prognosis. Application of nanotechnology in cancer diagnosis reduces the cost and time of diagnosis (Prasad et al. 2017b). A variety of nanomaterials such as gold nanoparticles, silicon nanowires, quantum dots, carbon nanotubes, and graphene have been successfully used to detect

different cancer types. Silicon nanowire (SNW) alone or in combination with field-effect transistors (FETs) has been used for the detection of prostate-specific antigen (PSA) and 8-hydroxydeoxyguanosine (8-OHdG) biomarkers in prostate cancer (Gao et al. 2014). FET-SNW and zinc oxide nanowires (ZnONWs) have been used for the detection of single-stranded DNA (ss-DNA) and micro-RNA (mi-RNA) involved in the progression of different cancer types (Lu et al. 2014). Electrochemical nanotubes have also been used for the detection of other prostate cancer biomarkers such as platelet factor-4 and interleukin-6 (Azmi et al. 2014; Chikkaveeraiah et al. 2009). In case of aggressive prostate cancer, the expression level of cancer-testis antigen (CTA) RNA was measured using nano counter analysis system – a nanowire technology. This technology can be fabricated into sensor chip for a simultaneous detection of panel of biomarkers in specific cancer type (Takahashi et al. 2015). A single nanoparticle dual-mode MRI probe was developed by using unique property of quantum dots. Coating of paramagnetic lipid and silica nanoparticles on quantum dots can provide information about the molecules involved in tumorigenesis (Swierczewska et al. 2011). Detection of some volatile organic compounds in breath samples may be an indicator of cancer. In this concept, carbon nanotubes and silicon wires were used to detect these compounds in lung and gastric cancers (Shehada et al. 2015). Gold nanoparticle-modified graphene oxide-based DNA biosensor was used to detect two breast cancer biomarkers – human epidermal growth factor receptor-2 (HER2) and the cell surface protein CD24 (Saeed et al. 2017). HER2 expression was also measured by immunohistochemistry (IHC) technique by using quantum dots-conjugated trastuzumab (a monoclonal antibody against HER2 expression). Hybridization chain reaction (HCR) is a method of signal amplification. The method has been used with quantum dots-Ru complex dyads to enhance the sensitivity of detection and cellular imaging (Zhang et al. 2018). Scientists reported that micro-RNA in circulation may have potential to be used as a noninvasive cancer biomarker. The study of Li et al. justifies the report. He used the quantum dots-based microarray to test the lung cancer patients and found the presence of significantly different micro-RNA such as smiR-16-5p and miR-17b-5p in cancer patients than in controls (Fan et al. 2016). Besides the nanoparticles, nano-based contrasting agents have also been used for detection of several cancers through imaging modalities such as MRI, PET, and so on. Nanoparticles are mainly used in imaging and point-of-care technology.

19.3.2 Cancer Detection Through Imaging

In imaging, several contrast agents are used for the detection of tumors. Bonding of contrast agents to the surface ligands of nanoparticles may be used as indicator biomarkers of tumors. However, screening of appropriate tumor binding ligand is very challenging. Nanoparticles as contrasting agents have several advantages over the conventional contrasting agents such as elimination of nanoparticles through biological clearance pathways in a controlled manner. They can bind with the targets in a very specific manner (Shilo et al. 2012) and remain in circulation for longer time, thus providing more time for imaging.

19.3.2.1 Magnetic Resonance Imaging (MRI)

MRI is based on the principle of nuclear magnetic resonance (NMR). NMR uses the magnetic properties of atomic nuclei for creation of medical images through MRI. When an atomic nucleus is placed in a magnetic field, it absorbs and emits the electromagnetic radiation with the resonance frequency of substance and creates the image. The resonance frequency is directly proportional to the strength of magnetic field and depends on location and thus can create images of different body organs. The contrasting agents create the image by the alteration of proton relaxation time in longitudinal (T_1) and transverse (T_2) dimensions and dismantle the local magnetic field. The difference in relaxation times of T_1 and T_2 discriminates between tissues, air, and biopsy (Chen et al. 2016). A superparamagnetic particle when used in MRI can perturb the magnetic field 50 times of its diameter and therefore can impact water protons to the deep layer of cells from original location (Shilo et al. 2012). To be used as contrasting agent in vivo, nanoparticles should be stable and nontoxic and remain longer in body circulation. These features can be modulated by change in size and coatings of nanoparticles (Cole et al. 2015). Iron oxide nanoparticles, gold nanoparticles, and gadolinium are frequently used as contrasting agents in MRI. Gadolinium is generally used as contrasting agent in T_1-weighted protocol, but due to toxicity generated by it, it is not suitable for use in patients with renal failure. Therefore, iron oxide nanoparticles can be used as a substitute of gadolinium in these patients. However, iron oxide nanoparticles have limited relaxivity. In general, paramagnetic nanoparticles and superparamagnetic particles are used as T_1 and T_2 contrasting agents, respectively (Lawaczeck et al. 2016).

Gadolinium (Gd^{+3}) is the most commonly used contrasting agent in MRI. Gd^{3+} has huge potential to catalase water signals. The presence of seven unpaired electrons and long electron spin relaxation time make it suitable as a contrasting agent to create positive contrast in MRI. FDA-approved five contrasting agents are based on the use of Gd^{3+} (Tian et al. 2015; Coughlin et al. 2014).

To get the images of cancer cells with higher spatial resolution and sensitivity, two imaging modalities (MRI and optical imaging) were combined to create dual modal imaging (DMI). To be used as contrast agent in DMI, they have luminescent and magnetic properties. For this purpose, Europium-doped gadolinium oxide (Eu-doped Gd_2O_3) nanorods were synthesized and coated with silica (Gayathri et al. 2017).

19.3.2.2 Superparamagnetic Iron Oxide Nanoparticle (SPION)-Enhanced MRI Imaging

Superparamagnetic magnetism occurs due to interaction of a permanent magnet and paramagnetic substance and lies between both of them. Iron oxide nanoparticles and other ferrous materials of diameter 1–100 nm come into the category of superparamagnets. Generally, iron oxide nanoparticles occur in two main forms – magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3). Maghemite is the oxidized form of magnetite. In MRI, they can be used to identify infection and inflammation. In contrast to the

conventional contrasting agents, these particles provide image of high quality and resolution. For better image quality, use of larger SPION for T_2 relaxation imaging and smaller SPION for T_1 relaxation imaging is recommended (Warlin 2013). SPIONs have also great potential for discrimination between benign and cancerous tumors. Seyfer et al. (2014) used SPION in T2-weighted MRI protocol and reported low contrast-to-noise ratio in abscesses than neoplasia.

19.3.2.3 Positron-Emission Topography (PET) Scanning

PET imaging is used in nuclear medicine to get the clinical information about the patients using radiotracers. PET works on detection of radiation produced by decay of tracer inside the body. PET-CT is an advanced form of PET scanning. It provides the information about the onset of disease much earlier than other methods used in imaging. In PET imaging, metal oxide nanoparticles were used as probes. They were used in a nuclear reaction-involved conversion of ^{18}O-enriched aluminum oxide to ^{18}F-labeled nanoparticles by the action of photons on ^{18}O-enriched aluminum oxide (Al_2O_3). Radiolabeled isotopes of nanoparticles as positron emitters have been used to monitor the level of tumors and activity of enzymes involved in tumorigenesis (Perez-Campana et al. 2013).

19.3.2.4 Ultrasound

Ultrasound is another modality of imaging. It is a type of mechanical sound called ultrasonic waves with frequency more than the hearing frequency of human ear (>20 kHz). It is an important tool in diagnosis and imaging in sonography. In imaging as per the point of diagnosis, these waves are focused at a particular depth. A scattered signal is produced due to different acoustic resistance of tissues. The signals are recovered and used to create the reconstructed images of tissues. Mattrey et al. developed perfluorooctylbromide nanoparticles (PFOB-NPs) encapsulated within a pluronic F-68 shells. They have significantly improved echogenicity of the liver than that of kidneys. Therefore, they can be used as a promising contrasting agent to improve the sensitivity of detection in the liver and tumors (Mattrey et al. 1982).

Microbubbles were used as contrasting agents to improve the echogenicity and signaling of tissues. Microbubbles consist of different gases enclosed in a lipid/protein/polymers shell and can create two-/three-dimensional images of tissues and organs (Nie et al. 2014; Daraee et al. 2016). Microbubbles were developed with the intention for imaging of blood flow and tissue perfusions. Perfluorooctyl bromide (PFOB)-gold core-shell complex as a contrasting agent was used in imaging of the kidney and liver of mouse (Ke et al. 2014). Gold and graphene oxide nanoparticles containing poly (lactic acid) microcapsules (PLA microcapsules) developed by Jin can be used to deliver payload in tissues (Jin et al. 2013). Another group of scientists used PLA microbubbles containing gold nanoparticles to deliver payload. Signal with 50% decrease was attained in this study (Teraphongphom et al. 2015).

Although microbubbles offer very sensitive detection due to their strong nonlinear response, their applications have several limitations such as in vivo short half-life span and high background signal. Nanoparticles overcome these limitations as they have a long circulation half-life and are able to accumulate in the interstitial space of tumors through enhanced electron paramagnetic imaging (EPR) (Zhang et al. 2014).

Ultrasound imaging offers several advantages such as real-time imaging, affordability than other imaging modalities, biocompatibility, and portability. The contrasting agents used in ultrasound imaging can be also used as theranostic purpose, i.e., therapy and diagnosis in major diseases like cancer. In theranostic applications, contrasting agents are conjugated with superparamagnetic iron oxide nanoparticles (SPIONs), CuS nanoparticles, DNA, siRNA, gold nanoparticles (GNPs), gold nanorods (GNRs), gold nanoshells (GNS), graphene oxides (GOs), polypyrrole (PPy) nanocapsules, Prussian blue (PB) nanoparticles, and so on to different types of UCAs (Fu and Ke 2016).

19.3.2.5 X-Ray/Computed Tomography

X-ray imaging is used to generate high-resolution images of internal structures of body through the use of X-rays – a high-energy electromagnetic radiation. It is the most popular method of imaging and accounts for 50–70% of all medical imaging done. It is a safe and cost-effective method of imaging and can be used by taking care of patient safety and limited exposure of radiation (Alric et al. 2008). When X-rays pass through the body, there is loss in beam intensity. This is due to the photoelectric absorption or scattering. The loss of beam intensity is called attenuation. Repeated use of iodine-based contrast agents offers adverse side effects such as allergies and nephrotoxicity. Previously, use of gold nanoparticles as contrast agent have been reported for X-ray imaging. Gold nanoparticles are safer and less toxic than other contrast agents and have higher absorption coefficient value at low energy for X-rays (Kim et al. 2007; Kojima et al. 2010). Hainfeld et al. (2006) reported the detection of intravenously injected gold nanoparticles through X-ray imaging.

The technique of Computed Tomography came into existence in 1973. The technique was able to create the three-dimensional X-ray images through the rotation of detector and X-ray source around the body (Hounsfield 1973). Iodine-based contrast agents are rapidly cleared from the body and thus provide very less time for imaging. They are also distributed unevenly in intracellular and extracellular vasculature; therefore, they are unable to create high-quality and high-resolution images of CT. To overcome these limitations, iodine-based contrast agents are developed in nm range and in the form of micelle, liposomes, and polymers.

Prolonged exposure of nanoparticles in circulation can lead to the high-quality contrast CT images. On the other hand, clinically approved contrast agents are smaller in size and therefore rapidly clear from circulation via excretion through the kidney. To remain longer in circulation, nanoparticles can be synthesized bigger than the size of fenestra (Choi et al. 2014). Nanoparticle-based contrast agent for longer duration in circulation was synthesized by Torchilin (Torchilin 2001; Trubetskoy et al. 1997). The use of gold nanoparticles as contrast agent showed

their existence for up to 12 h in blood vessels (Kim et al. 2007; Cai et al. 2007). Nanoparticle-based contrast agents can be synthesized in the form of a core containing atoms for contrast generation and coated by lipid, proteins, silica, or polymers. The coating layer can be easily modified for insertion of antibodies, nucleic acids, drugs, or other contrast-generating moieties for multimodal imaging (Lee et al. 2012; Jia et al. 2013). Therefore, synthesis of nanoparticles equipped with optical and/or magnetic properties potentiates them for multifunctional use (Xu et al. 2011). Nanoparticles in the form of lipid formulations such as liposomes, micelles, and lipoproteins and solid core nanoparticles like salt and alloy of metals are frequently used in CT applications (Ghaghada et al. 2016).

19.3.3 Nanocarriers as a Weapon for Drug Dissolution and Drug Discovery

Nanocarriers in drug delivery offer several advantages: (1) enhance solubility of very low-soluble drugs, (2) enhance targeted drug delivery specificity, (3) can move across epithelial and endothelial barriers, (4) improve direct delivery of large molecular drugs into cells, (5) can be used in single or combination delivery of drugs, (6) can be used in drug delivery site monitoring by tagging of therapeutic agent with molecules having imaging properties, and (7) can be used for real-time monitoring of drug delivery and high in vivo efficacy (Farokhzad and Langer 2009; Prasad et al. 2017b).

For efficient working, nanocarriers should be in circulation for a longer time for drug accumulation, but practically it is difficult. Immune system treats nanocarriers as foreign particles and rapidly clears it through opsonization (Torchilin 2012). Premature release of entrapped drugs at other sites than drug targets using nanocarriers leads to systemic toxicity (Jin et al. 2014).

To maintain the concentration of drugs across the target by means of active or passive transport, nanocarriers undergo conjugation with polyethylene glycol (PEG) molecules on its surface, resulting in low interaction of nanocarriers with blood, improved water solubility, and colloidal stability. This combination significantly improved the circulation time of nanocarriers. PEG is not suitable in all conditions; therefore, different approaches are being explored. It includes nonfouling material and zwitterions such as phosphorylcholine (PC), carboxybetaine (CB), and sulfobetaine (SB).

The efficacy of drug and bioavailability mainly depends on the physical and chemical properties of drugs such as aqueous solubility, pK_a, and partition coefficient-Log P. Solubility, permeability, and oral absorption of drugs are significantly affected by pK_a. One of the challenging problem of pharmaceutical industry is the aqueous insolubility of drugs (Cheng et al. 2006).

In case of drug delivery through intravenous route, aqueous-based formulations are highly desirable. To prepare such type of formulations, water solubility of drug is the prerequisite (Yeh et al. 2009). For oral drug administration, before the absorption, drug should be dissolved properly in aqueous environment of the gut (Aulton

2007). Therefore, the absorption rate of drugs with high permeability but low solubility taken orally depends on the rate of drug dissolution.

Growing demand to fabricate novel drug delivery systems for delivering high content of active ingredient with high drug-targeting capacities led to the use of nanostructures as drug delivery agents – "nanocarriers." Nanostructures such as nanocrystals, liposomes, nano-emulsions, solid lipid nanoparticles (SLN), polymeric nanoparticles, and polymeric self-assemblies have been successfully used to improve solubility of drugs.

Being smaller in size nanocarriers can easily cross the barrier of gut epithelium results in enhanced drug absorption and bioavailability (Ramesan and Sharma 2009). In nanocarrier delivery system, carrier matrix harbors the attached or adsorbed active ingredient either in dissolved state or in an encapsulated form (Caban et al. 2014).

Advantages of Nanocarriers to Improve the Solubility of Drugs

Nanocarriers are the materials of nanoscale. The miniaturization of nanocarriers offers several advantages:

(i) Nanocarriers can be used to enhance drug pharmacokinetics and reduce systemic toxicity of bioactive material by moving to the particular target site.
(ii) Nanocarriers can also be used to enhance solubility of hydrophobic drugs.
(iii) Nanocarriers can increases the stability of drugs and can be used for sustained or controlled release of drugs
(iv) Nanocarriers can easily cross the blood-brain barrier and tight epithelial junctions. Therefore, they can deliver drug across the barrier in a much better manner (Caban et al. 2014).

19.3.3.1 Types of Nanocarriers

Nanocarriers include the nanosized structures such as nanoparticles, nanocapsules, lipid complexes, polymeric micelles, and dendrimers (Sahoo and Labhasetwar 2003).

Nanosuspensions

Nanosuspensions are crystals in which 100–1000 molecules are arranged in the form of aggregates. Nanosuspensions are prepared by using a thin-coated drug containing one or mixture of surfactants. Nanonization is the method through which nanosuspensions are formulated (Rabinow 2004). In the first step, surfactants are dissolved in the water. Thereafter, macrosuspension of drug is prepared by dispersal of drug powder in aqueous solution through high-speed agitation. In the next step, macrosuspensions are homogenized using techniques such as wet milling (Liversidge et al. 2003), high-pressure homogenization (Müller et al. 2001), spray-drying, and nanocrystallization.

Nanosuspensions are capable of overcoming the problems associated with drugs such as poor solubility, poor bioavailability, difficulty in preparation in parenteral dosage form, and poor absorption pattern. In nanosuspensions for stabilization, mild quantity of surfactants or stabilizer is used. As per the dissolution property of

the drugs, aqueous (water/buffer) or nonaqueous (lipid solvents) media can be used in nanosuspensions (Shegokar and Müller 2010; Junghanns and Müller 2008).

Advantages of Nanosuspensions

(i) Nanosuspensions are smaller in size; therefore they provide larger surface area for increased dissolution and absorption and faster onset of action.
(ii) Nanosuspensions increase the dissolution of drugs.
(iii) Nanosuspensions increase the oral bioavailability.
(iv) Nanosuspensions can be used to decrease the dose of drugs.
(v) Nanosuspensions can be used to decrease side effects of drugs (Savjani et al. 2012).

19.3.3.2 Liposomes

Liposomes are spherical structures in which an aqueous reservoir is completely surrounded by phospholipid bilayer. The phospholipid membrane of liposome contains a hydrophilic (attract water) head and a hydrophobic (repel water) tail group (Rawat et al. 2006). The property of liposomes varies with size, charge, lipid content, and the method of preparation. Liposomes can prevent the degradation of encapsulated drugs and are able to reduce systemic toxicity. As per the need, availability of liposomes can be increased by the incorporation of polyethylene glycol (PEG) units to the lipid bilayer. Conjugation of liposomes with antibodies or ligands improves the precision of targeted drug delivery (Sahoo and Labhasetwar 2003). Biphasic nature of liposomes makes them suitable as a carrier for hydrophilic as well as for hydrophobic drugs (Farokhzad and Langer 2009). Liposomes have been successfully used as a carrier in the field of drug delivery, cosmetics, and diagnostics (Akbarzadeh et al. 2013).

Liposomes can be used as a potent carrier for ocular drug delivery due to the presence of natural phospholipid membrane and biocompatibility. In case of topical application, liposomes can attach with the epithelial cells of cornea and deliver the bound drug and therefore improve the pharmacokinetics and decrease the toxicity-related side effects of the drug (Chetoni et al. 2007). Nanosized version of liposome is called nanoliposome. Common laboratory methods of nanoliposome production include sonication, freeze-thawing, extrusion, micro-fluidization, and ether injection (Mozafari 2010).

Advantages of Liposomes

(i) Liposomes can be used for selective passive targeting of tumors.
(ii) Liposomes enhance stability, efficacy, and therapeutic index of the drug.
(iii) Liposomes also decrease the toxicity and side effects of drug.
(iv) Liposomes enhance the pharmacokinetic effects of drugs (Dua et al. 2012).

19.3.3.3 Solid Lipid Nanoparticles (SLN)

Solid lipid nanoparticles are the colloidal carriers of diameter 50–1000 nm. Solid lipid nanoparticles consist of solid lipids distributed in aqueous solution or surfactant solution in water. Solid core is the drug containing area and are rich in high fat

matrix. The fat matrix contains a chain of phospholipids which are hydrophobic in nature. The physical stabilization is attained through the addition of surfactant or emulsifying agent depending on the lipid contents and type (Rawat et al. 2006). SLN does not cause toxicity and can be prepared by several methods such as high-pressure homogenization, precipitation, lipid nano pellets, and so on (Mehnert and Mäder 2001; Müller et al. 1996). Positively charged SLN can be used as a potent non-viral carrier (Olbrich et al. 2001; Pedersen et al. 2006). SLN is an effective vaccine carrier. Chitosan-coated lipid nanoparticles have been employed in delivery of peptide drug through oral route (Fonte et al. 2011).

Currently, the use of lipid-based formulations has been emphasized to enhance the solubility of poor water-soluble drugs for oral bioavailability.

Advantage of Solid Lipid Nanoparticles

In comparison with nano particulate carriers, SLN offers the following advantages:

(i) SLN provides higher tolerability and biocompatibility.
(ii) SLN offers controlled release of drugs.
(iii) SLN also protects the incorporated drugs.
(iv) SLN significantly enhances the oral bioavailability.
(v) SLN can be prepared on a large scale.
(vi) SLN also provides the chemical stability (Varshosaz et al. 2010).

19.3.3.4 Dendrimers

Dendrimers are highly branched treelike structure. They consist of repeated units of monomers, a central core, an internal cavity, and peripheral groups. The macromolecule of dendrimers have large molecular weight and equipped with the entrapment property. They are formed from the monomeric units. Dendrimers have special physiochemical properties due to their components such as organic molecules and polymers. The internal cavity of dendrimers is used to encapsulate hydrophobic drugs. In comparison with traditional macromolecules, dendrimers have a higher functional group density which enhances the solubility of drugs (Svenson 2009). Higher reactivity of dendrimers is due to the presence of functional groups on its outer surface. These groups can be conjugated with other molecules (Yogesh et al. 2011). Therefore, drugs can be loaded in two ways: either conjugated with surface functional groups through the electrostatic bonds or encapsulated in internal cavity.

Dendrimers coming in the category of novel polymeric materials have spherical 3D structures and offer higher surface group functionality.

Dendrimer-based drug delivery includes two mechanisms:

(i) Cleaving of drug-dendrimer conjugation involves the presence of enzymes in vivo.
(ii) Drugs are released in vivo due to change in physiochemical environment such as pH and temperature.

These mechanisms come into play either on the outer surface or in the internal cavity (Liu and Fréchet 1999; Caminade and Turrin 2014).

Dendrimers as nanocarriers can deliver drugs to the pulmonary system, across transdermal route, and eyes and can be used for controlled release and targeted drug delivery.

19.3.3.5 Polymeric micelles (PM)

Polymeric micelles (PMs) were developed by Ringsdorf as potent vehicle for drug delivery to overcome the problem of low drug solubility and systemic toxicity (Williams et al. 2013). Thereafter, PMs have been used as delivery vehicle for anticancer drugs, contrast agents, lipids, proteins, plasmids, components of antisense technology, and RNAi-short interfering RNA (siRNA). These formulations are undergoing clinical trials (Kedar et al. 2010).

PM mainly consists of a bio inert material with a core and outer shell. The inner core is composed of a hydrophobic polymer, whereas the outer shell is from the hydrophilic polymer. The inner cores are meant for drug loading, and the outer shell is for the protection of core from bioenzymes and to prevent adsorption of proteins on the surface of PM (Miyata et al. 2011).

Being smaller in size, PM can withstand against the renal excretion and uptake by reticuloendothelial system and it also facilitates the use of PM in targeting tumors and prolonged retention in circulation. Several approaches have been described for the preparation of pH-sensitive PM (Tan et al. 2013). They can be prepared by attaching a titratable group, e.g., –COOH or $–NH_2$, into block copolymer. These groups release protons and also control the micelle formation. Micelles are formed when the concentration of block copolymer exceeds the critical micelle concentration (CMC).

Advantages of Polymeric Micelles

(i) The polymeric micelles impart thermodynamic stability in the living system; therefore, they decrease the in vivo dissolution (Xu et al. 2013).
(ii) The polymeric micelles can be used as a carrier for poor water-soluble drugs due to their core-shell structure.
(iii) The polymeric micelles are a suitable carrier for intravenous administration as the poor soluble drugs present in hydrophobic core and outer hydrophilic layer support dispersal in an aqueous environment (Ding et al. 2012).
(iv) Being smaller in size, RES cannot remove them from circulation.

19.4 Conclusion

Miniaturization of matter at nano scale founded the nano world. We can see one of the best applications of nanotechnology in the field of medicine. Nanotechnology in medicine revolutionized the diagnostic world and expanded the new approach

toward better healthcare. Conventional methods of disease diagnosis are expensive and time taking need expertise and large quantity of samples. Nano-based diagnostics diminished these problems through point-of-care diagnosis tests (POCTs). Nanomaterials and fabricated nanodevices are frequently in use not only in the field of diagnosis but also as efficient nanocarriers for drug dissolution and targeted drug therapy. Integration of nanotechnology with other techniques such as microfluidics enhanced the sensitivity of the diagnostic modalities and decreased the time of detection. In a nutshell, application of nanotechnology in medicine is a very promising approach and expanding new horizons in future diagnostics and pharmaceuticals.

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