Functionalized Nanocrystals and Theranostic Applications

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Abstract

Nanocrystals are pure drug crystals with sizes in the nanometer range. Due to the advantages of high drug loading, platform stability, and ease of scaling up, nanocrystals have been widely used to deliver poorly water-soluble drugs. They boost the drug's saturation solubility due to nanometer-sized particle size and improved dissolving rate due to larger surface area. Higher passive diffusion is produced by the increased concentration gradient between the epidermal membrane and the topically applied formulation due to the increased saturation solubility. Nanocrystal suspensions can be made using the most cost-effective and advantageous technique. In order to create capsules and tablets, the generated nanocrystal suspension can either be employed as a liquid dosage form or converted into dry solid powders. In the present review, we discuss several types of nanocrystals, preparation of nanocrystals, stability, functionalization of nanocrystals, theranostic applications of nanocrystals in various diseases, advantages of theranostic nanocrystals, and challenges and future goals

Keywords

Drug crystals · Stabilization · Surface area · Polymers · Surfactants · Functionalization

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K. Jain, N. K. Jain (eds.), *Multifunctional And Targeted Theranostic Nanomedicines*,
https://doi.org/10.1007/978-981-99-0538-6_14

14.1 Introduction

Despite having remarkable efficacy, nanocrystals were originally conceptualized in the nineteenth century, and their marketability is still constrained (Junyaprasert and Morakul 2015). In order to effectively transport the drug into or across the cells, nanocrystals of a parent drug with submicron particle size (100–1000 nm) are used (Müller et al. 2011; Chen et al. 2011a). They boost the drug's saturation solubility due to nanometer-sized particle size and improved dissolving rate due to larger surface area. Higher passive diffusion is produced by the increased concentration gradient between the epidermal membrane and the topically applied formulation due to the increased saturation solubility (Mishra et al. 2009; Al Shaal et al. 2011). Targeting of hair follicles was seen in particles of sizes in the nanometer range. Additionally, they showed higher cell surface or membrane adhesion, which can lengthen the period that a formulation remains in the skin (Müller et al. 2016). In the current medication development process, safe formulation, and pharmacoeconomic value, a growing number of poorly soluble pharmaceuticals have drawn attention as a problematic approach. Pharmaceutical firms may potentially profit by utilizing nanocrystal technology to redesign a product line for an already-existing formulation (Raghava Srivalli and Mishra 2014). The several methods used to create nanocrystals can be divided into bottom-up, top-down, and combination methods. According to the available literature, producing commercial nanocrystals does not frequently use the bottom-up technique. This approach comes with a number of issues, including the necessity to remove the solvent, difficulties with process optimization, and numerous medicines that are poorly soluble in both aqueous and organic mediums (Joshi et al. 2019; Liu et al. 2019).

The use of an organic solvent in precipitation procedures in bottom-up techniques, which must be entirely eliminated from the formulation and also results in the high manufacturing process, is their main drawback. Therefore, the creation of nanocrystals has not utilized the bottom-up method. An alternative method for producing nanocrystals is to use top-down technology (Junyaprasert and Morakul 2015). In the case of top-down technology, nanocrystals are made by the rapid wet media milling process. Nanocrystal suspensions can be made using the most cost-effective and advantageous technique. In order to create capsules and tablets, the generated nanocrystal suspension can either be employed as a liquid dosage form or converted into dry solid powders (Van Eerdenbrugh et al. 2009). Sols are typically used to obtain nanocrystals of different materials. Sols containing nanocrystals exhibit the same behaviour as traditional colloids. For instance, a dispersion's stability is influenced by the medium's ionic strength. Optical clarity is exceptionally good in nanocrystalline sols. The existence of a ligand shell, a layer of molecular species adsorbed on the surface of the particles, is a crucial component that contributes to the stability of nanocrystal sols. Without the ligand shell, the particles have a propensity to group together to create bulk species that settle or flocculate in the medium. The ligands contribute to particle stability in two distinct ways, depending on the dispersion medium. As a result, in an aqueous medium, coulomb interactions between charged ligand species create an electrical double layer, which

acts as a repulsive force to balance the attractive van der Waals attraction between the small grains. The requisite repulsive force is produced in an organic medium by the ligands' loss of conformational freedom and the apparent rise in solute concentration. Nanocrystals that are disseminated in liquids are either sterically or charge stabilized (Rao et al. 2007). In the drug development process, more than 40% of drug candidates have poor solubility, which results in poor and variable bioavailability (Ranjita 2013). Most medications have internal side effects due to their non-specific dispersion throughout the body, which further restricts their clinical usage (Trapani et al. 2012). Nanocarrier-based targeting methods are significant remedies for these issues. Selective delivery of poorly soluble medications to damaged tissues, organs, or cells has been successfully accomplished using nanocarriers, such as liposomes, nanoparticles, micelles, and nano-emulsions (Hollis et al. 2013a). However, the inherent disadvantages, such as unstable platforms, restricted drug loading, expensive production, scale-up challenges, and quality control challenges, limit the acceptability of these nanocarriers in clinic (Lu et al. 2015a). Only a few nanocarrier-based products, such as Doxils, Dauno Xomes, and Abraxanes, are commercially viable. The creation of nanocrystals came about as a result of many shortcomings in the targeted therapeutic delivery methods that were already in use. While pure drug crystals may occasionally be physically stabilized by surfactants and/or polymers (Keck and Muller 2006; Rabinow 2004; Xu et al. 2012), nanocrystals are drug crystals with particle sizes ranging from dozens to a few hundreds of nanometers. Absence of any carrier molecules provides a theoretical drug loading range of 50% to 90% (w/w) (Fuhrmann et al. 2013), resulting in therapeutic concentrations that are acceptable at modest doses (Muller et al. 2011). Excipients used for encapsulating and solubilizing medicines may no longer have any negative side effects. Most notably, the nanocrystal formulation generally avoids the physical instability problems associated with previous nanocarriers (Chen et al. 2011b; Junghanns and Muller 2008; Guo and Huang 2014). A dozen commercial products demonstrate the simplicity of scaling up for nanocrystals, and both top-down and bottom-up technologies have been well developed to create nanocrystals with required particle size and size distribution (Nagarwal et al. 2011).

14.2 Types of Nanocrystals

14.2.1 Chitin and Chitosan

The most prevalent amino polysaccharide polymer found in nature, chitin serves as the foundation for the exoskeletons of crustaceans, insects, and fungal cell walls. Chitin can be deacetylated chemically or enzymatically to produce its most well-known by-product, chitosan. Shrimp and crab shells, which are a plentiful by-product of the food processing industry and produce significant amounts of this biopolymer for use in biomedical applications, are the primary natural sources of chitin. Chitin production and breakdown in living chitin-synthesizing organisms must be strictly regulated enzymatically in order to preserve equilibrium. The key

enzyme in the chitin production process, chitin synthase, creates the chitin polymer using UDP-N-Acetylglucosamine (UDPGlcNAc), whereas chitinase enzymes break down chitin. The primary natural mediators of chitin breakdown are thought to be bacteria. Due to their distinct biochemical characteristics, such as biocompatibility, biodegradability, nontoxicity, and the capacity to form films, chitin and chitosan have found a wide range of interesting biomedical applications. In its most recent developments, nanotechnology has also increasingly used chitin- and chitosan-based products. A lot of chitin and chitosan have been used to create polymer scaffolds. Additionally, there is growing interest in using chitosan to create tailored nanocarriers and enable microencapsulation techniques for the delivery of pharmaceuticals, biologics, and vaccines. It is expected that each application will require specially created chitosan-based nano- and microparticles with certain size and cargo-release properties. Chitosan nano−/microparticles with high loading efficiencies can encapsulate protein cargos; however their consistent production is still difficult to achieve. With varying degrees of deacetylation, chitosan can be successfully employed in solutions, as hydrogels, nano- or microparticles, and to create an infinite variety of derivatives with specific biological capabilities (Elieh-Ali-Komi and Hamblin 2016).

14.2.2 Quantum Dot

Colloidal fluorescent semiconductor nanocrystals known as quantum dots are roughly spherical; have distinctive optical, electronic, and photophysical properties; and have exciting potential for use in biological labelling, imaging, and detection as well as effective donors of fluorescence resonance energy (William et al. 2006). The most often used quantum dots are made of a mixture of II-VI elements, specifically CdS and CdSe. Along with oxides, halides, and tellurides, additional sulphides and selenides have also been described (Wang and Herron 1991; Murray et al. 1993). It has also been used to combine III-V elements (InP and InAs) (Mićić and Nozik 1996; Pötschke et al. 2004).

A quantum dot has a diameter that ranges from 2 to 10 nm. Fluorescence cannot be seen after the quantum confinement effect is lost above this scale. Quantum dots have higher quantum yields and are brighter than typical small molecule luminophores. Additionally, because quantum dots of various compositions exhibit emission spectra with distinctive nuances (Bailey and Nie 2003), taking use of these properties would make it possible to do multiplexed assays like those suggested by Soman and Giorgio (Soman and Giorgio 2009). According to Chan and Nie (Chan and Nie 1998), a single crystal of 5 nm in diameter may function as a solid support for two to five molecules since a quantum dot surface can be activated with a wide variety of reactive moieties. Quantum dots are excellent contrast agents for imaging and labels for bioassays due to all of these features. Recently, several reviews on the creation, characteristics, and uses of QDs have been published (Mazumder et al. 2009; Jamieson et al. 2007; Huo 2007).

14.2.3 Colloidal Nanocrystals

Colloidal nanocrystals (or crystalline nanoparticles) have emerged as a significant class of materials with a wide range of potential uses, from electronics and optoelectronics to medicine. The enormous advancements in nanocrystal synthesis have led to the current substantial research emphasis on these compounds. For a wide variety of inorganic compounds, it is now possible to achieve impressively small size distributions of just a few percent, rational shape-engineering, compositional modification, electrical doping, and customized surface chemistries. Inorganic nanocrystal-based photovoltaic and light-emitting devices can now compete in performance with other cutting-edge materials (Kovalenko et al. 2015).

14.2.4 Cellulose Nanocrystal and Nanofibres

Two major categories can be used to classify nanocellulose: cellulose nanocrystals (CNCs) and cellulose nanofibres (CNFs). Based on its characteristics, sizes, techniques of extraction, and uses, nanocellulose was categorized. The cellulosic sources and the processing conditions have a significant impact on the CNMs' properties. Although the physical properties of the mechanically extracted CNFs and acid hydrolysed CNCs are different, their chemical properties are similar (Li et al. 2019a). CNFs are typically extracted from cellulose fibres using a mechanical technique, whereas CNCs are often obtained by a chemical acid hydrolysis procedure.

The CNFs are typically produced mechanically from the natural fibres that have already been treated. In this procedure, a greater shear stress is produced, which causes CNFs to be extracted from the pretreatment fibres in a longitudinal orientation. However, this manufacturing technique typically involves a high energy consumption, which results in the delamination of the fibre. Up to 98% less energy is used during the chemical preparation procedure (Li et al. 2019a). This section has a detailed discussion of the advantages and disadvantages of the most popular mechanical methods for the extraction of CNFs.

14.3 Preparation of Nanocrystals

14.3.1 Top-Down Techniques

The top-down procedures utilize high-energy mechanical forces, which are used to comminute big crystals either through medium milling (MM) (nanocrystals) or high-pressure homogenization (HPH) (IDD-Ps, DissoCubess, and Nanopures) (Shegokar and Müller 2010; Merisko-Liversidge et al. 2003). The top-down method's major benefit is that it is a universal method for creating crystalline nanoparticles (Rabinow 2004) and is adaptable in terms of production scale (Müller et al. 2001). As a result, the method has been widely used to create commercial nanocrystals. With the

exception of Triglides, almost all commercial items were created by nanocrystals. High energy and time requirements, as well as contamination from the grinding media, are drawbacks of this technology. For instance, even at high pressures of up to 1700 bar, it takes 50–100 cycles of homogenization to produce the correct particle size and size distribution (Keck and Muller 2006; Junghanns and Muller 2008). Similarly, milling times range from a few hours to several days, depending on the characteristics of the medication, the milling medium, and the degree of particle size reduction (Gao et al. 2008; Peltonen and Hirvonen 2010). The top-down method may not be the best option for preparing nanocrystals for intravenous injection since contamination from the grinding media causes unanticipated side effects.

14.3.1.1 Media Milling (Nanocrystals)

The media mill's main parts are a milling chamber, motor, recirculating chamber, coolant, and milling material. During the procedure, a crude slurry including the medication, water, and stabilizers is supplied into the milling chamber and stirred by the motor. The milling chamber is typically 2–30% (w/v) filled with slurry, with the milling medium occupying the remaining 10–50% (w/v) of the slurry. In order to lower the particle size during agitation, the milling medium rotates inside the chamber, creating high energy forces by shearing and hitting with the medicines. Depending on the scale, the operation can be carried out either in batch (discontinuous mode) or recirculation (continuous mode). Recirculation is beneficial for speeding up milling and reducing particle size. Depending on the scale, the operation can be carried out either in batch (discontinuous mode) or recirculation (continuous mode). Recirculation is beneficial for speeding up milling and reducing particle size. If recirculation mode is used, media separators can keep the milling medium in the chamber. Due to the tremendous energy produced during milling and long-term operation, the thermogenesis is intense, raising stability difficulties. As a result, the coolant is required to regulate the temperature when milling (Lu et al. 2016).

14.3.1.2 High-Pressure Homogenization (IDD-Ps, DissoCubess, and Nanopure)

Drug suspensions are delivered into a high-pressure homogenizer during the HPH process, where they are compelled to transit through an extremely short homogenization channel in a quick burst under high pressure. Drug particle fracture is caused by cavitation, high-shear forces, and particle collisions. The process typically consists of three steps: (1) dispersing the raw drug powders in a pure solution or a solution containing a stabilizer; (2) reducing the particle size by high-speed homogenization or shearing under low pressures; and (3) applying high-pressure homogenization to produce the desired particle size and size distribution. HPH can be further separated into three patented technologies based on the tools and substance used: the microfluidizer for IDD-Ps technology, the piston gap homogenizer for DissoCubess (water), and Nanopures (non-aqueous media) (Lu et al. 2016).

14.3.2 Bottom-up Techniques

The bottom-up method, which involves the two key phases of nucleation and subsequent crystal formation, produces nanocrystals from solutions. In contrast, nucleation is crucial for producing uniformly tiny nanocrystals. With a higher nucleation rate, more nuclei are produced from the supersaturated solution, which results in less supersaturation. As a result, it is possible to forecast that each nucleus will develop less in the long run (Hollis and Li 2010). Additionally, an arrow particle size distribution is obtained (Hollis and Li 2010) if several nuclei are formed simultaneously in the nucleation stage. Thus, it is crucial to encourage quick and uniform nucleation during the bottom-up process. Either combining with an antisolvent or removing the solvent can cause nucleation to occur (Hollis and Li 2010; de Waard et al. 2011). Common mixing tools, such as magnetic stirring and an agitator blade (Xia et al. 2014), are typically used to combine medication solution and antisolvent. Sonication can be used to create cavitation effects in order to promote the nucleation (Dalvi and Yadav 2015). It is known as sonoprecipitation. Nanocrystal preparation has also been carried out using confined impinging jet reactors (D'Addio and Prud'homme 2011), multiple inlet vortex mixers (Liu et al. 2008), and static mixers (Alvarez and Myerson 2010). With these tools, the two fluids are thoroughly mixed at the microscopic level in a matter of milliseconds. Even before nucleation begins, a homogenous solution with high supersaturation may be attained, promoting tiny nanocrystals with narrow size dispersion. Common techniques for removing solvent include freeze-drying and spray-drying. Additionally, controlled crystallization during freeze-drying techniques and spray-freezing into liquid have recently been developed to prepare nanocrystals by removing solvent. By utilizing the special physical characteristics of supercritical fluid (SCF), which combine diffusivity like a gas and solubilization like a liquid, SCF can be used to create nanocrystals. Additionally, the precipitation of nanoparticles can be substantially facilitated by quick and simple removal of SCF without extensive drying. The most preferred SCF is supercritical carbon dioxide (SCO2) because of its mild critical point (31 1C and 73.8 bar) and minimal environmental impact. SCO2 can be rapidly expanded from a medication solution, or it can be precipitated using SCO2 as an antisolvent, depending on how well a molecule dissolves in SCO2. Nanocrystals are a category of solid dosage forms that take advantage of the drug's crystal structure and the nanoscience idea to improve solubility, dissolution, and physicochemical qualities. When compared to other solid dosage forms, nanocrystal frequently presents a lot of difficulties in terms of chemical and physical stability during production and storage. As a result, crucial steps in the formation of nanocrystals include their physicochemical characteristics, hazardous effects on humans, and use in medication delivery via diverse routes of administration. To guarantee solid state consistency in the nanocrystals and its effect on therapeutic effectiveness, a variety of approaches are used (Lu et al. 2016).

14.4 Stability

Due to the lack of particle aggregation and the Ostwald ripening process, the nanocrystal suspension was shown to be stable (Im et al. 2020). A suitable stabilizer can be added, as well as other stabilizers, surfactants, and amphiphilic copolymers, to increase stability (Muller and Jacobs 2002a; Muller and Jacobs 2002b). The surfactants soon disperse, adhere to the crystal's surface, and stabilize the system by forming both a static and an electrostatic barrier between the crystals as homogenization progresses (Lee et al. 2005). For the purpose of stabilizing nanocrystals, the surfactant must meet certain requirements regarding its affinity for the particle surface (Kipp 2004). The second need is that a surfactant produces an adequate high diffusion rate during homogenization. In order to maintain the necessary steric or electronic repulsion between the particles, the stabilizer content should be sufficient to completely cover the particle surface. However, more stabilizers do not necessarily imply a better outcome (Mantzaris 2005).

14.4.1 Functionalization of Nanocrystals

The size range of nanocrystals is comparable to that of biomolecular and cellular systems, and this is coupled with their unique physical features. With these characteristics, these materials are very desirable for use in therapeutic and diagnostic scenarios. However, regulated interactions with biomacromolecules are necessary for these materials to be useful in biomedicine. Enhanced cellular internalization ability, non-cytotoxicity, and better payload binding capacity are all characteristics of well-designed nanocrystal monolayer architectures that are essential for efficient intracellular delivery. Surface functionality may also be modified to offer the selective or specific identification necessary for biosensing. Non-interacting "stealth" qualities, which inhibit immune system capture of particles, demonstrate that non-interaction itself may be a significant quality.

Customizing particle interfaces is difficult, but chemists have a wide array of tools at their disposal to synthesize useful materials. Small molecules, surfactants, dendrimers, polymers, and biomolecules are only some of the ligands that have been used in various methods to functionalize nanocrystals. Multiple medicinal medications or bio-macromolecules may be included by covalent or non-covalent conjugation using the various multivalent surface structures created using small molecules and polymeric ligands. Nanocrystals with attached biomolecules may also provide their host with desirable characteristics, such as enhanced specific recognition or biocompatibility. Due to the simplicity of such functionalization, chemists may easily produce the needed functionalities for their use in clinical applications.

Functional cellulose nanocrystals were generated by Boujemaoui et al. by combining acid hydrolysis and Fischer esterification with different organic acids. ATRP initiator, allyl, alkyne, and thiol functional groups were integrated as functionalities (Boujemaoui et al. 2015). Recent research has shown that elongated nanoparticles offer specific benefits over their spherical equivalents in drug delivery applications. Guo et al. developed functionalized cellulose nanocrystals with PEG-metal-chelating block copolymers in aqueous media via controlled conjugation. mPEG-PGlu (DPTA)18-HyNic and PEG-PGlu (DPTA)25-HyNic are coupled to CNCs for the first time to allow the chelation of radionuclides for diagnostic and therapeutic purposes. Preliminary testing on a human ovarian cancer cell line (HEYA8) revealed that these CNCs are nontoxic and that their penetration characteristics may be easily evaluated in multicellular tumour spheroids (MCTSs) using optical imaging (Guo et al. 2016). Pinheiro et al. created PBAT nanocomposites enhanced with nanocrystals containing functionalized cellulose. Functionalized cellulose nanocrystals (CNC) offer greater temperature resistance and enhance dispersion and polymer matrix interactions. These effective dispersion and interactions result in nanocomposites with enhanced characteristics (Pinheiro et al. 2017). Qiao et al. developed a new carboxylate-functionalized adsorbent (CNM) based on cellulose nanocrystals (CNC) to study the adsorptive removal of various cationic dyes (such as crystal violet, methylene blue, malachite green, and basic fuchsin). CNM demonstrated extensive adsorption capabilities for cationic dyes, as well as a quick adsorption rate and effective adsorption capacities for crystal violet. At least four times, CNM could be regenerated and employed for crystal violet adsorption (Qiao et al. 2015).

It is well recognized that the poor mechanical and thermal characteristics of biodegradable polymers (poly(3-hydroxybutyrate-co-3-hydroxyvalerate), polylactic acid, and polycaprolactone) limit their extensive usage as environmentally friendly and biomedical products. Since a result, intensive efforts have been undertaken to produce innovative green materials used to make on biodegradable polymers and renewable polysaccharide materials (cellulose, starch, and chitin), as these nanocomposites might replace certain petrochemical polymers and combat "white pollution". Particularly, cellulose nanocrystals (CNCs) derived from natural cellulose sources may serve as reinforcing agents for several biodegradable polymeric matrices. Functionalized cellulose nanocrystals (PHCNs) were created by Yu et al. by grafting poly (3 hydroxybutyrate-co-3 hydroxyvalerate) (PHBV) onto cellulose nanocrystals (CNCs). The nanocomposites demonstrated a larger window for melt processing than PHBV alone. In addition, the crystallinity and hydrophilic characteristics of the nanocomposites may be modified by varying the PHCN concentration. In addition, human MG-63 cells were not harmed by the nanocomposites. These high-performance bio-nanocomposites have the potential to increase the use of CNCs derived from natural resources and their practical use as PHBV-based bioplastics and biomedical materials (Yu et al. 2014).

14.5 Theranostic Applications of Nanocrystals in Various Diseases.

14.5.1 Cancer

According to 2008 research from the International Agency for Research on Cancer, incidence rates have been quadrupled since 1975, leading to an estimated 13–17 million cancer deaths globally by 2030. While novel medicines are being developed and approved for many forms of cancer, the primary method of preventing cancer mortality is by early identification, detection, and treatment of malignant cellular proliferation. Fluorescence imaging and magnetic resonance imaging (MRI) are two emerging nanoimaging techniques that may one day allow for the early detection and diagnosis of cancer, something that is presently impossible with traditional imaging methods. The unique features of nanocrystals result in their theranostic potential, which enables disease diagnosis and therapy simultaneously (Fig. 14.1) (Lu et al. 2015b).

Radiation and chemotherapy are currently used to treat cancer – however, their treatments are inaccurate, nonspecific, and often given at excessive doses, causing significant side effects that are detrimental to the patient's well-being. There is now a wide range of cancer-targeted nano-therapy systems designed to tackle the drawbacks of conventional treatments. These systems combine therapy, imaging, and tumour targeting capabilities in one platform.

Magnetic resonance imaging (MRI) is among some of the imaging technologies used in cancer treatment since this technique provides superior imaging of deep tissues and is combined with certain other imaging techniques to provide additional diagnostic data for identifying tumours accurately and guiding cancer therapy. A broad variety of medical imaging approaches may benefit from the use of inorganic

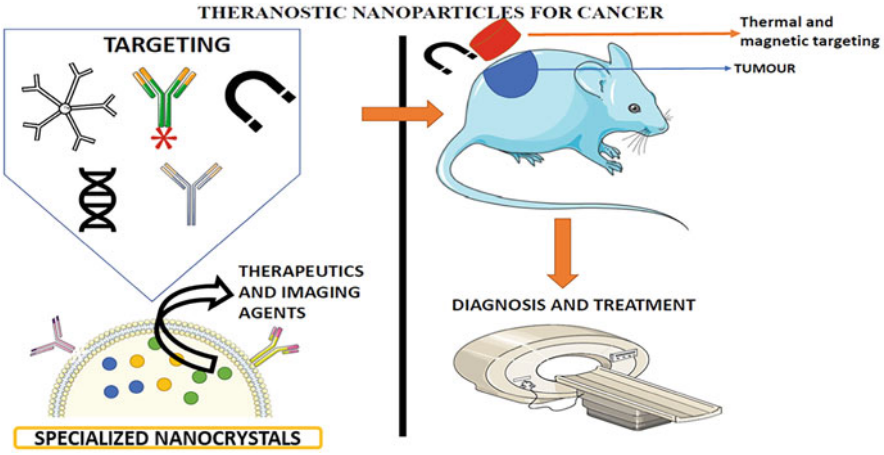

Fig. 14.1 Theranostic nanocrystals for cancer

nanocrystals, including drug or gene delivery complexes, therapeutic hyperthermia agents, and diagnostic systems. Nanocrystals may either create their own contrast, such as iron oxides, or gold nanoparticles covered with gadolinium chelates. It is possible to employ these MR-active nanocrystals for a variety of imaging applications, including the imaging of blood vessels, the liver, the brain, and other organs. Nanocrystals with water-soluble and biocompatible properties are consequently widely sought after because of their many uses (Cormode et al. 2013). Hollis et al. created unique hybrid paclitaxel (PTX) nanocrystals with bioactivatable (MMPSense® 750 FAST) plus near-infrared region (Flamma Fluor® FPR-648) fluorophores that were tested for anticancer effectiveness and diagnostic characteristics in a mouse breast cancer xenograft model. The anticancer activity of hybrid nanocrystals was shown, as well as the possibility of multi-modular biological imaging for diagnostic investigations. Furthermore, this nanocrystal formulation was shown to be equally effective as Taxol® but with lower toxicity when injected (Hollis et al. 2013b). Recently Hollis et al. also prepared paclitaxel (PTX) nanocrystals (200 nm) by crystallization. A near-infrared fluorescent dye was physically incorporated into the crystal lattice to make PTX nanocrystals tagged with tritium. A 20 mg/kg intravenous dosage was shown to accumulate in the tumour at a rate of less than 1%. According to the results of a survival trial, the nanocrystal treatments had equivalent anticancer efficacy to that of the standard solubilization formulation (Taxol®) (Hollis et al. 2013c). Fluorescent optical probes based on near-infrared quantum dots have received a lot of interest recently. Water-dispersible, highly luminous AgInS2 nanocrystals were successfully fabricated by Liu et al. as near-infrared probes for tumour targeting and imaging in vivo. An emission in the near-infrared band with a QY of up to 35% was achieved using this micelle-capsulated nanocrystal formulation. Liu and colleagues were able to passively administer AgInS2 NCs formulation to the tumour location by using an optical imaging equipment that allowed them to see the whole body of the tiny animal subjects being studied. The ultra-small crystal size, near-infrared emission luminescence, and high quantum yield of AgInS2 NCs make them a promising option for use as a biological contrast agent for tumour sensing and imaging (Liu et al. 2013).

Cancer patients may also benefit from heating tumours as a treatment method. There has been a resurgence of interest in thermal therapy in recent decades due to several scientific papers showing significant improvements in cancer therapies, a deeper understanding of how temperatures cause cell death, and the development of new technologies for localized and controlled heating of tumours. Traditional thermal treatments have focused on whole-body warming, but tailored thermal techniques may provide precise thermal therapy at the cellular or tissue level. Cancer theranostics may be made more efficient and precise by combining MRI with photothermal treatment (PTT) (Chu et al. 2018). For example, to establish an effective MNC (magnetic nanocrystal)-mediated theranostic technique, the work of Xie et al. has focused on developing a combination of simultaneous diagnostics and heating therapy of tumours utilizing MRI and alternating current magnetic field (ACMF). They synthesized PEG-phospholipid-coated Mn–Zn ferrite MNCs which were able to achieve a magnetism coefficient (r2) of 338 mM^{-1} s^{-1} and specific

absorption rate (SAR) of 324 W g^{-1} Fe, respectively. It has been shown that they significantly reduce macrophage phagocytosis while simultaneously enhancing their biocompatibility in vitro. Because of their increased permeability and retention (EPR) properties, the passive targeting of tumours and magnetically induced heating of tumours was made possible. The tumour surface could be heated to roughly 43 °C in 30 minutes with an ACMF of 12 A at 390 kHz based on intravenous injections of MNCs. Long-term hyperthermia may efficiently cause tumour cell death, block tumour angiogenesis, and eventually reduce tumour development within a certain time frame (Xie et al. 2014). Liu et al. presented an effective synergistic treatment for tumours. They effectively generated tumour neovascular-targeted Mn–Zn ferrite MNCs (magnetic nanocrystals) that contained paclitaxel (PTX) inside a biocompatible PEG-phospholipid (DSPE-PEG2000) film and interface, connected with a tripeptide of arginine-glycine-aspartic acid (RGD). The high-performance modified nanocrystals exhibited exceptional magnetic features, such as magnetic resonance imaging (MRI) with great contrast and outstanding magnetically induced heat generating capability. MNCs-PTX@RGD were capable of efficiently penetrating tumour tissue from tumour-fenestrated vascular networks in order to acquire a sufficient temperature (about 43 °C) when subjected to an alternate current magnetic field (ACMF, 2.58 kA m-1, 390 kHz), resulting in a successful TMH effect (Liu et al. 2021).

Developing gene therapies for a number of illnesses, including cancer, has sparked tremendous interest. However, the effectiveness of nucleic acid transport to tumour cells and in vivo efficacy are challenging to predict. These nanoparticles may be employed for gene transfer by combining anticancer therapy with imaging or diagnostic skills, to monitor the efficacy and activity of therapeutic substances in tumours (Lu 2014). To deliver siRNAs to human neural cells for gene therapy, Law et al. used quantum rod (QR)-based formulations. Imaging and gene delivery were integrated into a single nanoparticle technology that showed minimal toxicity, high transfection efficiency, and great biocompatibility (Law et al. 2012).

The pH differences between the tumour microenvironment (pH 6–7), endosomes (pH 5–6), and lysosomes (pH 4–5) have also been used to deliver chemotherapy to tumours. Several strategies have been proposed, including the utilization of ionizable chemical groups (e.g., carboxylic acids and tertiary amines), acid-labile chemical bonds (e.g., acetal and acyl hydrazine linkages), anionic and cationic pH-responsive polymers, and pH-sensitive peptides (e.g., GALA peptide). Zhou et al. created DOX-encapsulated PLGA with Ce6 (PDT and fluorescence imaging), Gd-DTPA (T1 MRI tracking), and folate (targeting) as a tumour-targeted, charge-switchable nanomaterial with multistage pH-sensitive behaviour for combined chemotherapy-PDT of cancer. At pH 6.5, the nanomaterial's charge reverses to positive without releasing DOX or Ce6, and it then progressively releases DOX into the nucleus of MGC-803 cancer cells through the endolysosome (pH 4.5–5.5). This multistage pH-sensitive characteristic resulted in increased tumour penetration (as measured by MRI and NIRF imaging), a prolonged retention duration, and good chemotherapy-PDT synergistic anti-tumour activity against MGC-803 tumours in mice, with total tumour eradication reported after 15 days (Wang et al. 2017; Chen et al. 2017; Zhou

et al. 2018). Liu et al. designed ultra-small pH-reactive Nd-doped NaDyF4 nanoagents for enhanced cancer theranostics through in situ aggregation. NaDyF4: 10% Nd was further combined with GA-Fe in consideration of its theranostic capabilities. The resulting NaDyF4:10% Nd-Fe-GA demonstrated a high R^2, significant NIR II DCL, remarkable photothermal conversion efficiency (60.12%), and no detectable toxicity. In addition, the efficient pH-responsibility features cause nanoagents to assemble in acidic conditions. Furthermore, both in vitro and in vivo investigations indicated improved contrast in tumour regions, indicating that ultra-small NaDyF4:10% Nd-Fe-GA has the potential to be used as a pH-responsive in situ aggregation-based cancer theranostic.

14.5.2 Cardiovascular Disease

Cardiovascular disease (CVD) is a term that refers to a collection of disorders that affect the blood vessels and the heart. It is a leading cause of morbidity and mortality worldwide. Despite great advancements in research on CVDs, they continue to be the major cause of mortality globally. As healthcare interventions, a range of techniques have been used. As medical technologies advance, more concise and targeted strategies are required to further enhance treatment outcomes. Among them, theranostic materials are a relatively new and promising technique that relates to the coupling of therapeutic elements with imaging agents, allowing for early identification and treatment of disease (Fig. 14.2). Additionally, since theranostic agents are capable of tracking medications and monitoring treatment, they provide a very efficient method for focused, safe pharmacotherapy that is patient centred. Theranostics is a modern discipline of medicine in which specialized targeted medication is provided in response to particular targeted diagnostic tests. Although theranostic research on CVDs is still in its infancy, theranostic nanoparticles have grown in popularity over the past decade owing to the benefits of integrating detection and therapy in a single agent. There are a few studies describing the emergence of the diagnostic or therapeutic nanoparticles (Organization WH 2020; Krumholz et al. 2005; Mendis et al. 2011).

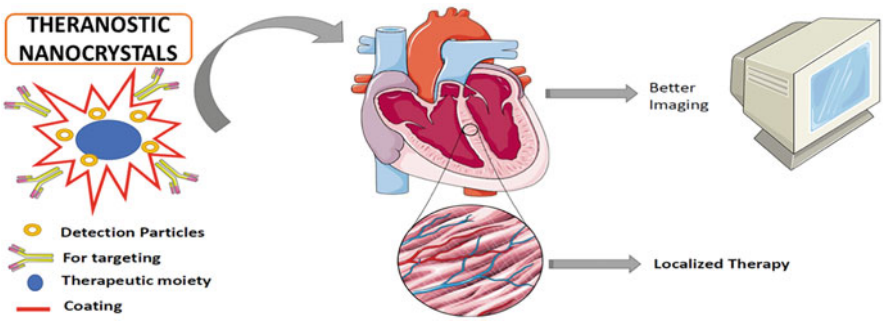

Fig. 14.2 Theranostic nanocrystals for cardiovascular disease

Limited and regulated drug delivery to the heart still remains a concern giving numerous off-target events along with limited accumulation of pharmaceuticals in the heart. There is a need to create and enhance technologies to enable for better creation of pharmaceutical candidates for management of cardiac disorders. Over the past decade, innovative pharmacological platforms and nanomaterials were devised to localize bioactive molecules to the heart. Yet, the research continues in its inception, not only in the creation of instruments but also in the knowledge of impacts of these materials on heart function and tissue viability. Upconverting nanocrystals are nanomaterials that lately stimulated interest in theranostic nanomedicine technology. Their unique photophysical features enable for sensitive in vivo imaging that may be paired with spatio-temporal control for selective release of encapsulated medicines. Recent research by Kermorgant et al. on the potential upconverting NaYF4:Yb, Tm nanocrystals demonstrates for the first time their safety when injected into the myocardial or pericardial region of mice. The accumulation and upconversion of nanoparticles in the cardiac zone did not affect heart rate variability or cardiac function even 15 days after a single injection. Overall, these nanoparticles demonstrate nontoxicity in the pericardial area and are safe for regulated spatiotemporal drug delivery. These findings suggested the use of upconverting nanocrystals as prospective theranostic instruments capable of overcoming a number of the most significant constraints of traditional experimental cardiology techniques (Kermorgant et al. 2019). For the evaluation and diagnosis of pressure-related disorders, Li et al. manufactured implantable pressure biosensors. This approach was used to create core/shell polyvinylidene difluoride (PVDF)/hydroxylamine hydrochloride (HHE) organic piezoelectric nanofibres with well-controlled and self-orientated nanocrystals in the spatial uniaxial orientation (SUO) of β-phase-rich fibres. Piezoelectric efficiency, wear resistance, consistency, and biocompatibility were all much improved by these nanocrystals. Li and colleagues implanted PVDF/HHE OPNs sensors into the pig's heart, which demonstrated ultrahigh detecting precision and accuracy to record micropressure variations at the exterior cardiovascular walls, cardiovascular flexibility, and the occurrence of atrioventricular cardiovascular blockage as well as thrombus formation (Li et al. 2019b).

14.5.2.1 Atherosclerosis

Atherosclerosis is a deadly disease that damages the heart and brain among other vital organs. The endothelium and smooth muscle of the arterial wall are damaged when noxious substances associated with factors such as high levels of cholesterol, high blood pressure, diabetes, smoking, and homocysteinaemia interfere with the homeostatic state of the artery wall. We term this disease process atherosclerosis because of the excessive inflammatory, fibroproliferative, and defensive response that ensues as a consequence (atherosclerosis) (Ross 1995).

Heart and brain problems caused by atherosclerosis are very harmful to human health. However, nano-photothermal technologies has already been proved to reduce vascular inflammation, but existing photothermal agents are ineffective in monitoring the disease's progression. For the treatment of arterial inflammation, Lu et al.

devised and manufactured a highly effective bifunctional nanoplatform. A straightforward hydrothermal process was used to create Cu3BiS3 nanocrystals with a diameter of around 12 nm. It was found that the Cu3BiS3 nanocrystals displayed an incredible photothermal effect because of their strong NIR absorption. Atherosclerosis can be prevented by using Cu3BiS3 nanocrystals to kill macrophages in vitro and in vivo, which play a critical role in the development of the atherosclerosis. Furthermore, Cu3BiS3 nanocrystals may be employed as a CT contrast agent for the detection of inflammation of the carotid arteries (Lu et al. 2020). Furthermore, gold, iron oxide, or quantum dot nanocrystals were used in the development of multimodality HDL-mimicking nanoparticles by Cormode et al. for computed tomography, magnetic resonance, and fluorescence imaging, respectively. Multimodal characteristics were obtained by including gadolinium and rhodamine in the nanosystem. Macrophages were able to effectively ingest the HDL-like nanoparticles confirmed utilizing confocal microscopy (CM), TEM, CT, T1-weighted MRI, T2-weighted MRI, and fluorescence imaging. Multimodality scanning of atherosclerosis utilizing targeted HDL nanocrystals was also performed in vivo (Cormode et al. 2008).

14.5.2.2 Thrombosis

Haemostasis is the process that preserves the viability of a sealed, high-pressure circulatory system following vascular injury. Vessel wall damage and the efflux of blood from the circulation swiftly trigger actions in the vessel wall and in blood that close the gap. Circulating platelets are drawn to the site of injury, where they constitute a key component of the growing thrombus; blood coagulation, triggered by tissue factor, culminates in the synthesis of thrombin and fibrin (Shibata et al. 1979).

Ma et al. investigated the viability and effectiveness of target thrombolysis using recombinant tissue plasminogen activator (rtPA) covalently linked to a magnetic nanoparticle (MNP) and held in vivo at the target location by an external magnet. They produced and studied polyacrylic acid-coated magnetite (PAA–MNP, 246 nm); rtPA was bound to PAA–MNP through carbodiimide-mediated amide bond formation. In conclusion, covalent immobilization of rtPA to PAA–MNP resulted in a stable rtPA formulation and a predictable quantity of rtPA in the vicinity of the target site under magnetic direction; this strategy may result in repeatable and effective target thrombolysis with more than 20% of a standard dosage of rtPA (Ma et al. 2009). Recently, Jung et al. designed thrombus-specific theranostic (T-FBM) nanoparticles that might be used as an antithrombotic nanomedicine by amplifying photoacoustic signals caused by H2O2. These T-FBM nanoparticles were engineered to specifically target fibrin-rich thrombi and were triggered with H2O2 to create CO2 bubbles that amplified the photoacoustic output. Inside endothelial cells, these T-FBM nanoparticles also exhibited antioxidant, anti-inflammatory, and antiplatelet activity when they are activated with H2O2. Also, these T-FBM nanoparticles greatly increased photoacoustic contrast in thrombosed arteries and significantly inhibited thrombus formation in animal models of carotid artery damage. Based on their research findings, T-FBM nanoparticles will have

significant translational potential as nanotheranostics treating cardiovascular disorders connected with H2O2 (Jung et al. 2018).

Nanocrystals of EP-2104R, a fibrin-targeting Gd-based MR CA with six amino acid cyclic polypeptide linked to four Gd (DOTA) chelates, were produced by Uppal et al. Dual PET-MR probe EP-2104R was partly depleted of Gd3+ and subsequently chelated with 64Cu to produce a fibrin-targeting dual PET-MR probe enabling concurrent PET and MR scanning of thrombus. By using combined PET and MR imaging, we could clearly identify the thrombosis in a rat artery thrombus model (Uppal et al. 2012; Yang et al. 2018).

14.5.2.3 Myocardial Infarction

Myocardial infarction (MI) is a kind of heart muscle damage caused by a restriction of the heart's blood supply, most often owing to thrombosis. Myocardial infarction (MI) may be identified clinically by electrocardiographic (ECG) abnormalities, high levels of biochemical markers (biomarkers) indicating myocardial necrosis, and imaging, or it can be characterized pathologically. MI may develop as the initial symptom of coronary artery disease (CAD), or it might recur in people with preexisting disease. Between 60% and 80% of MI induced by thrombosis are initiated by the fracture of susceptible atherosclerotic plaques. The remaining 20%–40% is due to intimal surface erosion. MI may result in major complications such as arrhythmia, heart failure, cardiogenic shock, or cardiac arrest, resulting in increased disability and mortality worldwide (Zia et al. 2020; Ta et al. 2017; Thygesen et al. 2012).

TNF-α, a pro-inflammatory cytokine, is thought to be involved in irreparable cardiac damage at the outset of MI. TNF-α-mediated MI is caused by a number of mechanisms, including the stimulation of proinflammatory cytokine networks and the generation of RNS and ROS. As a result, efficient TNF-α inhibition in the course of inflammatory phase seems to be critical for MI therapy (Bozkurt et al. 1998; Kleinbongard et al. 2011; Pagani et al. 1992). Somasuntharam et al. employed gold nanoparticles (AuNPs) functionalized with deoxyribozyme (DNAzyme) to catalytically suppress tumour necrosis factor-α (TNF-α) in vivo as a possible treatment for myocardial infarction in this work (MI). They achieved 50% of TNF-α silencing utilizing primary macrophages as a model, which was not possible using lipofectamine-based techniques. Local injection of DNAzyme coupled to gold nanoparticles (AuNPs) into the rat myocardium inhibited TNF-α by 50%, resulting in considerable anti-inflammatory actions and improved acute cardiovascular output after MI (Somasuntharam et al. 2016).

Ischemic heart disease is the initial stage of myocardial infarction (MI). The atherosclerotic plaque inside the coronary artery causes stenosis resulting in inadequate blood flow and decreased supply of blood to the myocardium. This plaque may also break inside the vessels as the condition advances, causing thrombosis and finally blockage. Therefore, treatment of ischemic heart illness in its early stages may be an effective technique for the treatment of myocardial infarction (Anderson et al. 2017; Manfroi et al. 2002; Nabel and Braunwald 2012). Feiner et al. revealed a synthetic cardiac patch that merges cardiac cells with elastic, independent electronics

and a three-dimensional nanocomposite framework to provide a more effective treatment for heart failure. In addition to exhibiting strong electronic features, the patch was also capable of monitoring cellular electrical activity and providing on-demand electrical stimulation to synchronize cell contraction. Moreover, they have shown that electroactive polymers comprising biological components may be coated on specific electrodes in order to deliver medications into the patch microenvironment upon demand (Feiner et al. 2016).

14.5.2.4 Vascular Injury and Restenosis

Vascular damage produced by stenting and restenosis may result in a range of cardiovascular problems, including thrombosis, myocardial infarction, and ischemic heart disease if not treated promptly.

In the study done by Lanza and fellow investigators, they have incorporated paclitaxel or doxorubicin into perfluorocarbon nanoparticle which was attached to the anti-recombinant porcine tissue factor to target smooth muscle cells. The nanosystem developed provides unique and quantitative drug delivery system through MRI (Lanza et al. 2002). Cyrus et al. have also prepared perfluorocarbon nanoparticle with αvβ3-target and loaded with rapamycin. The result obtained demonstrates that αvβ3-targeted nanoparticles may quickly block the restenosis of New Zealand white (NZW) rabbit. This will offer MRI imaging with accuracy within few minutes after giving injection (Cyrus et al. 2008). In another study Gu et al. have synthesized theranostic layered double hydroxide nanoparticles which contain low molecular weight heparin (used for therapy) and CdTe quantum dots (required for imaging). The results showed that the nanoparticles synthesized were targeting wounded arteries and can minimize the injured area for rats (Gu et al. 2012). The shape of the particle is anticipated to be important in the targeted delivery of therapeutic medications or imaging compounds to wounded blood arteries using nanocarriers. He et al. and colleagues proved that cuboidal cyclodextrin frameworks outperform spherical counterparts in terms of haemostasis and wounded vascular targeting. Cuboidal and biocompatible cyclodextrin metal-organic frameworks (CD-MOFs) were created and coupled with GRGDS peptide by bridging and surface modification (GS5-MOFs). Cuboidal nanocrystals exhibited increased adherence and aggregation with activated platelets in vitro under static and biologically relevant flow conditions. They also demonstrated effective haemostatic effects, with bleeding duration and blood loss reduced by 90% and robust damaged vascular targeting in vivo, much outperforming spherical-CD nanosponges with about the same chemical makeup (He et al. 2019).

14.5.3 Neurodegenerative Disorders

There are a range of diseases known as neurodegenerative disorders that affect different parts of the brain, such as the hippocampus, the cerebellum, and the brain stem, and are caused by protein build-up in the cells, gene alterations, synaptic degeneration, and mitochondrial malfunction. Inconsistent neuronal performance

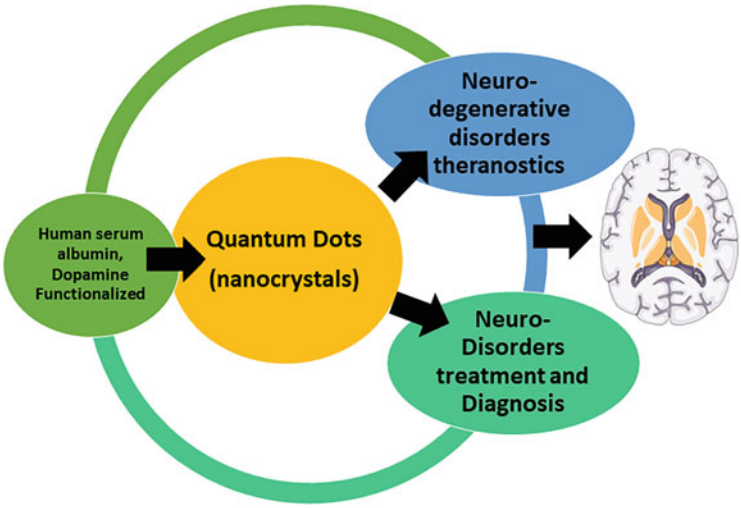

Fig. 14.3 Quantum dots (QDs) as theranostics for neurodegenerative disorders

and disruptions between neuronal cells or any region of the brain result in neuronal cell death, leading to ND-related disorders. Neurodegeneration refers to the destruction of neuronal cells or the degradation of the brain. AD, Parkinson's disease (PD), and prion disease are all examples of neuronal impairments induced by a combination of numerous variables. The blood-brain barrier (BBB) acts as a protective barrier to the central nervous system (CNS) by regulating homeostasis. Besides reducing the passage of toxic xenobiotic compounds and endogenous compounds to CNS, BBB also inhibits the entry of therapeutic substances. Nanotechnology gives the opportunity to deliver smaller molecules/drugs against CNS ailments through BBB (Nirale et al. 2020a; Sweeney et al. 2018; Norrara et al. 2017; Sharma et al. 2019; Barnham et al. 2004; Lin and Beal 2006). Quantum dots (QDs) are most prominently used for the treatment of neurodegenerative disorders (Fig. 14.3).

QDs are semiconductor type of nanocrystals with exceptional and unique features such as fluorescence, greater photostability, and electrochemical capabilities. These features of Qds are a result of their zero-dimensional construction, in which the quantum confinement effect among bulk and discrete molecules confines them. Due to their size-dependent qualities, they possess adjustable fluorescence properties: big QDs emit red light because of their tiny energy gap, whereas small QDs emit blue light because of their wider energy gap. In the biological and pharmaceutical areas, they are particularly useful for pharmaceutical targeting, cell diagnostics, and visualization. They are also utilized in the diagnosis and treatment of NDs because of their small particle size and high permeability. QDs are nanostructures that exhibit low cytotoxicity, cell proliferation, cell differentiation, and cellular metabolic activity (Singh et al. 2021).

14.5.3.1 Alzheimer's Disease (AD)

This progressive neurodegenerative ailment, Alzheimer's disease (AD), is one of the most frequent causes of dementia in the elderly and ultimately results in death. Initial minor memory impairment leads to a fully devastating loss of physically and mentally abilities, which is defined as a degenerative dementing illness. Following the commencement of symptoms, the disease's course may range from a few years to more than 20 years, with an average survival time of around 8 years. Ten to fifteen percent of people over 65 and up to 47% of those over the age of 80 are affected by Alzheimer's disease. In Alzheimer's, the -amyloid peptide builds up in the brain's nerve cells (neurons), causing memory loss and deteriorating cognitive abilities (Smith 1998; Cai et al. 2020; Cummings and Cole 2002). To improve treatment outcomes, drugs needed to be targeted across the blood-brain barrier (BBB) and into the central nervous system (CNS) at the ideal therapeutic dosage. Diagnostic tools, drug carriers, and theranostics based on nanotechnology provide very sensitive molecular detection, efficient drug targeting, and their combination. Significant research has been conducted in this field over the last decade, and we have witnessed great results in AD treatment. Numerous nanoparticles from the organic and inorganic nanomaterial categories have been successfully explored for their anti-AD properties (Ahmad et al. 2017).

Numerous publications have examined various tactics and approaches for successfully delivering drugs to the CNS while also diagnosing (Amiri et al. 2013). Wang et al. synthesized a multifunctional theranostic nanocomposite (HSA-BFP@CDs) by conjugating triple-functionalized human serum albumin (HSA-BFP) with carbon dots (CDs) as a ROS scavenger. When HSA-BFP@CDs interact with Aβ aggregates, a fluorescence "off-on" effect at 700 nm was seen, demonstrating the capacity to detect Aβ plaques and the possibility for earlier diagnosis of Alzheimer's disease. It also efficiently suppresses Aβ aggregation, resulting in an increase in cell. Moreover, numerous ROS, including hydroxyl radicals, superoxide radicals, hydrogen peroxide, and Aβ-Cu2 + −induced-ROS, may be scavenged by using HSA-BFP@CDs, thereby leading to the reduction of cellular oxidative damages. It has been shown that HSA-BFP@CDS may be used to detect and treat amyloid plaques, reduce Aβ deposition, and alleviate the effects of oxidative stress in the brain of *Caenorhabditis* worms, an animal model of Alzheimer's disease (AD). A new understanding of protein-carbon dot conjugate design and the development of AD multi-target treatment were gained via this research (Pansieri et al. 2017). Chen et al. devised a quick, ultrasensitive detection approach for tau protein and other neurological biomarkers. They synthesized CuInS2/ZnS quantum dots functionalized using dopamine to detect tau protein utilizing a new tyrosinase (TYR)-induced tau aptamer–tau–tau antibody (anti-tau) sandwich fluorescence immunoassay. Quantum dots with high brightness, low toxicity, and great biocompatibility were successfully synthesized and decked with dopamine using amide conjugation. The fluorescence intensity of the immunoassay based on DA-functionalized CuInS2/ZnS quantum dots demonstrates excellent performance in terms of linearity with the logarithm of tau protein concentration (Chen et al. 2019).

14.5.3.2 Parkinson's Disease (PD)

Parkinson's disease is the second most prevalent neurodegenerative condition, affecting 2–3% of the 65-year-old population. Parkinson's disease is characterized by neuronal death in the substantia nigra, which results in striatal dopamine insufficiency, and intracellular inclusions containing clumps of α-synuclein. Parkinson's disease is a diverse illness with variants that advance swiftly and slowly. Deep brain stimulation and therapy with levodopa-carbidopa enteral suspension may assist persons with drug-resistant tremor, symptoms that increase after the medicine wears off, and dyskinesias. However, poor brain transfers and limited bioavailability during traditional therapy pose a formidable obstacle in the treatment and diagnosis. In response to these shortcomings, drug delivery nanocrystals (NP) may serve as an exceptional tool for enhancing the therapeutic efficacy of anti-Parkinson's medications for simultaneous therapy and diagnostics (Poewe et al. 2017; Armstrong and Okun 2020; Ghazy et al. 2021).

Theranostic nanocarriers based on liposomes, quantum dots (QDs), and an anti-Parkinson's medication have been created by Wen et al. for long-term monitoring and drug delivery. In this research, apomorphine was employed as a model drug. It has been licenced for use in the treatment of "off" phases of Parkinson's disease by injection as a rescue medicine. However, its short half-life (approximately 41 minutes) and intrinsic instability have limited its clinical use. Incorporating it into nanoparticles may help to mitigate these drawbacks (Wen et al. 2012). Liposomal QD/apomorphine-integrated multifunctional liposomes have emerged as useful diagnostic and therapeutic tools. Cancer, Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, diabetes, and heart failure are all triggered by mitochondrial malfunction. Hua et al. used chitosan, ethylenediamine, and mercaptosuccinic acid as carbon sources to make a new form of luminous CDs (carbon dots). High mitochondrial targeting specificity, wash free and long-term imaging, great photostability, and multicolour FL imaging are only some of the advantages of CDs manufactured in this way. Aside from that, the synthetic process for CDs is easy, inexpensive, and environmentally benign, making it an excellent choice for large-scale manufacture and potential biological uses in the future. CDs may enter cells through temperature-dependent transport and caveolae-mediated endocytosis and then precisely target mitochondria (Hua et al. 2017).

14.5.3.3 Prion Disease

Prion disorder is known as spongiform encephalopathy (SE) because of its sponge-like development in the brain. In the case of the prion's sickness, the brain becomes a sponge-like structure because healthy tissues are replaced by cysts or vacuoles. Prion disease is caused by misfolded prion proteins aggregating in the cerebrum and cerebellum, mostly. The infectious proteins are called prions, which are found in the cell membranes of certain neurons and contain 253 amino acids in the form of three helices and two pleated sheets that are found in the cell membranes of some neurons (Forloni et al. 2019; Hagiwara et al. 2019; Nirale et al. 2020b). Xiao et al. constructed a technique using two aptamers that recognize two distinct epitopes from PrPSc to differentiate it from PrPc in serum and brain tissue homogenate. The

aptamers are bound to the surface of magnetic microparticles and quantum dots. It forms a sandwich structure with strong fluorescence in aqueous media in the presence of PrPSc, which may be separated by an external magnetic field (Xiao et al. 2010). Xie et al. have shown that QD-PEG dispersed in nitrile acetic acid may serve as a site-specific marker for the in vitro PrP expressed at the cell surface (Furmanski et al. 2009).

14.6 Advantages of Theranostic Nanocrystals

Although the discipline of theranostics is still in its infancy, significant research and development efforts have been made toward theranostic nanocrystals for cancer and cardiovascular-guided imaging and treatment. Biodegradable and metabolizable polymeric nanoparticles have been created and evaluated in small animal models using a variety of theranostic nanoplatforms. These particles have a long circulation life, are biosafe, can be decorated with targeted moieties, and can be loaded with medicinal and contrast chemicals. These multifunctional polymer nanocrystals containing anatomical information may be employed for noninvasive diagnostics of some disorders. Additionally, the pharmacokinetics, biodistribution, and targeting efficacy of conjugated or encapsulated medicinal compounds, as well as therapeutic responses, may be determined. These capabilities may aid in the preclinical and clinical stages of drug development. When it comes to accomplishing the objective of theranostic activity, the nanocrystal semiconductors known as quantum dots (QDs) are by far the most efficient and effective medicine delivery methods. This is because they are an intermediate between bulk semiconductors and discrete entities in terms of qualities like luminescence, photostability, electrical properties, high excitation capacity, and size adjustable emission. They also have remarkable optical and electrochemical properties. There are a wide range of uses for these devices, including diagnostics, bioimaging, and bio-sensory applications as well as therapeutic treatments.

Nanocrystal formulation allows for the delivery of poorly soluble pharmaceuticals and provides significant benefits over current methods. In addition to oral and intravenous drug administration, nanocrystal formulations have demonstrated promising outcomes for transdermal, ophthalmic, and pulmonary drug delivery. With the continuous development of much more poorly soluble pharmaceuticals, the demand for nanocrystal-based products will become crucial for the development of innovative ways to assess and comprehend the in vivo destiny of these substances. The hybrid nanocrystal idea offers a platform for nanocrystal bioimaging in vivo. Embedding fluorescent probes in drug nanocrystals does not need additional stages in the manufacturing of nanocrystals, which is an additional benefit of using hybrid nanocrystals as an innovative theranostic tool (Lu et al. 2019).

14.7 Challenges and Future Goals

Evidently, theranostic nanocrystals are being used to combine diagnostic and therapeutic capabilities, resulting in much enhanced individualized illness treatment. Many important hurdles must be solved in order for clinical translation to occur, including selecting the optimum nanoplatform, improving ligand conjugation efficiency, and developing an ideal synthesis process with fewer steps, greater repeatability, and reduced costs.

Despite significant technology advancements in prevention of disease, diagnostics, and treatment, nanotheranostics, which is emerging as a new paradigm for disease diagnosis and treatment in clinics, is still in its early stages. The nanobiointeraction is one of the most difficult aspects of bringing theranostic nanomedicine to clinics. The hazardous impact of nanoformulations is highly reliant on numerous aspects such as size, ζ-potential, and solubility. According to experimental research, nanoparticles with high therapeutic qualities may not always be appropriate diagnostic tools. Anti-EGFR-coated gold nanoparticles with a 20 nm size exhibited excellent tumour uptake, whereas gold nanoparticles with a 50 nm size demonstrated the best CT contrast enhancement. This review demonstrates the importance of nanoparticle size in their use as medicinal agents or diagnostic instruments. Another important issue with clinical application of theranostic nanomedicines is the complexity in developing a repeatable and controlled production process. Large-scale nanoparticle synthesis suffers from poor batch-to-batch repeatability, a wide range of altered physical and chemical properties, and insufficient yield. Good manufacturing practices, as well as more accurate manufacture, control, and chemistry, are required for the development of multifunctional theranostic nanoparticles that can be transferred from the laboratories to health centres, which is a tough undertaking to do on a big scale. The large divide between the research community and regulatory agencies is a third important problem that must be addressed. Many government rules based on regulatory variables linked to quality management, manufacturing methods, safety profile, and intellectual property protection are being used to oversee the commercialization of nanomedicine. The lack of defined regulatory and safety criteria has a significant impact on the timely and successful applicability of the theranostics to market.

Theranostic nanoagents have the potential to significantly improve disease detection and treatment by incorporating several capabilities, including those used for targeting, imaging, and therapy, into a single nanoscaffold. However, many concerns must be addressed before the discipline can progress beyond its infancy, including whether to use nanoagents and how to effectively match the dose of diagnostic and therapeutic components. Most critically, scientists creating nanoparticle preparations must reconcile their synthetic approaches with the nanoagents' eventual therapeutic value. This can only be accomplished via the establishment of productive relationships with scientists and physicians working in domains unrelated to their own. Given these obstacles, the field of theranostics is fast expanding and, like a toddler, is certain to have a few bumps and bruises along the way.

Diagnostic imaging using disease-related molecular targets, downstream molecular targets influenced by therapy, and a nanostructure analogous to a therapeutic nanostructure might be utilized to assess therapeutic response and effectiveness during or after treatment. Unfortunately, theranostic technology for medication response monitoring is still in the early stages of research; few studies have focused on combining treatment and response imaging into a single theranostic system. However, the need for a more individualized approach to medical care, as well as considerable continuing breakthroughs in nanotechnology and diagnostic imaging technologies, may soon change theranostic systems. However, certain critical difficulties must be addressed first in order to achieve effective assimilation into theranostic systems. Theranostic systems, in particular, must address the apparent mismatch between the ideal concentrations of imaging and therapeutic agents for prospective clinical application, since the optimal concentration for a desired treatment is often considerably greater than that necessary for imaging. Furthermore, a theranostic system might incorporate numerous functions inside a single system, which can add to the system's complexity. As a result, developing repeatable and straightforward approaches for constructing theranostic systems may aid in the effective integration of imaging and treatment. Furthermore, using clinically proven nanoparticles to hasten the clinical translation of theranostic NP might reduce the risk of translation. Diagnostic imaging has been demonstrated to play a significant role in several aspects of personalized medicine, including monitoring medication effectiveness. The development of diagnostic imaging after treatment, ideally in a single system, might enable customized medicine by allowing therapy selection, treatment planning, objective response monitoring, and follow-up therapy planning based on the individual molecular features of a disease, thereby laying the groundwork for personalized medicine.

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