Smart Nanomaterials for Bioimaging Applications: An Overview

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Abstract

Nanomaterials are the classes of nanomaterials which basically fall in the range of 1–100 nm dimensions and have achieved its ubiquitous role in the domain of bioelectronics to biomedical area. The applications in the biomedical domain comprise bioimaging, targeted drug delivery, anti-cancerous activity, etc., which have attracted much attention in the recent times. Due to the specific unique activity of nano-scaled materials such as its higher surface to volume ratio, higher surface energy, more surface reactivity, etc., such materials find applications in the field of biological domain to electronical area. The electron confinement activity to differentially capped nano-scaled materials have been used extensively now-a-days in the bioimaging and applications. Due to the higher quantum yield and more stability in the biological systems, nanomaterials have been a material of choice for an augmented biological activity as compared to their bulk counterparts. Such nanomaterials due to their biocompatible dimensions having

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resemblance to biological systems, enable for an effective drug delivery carrier molecule as compared to other drug carrier systems. Moreover, such materials bear unique photo-physical and luminescence properties which are harnessed for different bioimaging applications, showing robust imaging behaviour as compared to the bulk systems. Finally, targeted drug delivery (TDD) means has been achieved in a better and refined manner using such nano-scaled materials owing to their unique specificity and sensitivity attributes in the biological interface. Understanding the comprehensive role of nano-scaled materials in diverse biomedical area specifically in myriad imaging techniques makes nanomaterials of different types a preferred choice in bioimaging applications making a revolutionary measure in the biomedical field of research and applications.

Keywords

Nanomaterials · Biomedical · Bioimaging · Surface area · Luminescence

16.1 Introduction

With the introduction of nano-scaled targeted drug delivery systems, the efficiency of many conventional pharmaceutical therapies can be significantly improved. It helps to avoid unnecessary drug loss because nanocarriers show higher loading efficiency, thereby providing protection from the harsh surrounding. It helps to minimise unwanted side effects because it possesses higher specificity, biocompatibility and biodegradability behaviour (Naeem et al. 2020).

Nanotechnology is used for multiple purposes like titanium dioxide (Tio2) or zinc oxide (ZnO) which absorbs UV radiation and is thus used in sunscreen (Petrick and Ibadurrohman 2020), silver (AgNPs) which is used in antimicrobial activity and is used in soap formulations, surgical implants, etc. (Gunputh et al. 2020). It is also reported that Gold (AuNPs) nanoparticles were also used in different bioimaging applications and diagnosis (Mousavi et al. 2020). Nanoparticle formation and distribution has diverse bioimaging varieties thereby finding advantages in early diagnosis and treatment of diseases (Viana et al. 2020). Upon using such nano-scaled bioimaging materials cellular localisation, interaction dynamic changes of a variety of bioactive substances can be observed (Placido et al. 2019). It can be observed that environmental nanoparticle from atmospheric, terrestrial, aquatic regions is obtained and synthesised biogenically (Órdenes-Aenishanslins et al. 2020) for different bioimaging applications. Nanomaterials of different types are basically synthesised using bottom-up method and top-down technology. Bottom-up technology refers to the process where the smaller subunits are added to form larger complex materials whereas in case of top-down technique, the larger chunk of precursor material is broken down into smaller subunits or monomers for different applications. Usually bottom-up technique is mostly preferred as compared to the top-down principles because of the sensitivity approach involved in the formation of the polymeric molecules upon gradual addition of smaller contributing monomeric forms resulting

into sensitive applications in diverse fields mostly in bioimaging, tagging agents, etc. (Li et al. 2019).

In the recent times, nanomaterials both chemically synthesised and biogenically synthesised are used in diverse applications ranging from toxic contaminant chelation and removal mechanism to dreaded disease treatment. In case of environmental detection and removal of heavy metals from the polluted sources like contaminated water bodies, industrial belts, etc., several tailor made nano-scaled materials were employed by several groups for the successful detection and removal of the pollutants like iron oxide nanoparticles (FeONPs) for heavy metal removal from water bodies, etc. (Samrot et al. 2019). Similarly, several groups have also fabricated pristine as well as decorated/functionalised nanomaterials for the effective detection mechanism of the heavy metal ions like Cadmium, Arsenic, etc. (Shi et al. 2019). Also, in the biomedical field of research, different classes of nanomaterials like Gold nanoparticles, etc., are used extensively these days for effective cancer diagnosis and treatment (Sayyadi et al. 2019) for bearing the sensitivity and selectivity properties of such nano-scaled materials thereby achieving a targeted drug delivery response in the cancer treatment process. In this chapter, specifically the bioimaging nature and mechanism of different classes of nanomaterials has been studied besides different bio-activity of nanomaterials in the current scenario to uncover and present the imaging potentialities of such nanomaterials in the biomedical field of research which can aid in understanding and formulating nano-based future imaging agents which can outcompete the conventional manner of imaging of the bio systems.

16.2 Inorganic Nanocarriers in Bioimaging and Drug Delivery

Inorganic nanomaterials find widespread applications in the field of biochemistry, biotechnology and biomedical domains (Yang et al. 2019). Such applications include Gold nanoparticles, 2D-graphene, carbon nanotubes, quantum dots, mesoporous silica nanoparticles, quantum dots, magnetic nanoparticles, multifunctional composite nanoparticles, etc., which have become a promising choice in diverse biomedical research fields (Yogesh et al. 2020). In bioimaging, inorganic nanoparticles have shown great potential and diverse applications and are beneficial for targeted drug delivery and cancer therapies (Caires et al. 2020).

16.2.1 Carbon Nanotube as Imaging Agents

For a plethora of biomedical applications, carbon nanotubes (CNTs) have been used extensively in the current scenario (Yadav et al. 2020). Carbon nanotubes are also useful for delivery vehicles for carrying drugs, proteins, DNA, imaging agents and other materials (Prajapati et al. 2020). New CNT based contrast agent (CA) synthesis can be used for X-ray computed tomography (CT) imaging (Deshmukh et al. 2020). The CA is a hybrid material derived by using ultrashort single-walled carbon nanotubes (20–80 nm long, US-tubes) & Bi (iii) oxo-salicylate clusters with four

Bi (iii) ions per clusters (Bi4C). Over iodine, bismuth element was chosen that is conventional element used for CT Cas in the clinic because of its high X-ray attenuation capability and its low toxicity, due to this bismuth is a more promising element for new CT CA design.

16.2.2 Colloidal Gold Nanoparticles as Imaging Agents

Colloidal gold nanoparticles can be used for the biomedicine and drug delivery purposes (Masse et al. 2019). By preparation of the monodispersed GNPs (Gold Nanoparticles) by using the citrate reduction method, it helps to find out the importance of colloidal gold (Biterge-Süt and Canpolat 2019). For a variety of purposes like contrast agents, drugs, in vivo delivery of genes, colloidal gold nanoparticle is of choice by several researchers. It is because of its easy synthesis, large surface area, it has become proposed DDSs (Drug Delivery Systems) in different biomedical fields (Daraee et al. 2016). It can create DDSs with the help of smart polymers that help to release their payload to respond to external stimuli. It can also be used as photothermal agents in photothermal therapy because of bearing the property of higher molar absorption coefficient (Takeuchi et al. 2017). GNPs lie in the visible to near infra-red region. Also, biological applications of GNPs range from biomolecular sensing to therapeutic interventions due to its intrinsic surface plasmon resonance behaviour (Weissman et al. 2016). The Schiffrin–Brust biphasic method has been the most acceptable choice owing to the requirement of lesser reagents and solutions for the synthesis of GNPs, which was developed in the year 1994. Owing to the lack of different types of surface capping ligands and the presence of available chemical modifications over the surface of the GNPs structure, the same has been in use in diverse applications from nanotechnology to biomedicinal domains (Shimoni and Valenzuela 2017). Different steps are been employed for the production of water-dispersive GNPs with functionalised moieties for applications in different fields. Several groups have introduced various ligand exchange reactions on alkane thiol protected GNPs via careful surface modification (Lopez-Chaves et al. 2018). It is also possible to create gold nanostructures with active targeting capabilities and would be really useful for the detection of overexpressed cancerous cells using the mechanism of target-receptor modalities.

Making the recognition specific in nature (Wolfe et al. 2016) and their cellular toxicity has indeed been examined by several research groups as for the cytotoxicity of GNPs (Jia et al. 2017). The requirement of distinction between the toxicity of the GNP core and the exterior ligands is of paramount importance. It is found that upon carboxylate terminal capping using alkylthiolate-GNPs, the toxicity of the GNPs seems to be reduced, whereas the cationic GNPs are seem to be non-toxic in nature (Bhawawet et al. 2018). It has been reported that Human leukaemia cells (K562), upon treatment with functionalised GNPs with glucose, citrate, cysteine, biotin exhibit no significant toxicity in the cell lines as comparted to the salt solutions of Gold chloride (HuCL4), which has a tremendous toxicity of 90% inhibition when treated to same cell lines (Martínez-Torres et al. 2019). For the cancer treatment,

most of the work on drug delivery of GNPs has been studied thereby limiting the exposure towards the healthy tissue through both passive and active targeting, where the concentration of drug can be increased at the tumour site resulting in return a robust targeted anti-cancerous activity as compared to the conventional way of cancerous treatment (Penon et al. 2017).

16.2.3 Mesoporous Silica Nanoparticles

Another important group of inorganic delivery system is colloidal mesoporous silica nanoparticles (MSNPs). Owing to their unique controlled morphologies, significant mesostructures with tremendous biocompatibility with a flexibility of effective functionalisation approach, such mesoporous silica nanoparticles find effective applications in the biological domains (Manzano and Vallet-Regí 2020). It can be also made hydrophilic by decorating them with the abundant silanol groups on the surface of MSNPs. Using various means, the controlled holding/release of cargo molecules has also been achieved by several groups. The mesoporous materials pore capacity and large internal surface area enable the effective entrapment of the therapeutic cargo molecules inside the porous structure of the material leading to the efficient therapeutic efficiency towards the desired target moieties (Siminzar et al. 2020). To improve the efficacy of the delivery of various hydrophobic anticancer drugs within the bloodstream the MSNPs, it takes advantages of the larger intrinsic pore capacity which make the payload drug solubilised. It is because of the effectiveness of such drugs encapsulation, the efficacy of the drug release and the kinetics is achieved more robustly than other delivery means. On both the exterior and the interior surfaces, the modification of MSNPs can be achieved. In order to improve the nanocarrier drug delivery mechanism and provide a range of functionalities, modification of SNPs is more acceptable. MSNPs in their mesoporous structure with a high surface area to volume ratio contribute to the extensive functionalization via covalent or electrostatic interactions, where there the augmented rate of organic molecules is placed in the silanol groups of the outside surface of the material structures. The side effects of the drug delivery approach could be reduced and the increasing in the specificity of the drug delivery modalities could be harnessed using such versatile MSNPs surface properties as potential drug delivery vector platform.

Functionalisation of the internal structures of the MSNPs intrinsic structure could also augment the rate of drug delivery approach using such nano-scaled mesoporous structure for potentially viable molecules like proteins, nucleic acids for myriad therapeutic areas along with the underlying exploration of effective cytotoxicity regime of the material towards the biological systems (Downing and Jain 2020). With both healthy cells and cancer cell lines cellular uptake phenomenon of MSNPs and their good biocompatibility properties were confirmed. Surface charge, effective shape and overall dimension of the nanomaterials determine the effective cellular uptake behaviour and their associated cytotoxicity when introduced into the biological. It has been reported that non-modified MSNPs in the concentration up

to 100 mg/ml, dimensions ~100 nm exhibits no significant cytotoxicity has been observed which is not significant for the effective therapeutic efficacy. The effective therapeutic activity of the drug delivery mechanism is only been achieved by the utilisation of the lowest drug molecule when confronted in the healthy tissues with the compromised side effects in the healthy cells, which is especially important in the cancer therapy regime. Depend on chemically modifying MSNPs with targeted moieties most strategies used for cell targeting (Choi et al. 2020). Some of the moieties includes the proteins, FA, antibodies, peptides molecules, etc. For cancer cell targeting based on PEI-functionalised and FA- conjugated MSNPs developed a selective nanoparticulate system. Using FA as the targeting ligand the PEI-MSNP hybrid nanoparticles are non-toxic and can be specifically endocytosed. In order to gain a tremendous cancer treatment effectivity, Folate receptors play a significant role in the treatment of the disease and the higher rate of material internalisation is achieved when diagnosis of the tumour cells in the cancer therapy management is concerned (Song et al. 2020).

16.2.4 Quantum Dots in Imaging

The engineering of multifunctional nanodevices Quantum dots (QDs), semiconductor nanoparticles with unique photo-physical properties have become one of the dominant classes of imaging probes as well as universal platforms (Shukla et al. 2020). The exceptional photostability along with the one photon-multiphoton absorption behaviour with the size dependent tunable absorption and emission attributes is achieved using the QDs (Quantum Dots). The bleeding nature during the multiplexed bioimaging process could be achieved using such QDs due to the narrower photoluminescence band phenomenon of such material of zero electronical dimensions. At the single molecular level, such QDs play a crucial role in achieving the durability and the sensitivity along with the brightest and stable photoluminescence properties associated with them, making the bioimaging approach using QDs a significant choice in the current imaging research (Wang et al. 2020b). The narrow photoluminescence bands of QDs are beneficial in advancing device technology and in the area of biotechnology (Arshad et al. 2019). The effective biological applications of the QDs are bestowed in their structure due to the intrinsic optical properties in their structure which make the mediation of the organometallic routes along with the ligand exchange phenomenon associated with the QDs treatment modalities making them an ideal choice in the bioimaging regime (He et al. 2020). Generally, highly fluorescent QDs can be prepared for both exchanging hydrophobic QDs from organic to aqueous phase and introducing functional groups for bioconjugation. The effective stability against the hydrolysis and the biochemical reactions for the QDs could be achieved by capping the QD surface using the thiol groups, which enables the QDs a best choice in achieving the enhanced biocompatibility phenomenon when introduced into the biological systems (Shi et al. 2020). Coating or conjugation of polymers onto QD surface is another method with a tri-block amphiphilic copolymer successfully

over-coated CdSe/ZnS QDs which protect QDs against hydrolysis and enzymatic degradation. Previous study have shown that entrapping the QDs inside the silica shells significantly improves the coating of a silica layer from sodium silicate initially by conjugating a layer of 3-mercaptopropyl trimethoxysilane (MPS) on the surface of citrate-stabilised CdS QDs for sensing gene and drug delivery, and cellular and biomolecular imaging (Rathee et al. 2020). Recently, bioconjugated QDs have become regular parts of biology by using bioconjugated QDs, which can be classified into nonspecific and targeted formulation (Díaz-González et al. 2020). QDs are also conjugated with bio-entities like proteins, peptides, nucleic acids, liposomes, etc., making such QDs used in the direct and indirect labelling of the extracellular proteins and subcellular organelles for an effective bioimaging process. CdSe/ZnS QDs coated bind to human epithelial kidney (HEK) cells to a greater extent than to mouse fibroblast cells (NIH3T3) with the cytoplasmic location of rhodamine dextran. The nuclear localisation signal (NLS) conjugated QDs have been shown by several groups by co-localisation of QDs and MitoTracker Red (Paesano et al. 2020). Similarly, mitochondrial localisation signal (MLS)-conjugated QDs were observed around mitochondria, thereby making the application of mitochondria in diverse biomedicine and diagnosis (Jiang et al. 2019). The specific labelling of cellular tissue for in vivo applications would result in higher resolution and sensitivity cell, where the main applications of QDs lie in the multimodal imaging probes, biological applications, which is used by using a mixture of magnetic nanoparticles, quantum dots and an amphiphilic polymer, followed by functionalization of the bead surface with folic acid (Feng et al. 2020).

It is further noted that multicolour Quantum Dots (QDs) capped magnetic nanorings are 4 times larger than the superparamagnetic iron oxides, which find applications in diverse fields of applications in imaging, etc. (Yue et al. 2019). The major obstacle which comes in the pathway of QDs for bioimaging lies in the fact that several QDs release heavy metal ions such as Cd+ while treating the cells with CdSe quantum dots in bioimaging (Yadav et al. 2019). Such research challenges are the major impediments while dealing with the quantum dot based in vivo bioimaging applications. The understanding of the basic degradation phenomenon and the accumulation attributes of the inorganic QDs along with the association of the intrinsic toxicity of the material remains a serious concern while researching bioimaging using QDs (Garmanchuk et al. 2019).

16.3 Multifunctional Composite Nanoparticles

16.3.1 Graphene

Graphene is a 2-dimensional carbonaceous sheet, which is having several unique physico-chemical properties like higher mechanical strength, robust conductivity, larger surface area (2630 m^2 per gram), etc. (Thamer et al. 2020). Owing to such higher level of enhanced physico-chemical attributes, Graphene has been used in diverse applications like Quantum communications, nanoelectronic applications,

energy research, etc. (Stanford et al. 2020). Besides electronic and energy applications, the Graphene Oxide sheets and its different allied forms are extensively been used in biological applications like anti-bacterial activities, anti-cancerous activities, bioimaging, etc. (Biswas et al. 2018; Yogesh et al. 2020).

The higher surface to volume ratio of Single layered Graphene Oxide sheets enables it to be used in myriad applications like drug delivery and other physico-chemical applications in biomedical fields (Liang et al. 2020). Using Graphene, anti-cancerous activities using NIR based photothermal ablation mechanism have been achieved by several researchers (Wang et al. 2020a). It has been also reported that decoration of several inorganic nanoparticles like Silver nanoparticles, Gold nanoparticles over the Graphene surface, resulted into the synthesis of Graphene based composite systems, which bears augmented optical and superb magnetic properties, finding applications in diverse imaging applications (Griep et al. 2020). The toxicity of Graphene based materials has been studied by several researchers in different biological systems both in vitro and in vivo. The mechanism of bio-distribution and the associated toxicity in the biological systems is mainly regulated by the particulate size of the sheets and the surface chemistry properties. The effect of functionalisation of the Graphene sheets plays a significant role in reducing the toxicity of the nano-scaled Graphene sheets when treated in the biological models like mice at a particular dosage concentration (Chen et al. 2020).

Several techniques are available for the synthesis of Graphene Oxide sheets using chemical vapour deposition (CVD), chemical route of synthesis, etc. Using chemical route of synthesis, Hummers method and its different modification protocol has been used like Improved Hummers method, Modified Hummers method, etc. (Kudus et al. 2020). The interplay of reducing agents and oxidising agents plays a critical role in the synthesis of Graphene from Graphite powder using such methods. The purity of Graphene production has been achieved in large scale at the industrial level using scale-up technologies yielding ultrapure graphene powder of 99.99% purity. Based upon such advantageous properties of Graphene, zero dimensional Graphene Quantum dots (GQDs) (Kang et al. 2020) were also been employed in the different biomedical applications bearing enhanced shelf life and net quantum yield as compared to the conventional tagging agents like rhodamine, etc., which has a compromised shelf life and quantum yield phenomenon.

16.3.2 Magnetic Nanoparticles

Due to their superparamagnetic properties, tunable size and other biological functionalities magnetic nanoparticles (MNPs) such as Fe3O4 magnetite and y-Fe203 maghemite are particularly appealing (Krans et al. 2020). MNPs exhibit superparamagnetism at room temperature, when the particle size is smaller than the single domain limit. Owing to the unique magnetic properties of the nanoparticles, such low scaled nanomaterials having intrinsic magnetism have been employed for the applications in the fields of cancer therapy, biomedical treatment, gene delivery, etc. (Alphandéry 2020).

It is because of the presence of higher proportions of iron as an element, MNPs are used safely with huge prospects of lower rate of immuno rejection and a higher rate of clearance from the body system (Fopase and Pandey 2020). It has been reported previously that Fe per kg determines the overall toxicity in the biological system. A study reported that at a higher concentration of 60 mg Fe per kg, it exhibits a Fe toxicity in the biological systems. In comparison to the bulk Fe content, the proportion of Fe in coatings as microemulsions, nanoparticulate encapsulations exhibits a lesser value or negligible toxicity in the biological systems (Sosa-Acosta et al. 2020). Also, the average particulate size of the nanoparticles and its hydrodynamic size determines the net toxicity in the systems. The study enables to understand that the positive attributes of the magnetism and the nano-scaled materials properties make the magnetic nanoparticles (MNPs) an ideal candidate in the applications of different biological imaging applications (El-Sherbiny et al. 2020). Co-precipitation of iron salts and thermal decomposition of organometallic compounds determine 90% of the available reports, which find applications in diverse biomedical applications.

Modification of an organic shell surrounding the magnetic core is the first step for the preparation of targeted/therapeutic MNPs. With chemically reactive groups available this reaction would yield a water-soluble biocompatible product. The best methodology of stripping off the organic molecular capping of nanoparticles is the ligand exchange technique (Reaz et al. 2020). Different technique for the modification of the nanoparticles is the functionalisation of the nanoparticles using terminal carboxylic groups. Several reports have been highlighted that decoration of the nanoparticles with the specific targeted molecules or specific drugs for achieving targeted drug delivery (Ahmad et al. 2020). In that regard, various synthetic materials like FA (Folate receptors), RGD peptides (directed against avb 3 integrin), etc., have been employed for the purpose of model targeting moieties (Aisida et al. 2020). MRI stands for the magnetic resonance imaging which is based upon the resonance between the radio frequency emanated from the bodily system and the external source (Le Page et al. 2020). The major drawbacks of the instrumentation lies in the drawbacks associated like it has minimised sensitivity as well as insufficient spatial or temporal resolution, although MRI currently can be used for combining two or more imaging modalities. The disadvantages of MRI have been made by MRI/PET, MRI/CT and triple-modality imaging. In order to realise the high resolution, higher sensitivity and excellent soft-tissue contrast, the combination of MRI and CT imaging is highly desirable for MRI/optical properties from CT and MRI (Lally et al. 2019). Few research groups have explained that Fe3O4–TaOx core–shell NPs can provide complementary information by CT (computed tomography), and the internal tumour microenvironment with newly formed blood vessels in the tumours can be clearly imaged using MRI (Khmara et al. 2019). Such imaging technique shows the hypoxic and oxygenated regions, which can be evaluated for both optical and MR imaging and is highly desirable to understand and develop NIR dyes and specific contrast agents to determine quantitatively the long-term bio-distribution and tumour localisation both in the presence and absence of the external magnetic fields when injected in the xenograft breast tumour cases in mice

(Mohd Tamsir et al. 2019). The optical means of the MNPs make them an ideal candidate for the soft-tissue and superior spatial applications (Chaves et al. 2019) with the mediation in the clinical oncology applications (Basini et al. 2019). Moreover, MRI/PET bimodal imaging has great potential impact of voxel-based MRI-guided PVE correction in functional FDG-PET brain imaging. Different imaging modalities have been designed and discovered which find applications in diagnosis, soft-tissue contrast and different clinical studies involving cells and tissues of the biological systems. Also, the interstitial hyperthermia and thermoablation based method based upon magnetic field-induced excitation of biocompatible superparamagnetic nanoparticles has been designed (Shakil et al. 2019). Previous reports have shown that a new technique based upon thermotherapy means using the magnetic nanoparticles, in which there is an involvement of the external alternating magnetic field exposed to the targeted cells or tissues like cancerous tumours, where upon subjection of the combination of magnetic nanoparticles and magnetic field, the targeted area of interest gets ablated upon increase in the temperature at around 42–43 °C (Kandasamy et al. 2019). Different functionalised MNPs have been used in varied rat tumour model studies. Using the histopathological examinations of the brain and tumour, it is noticed that aminosilane and dextran-coated superparamagnetic iron oxide nanoparticles (SPIONS) have exhibited potential good rate of thermotherapy (Alphandéry 2019). As compared with the dextran-coated particles, thermotherapy with the aminosilane coated nanoparticles exhibits a 4.5 fold prolongation in the survival process. The effectiveness of treatment was determined using the properties of average size distribution profile, magnetic anisotropic nature as well as heat efficiency properties (Yalcin 2019). Further, few research groups have demonstrated that SPIONS have a good properties to exhibit a higher rate of magnetic hyperthermia in various media and is acting a good platform for attaching other target molecules. Togetherly, in combination with the other magnetic based chemotherapy and radiation therapy, such nano-based magnetic therapeutic modalities can act as a suitable and a prospectus means for the treatment of cancer and allied therapy (El-Sherbiny et al. 2020).

16.3.3 Layered Double Hydroxides

The class of nanosystems could be denoted by the formula [M2 + 1 × M3 + x(OH)2](An)x/n − mH2O, in which M^{2+} and M^{3+} cations are located in the brucite-like layers and Anis the charge-balancing interlayer anion (Barik 2019). Layered double hydroxides (LDHs) are the class of molecular therapeutic modalities where 2D layered structure and allied are used in the different gene and drug delivery mechanisms in various biological domains (Sanjay et al. 2019). By virtue of the versatility in chemical composition as well as the stability and biocompatibility of LDH materials in drug/gene delivery and biomedicine, LDH materials show the following advantages which make LDHs an ideal drug nanocarrier system because of its superior biocompatibility and low cytotoxicity behaviour (Yan et al. 2019).

Due to the intrinsic layered structure of the LDHs, the payload of interest like proteins, peptides, drug molecules, antibodies can be safely loaded into the layered structure of the LDHs, resulting into an effective treatment regime outcompeting the conventional drug delivery systems which is further associated with the disadvantages like ligand exchange reaction, surface modification requirement, etc., which makes the LDHs based drug/gene delivery mechanism a suitably controlled approach (Yazdani et al. 2019).

16.4 Graphene Based Bioimaging

16.4.1 Role in Fluorescence Imaging in Biological Tissues

It is a probe imaging technique which is a non-invasive approach (Wang et al. 2019b) used for the specific binding to Raji B cells, which is sensed using InGaAs detector upon subjection to laser excitation of 658 nm wavelength. The first report was performed for the B-cell specific antibody rituxan (anti –CD 20) which is further conjugated to pegylated nGO(nGO-PEG-Rituxan). Owing to the extraordinary intrinsic photoluminescence properties of the nano Graphene Oxide (nGO) sheets, such behaviour of the material is exploited in diverse in vivo applications (Lu et al. 2020).

Fluorescence imaging of nGO exhibits a lower quantum yield both in vitro and in vivo imaging. In order to image the tumour xenografted mice, some research group first demonstrated the NIR fluorescent dye (Cy 7 conjugated nGO-PEG-Cy7). Also, the tagged graphene oxide sheets with the Cystein molecules enabled a good rate of cell permeation and tumour accumulation after the post injection at 24 h time period, indicating a promising tagging agent in bioimaging applications (Zaboli et al. 2020).

16.4.2 Implication in the Two-Photon Fluorescence Imaging

In the basic biomedical diagnostics and research, laser imaging depth analyses have been done owing to the lower Rayleigh scattering and lower tissue absorption of the NIR light. Such result caused into reduced photobleaching and phototoxicity as compared to single-photon Fluorescence imaging (Hu et al. 2020). Because of the minor autofluorescence background, more detailed analysis of various cellular/subcellular activities in the deep location of biological samples is achieved. It can obtain a high reflux of excitation photons as compared to one-photon excitation wavelength using simple continuous-wave lasers, two-photon nonlinear excitation usually uses a nonlinear femtosecond laser (Li et al. 2020a).

The appropriate wavelength range used for the deep-sited organ imaging and tissues, two-photon excitation is employed which lies in 700–1350 nm. The field of two-photon fluorescence imaging (TPFI) in context to Graphene sheet has been used rigorously by many researchers. Also, few research groups have also reported the

first instance of transferrin functionalised GO-PEG employing the two-photon luminescence behaviour as a non-bleaching optical probe for the three dimensional TPFI and cancer microsurgery therapeutic mechanism (Gong et al. 2019).

For the cellular and deep-tissue imaging purpose, several nanoprobes were designed by several research groups. Among the probes, nitrogen-doped GQDs (N-GQDs) bearing an average size of ~3 nm have been employed as efficient two-photon fluorescent probes (Kuo et al. 2020). N-GQDs were synthesised by wet-chemical approach by several research groups. Some research groups have shown that by a facile one-pot solvothermal method for the synthesis of N-GQDs (Fu et al. 2019b). The method employed by taking dimethylformamide as solvent and nitrogen sources, the nitrogen was successfully doped to GQDs enabling the extraction of smaller sp^2 domains from the large GO sheet, which shows chemical structure of N-GQDs with dimethylamine binding to GOs under 800 nm femtosecond pulse laser excitation, at 400 μm. The fluorescence imaging is significantly differed as compared with the Two-photon microscopy of the GQDs at 1800 μm. In the one-photon fluorescence imaging (OPFI) (Liu et al. 2019a) technique, for in vivo investigation of biostructures in the 800–1500 μm region, TPFI using N-GQDs as fluorescent probe is particularly suitably accepted (Singh et al. 2019).

16.4.3 Effect in the Radionuclide Based Bioimaging

Radionuclide bioimaging comprises the photo bleaching or the fluorescence quenching phenomenon along with the light absorption nature scattering of tissues with an auto fluorescence background (Day et al. 2020). Optical imaging cannot provide quantitative results and sometimes may be interfered at the in vivo applications in a quantitative manner with excellent sensitivity ~10–12 mol/l and nearly no penetration depth limit (Wu et al. 2019). Radiolabelling method would be able to accurately track the labelled substances (Knight et al. 2019). PET and SPECTe radionuclide-based imaging mainly comprises over a nominally low background signal PET and SPECT images, which are acquired and required little signal amplification in PET/SPECT imaging (Edem et al. 2019). Graphene based nanomaterials are promising nano-platforms which play an important role in such imaging modalities. It is reported that upon decorating iodine atoms onto the available defects and the surface edges of the GO sheets, few groups have demonstrated a method to label nGO–PEG with ^{125}I (Farzin et al. 2019). Using ^{64}Cu labelled nGO–PEG, a research group has explored the in vivo active tumour targeting behaviour by conjugating nGO–PEG with an antibody, also the in vivo PET imaging results confirmed the active tumour targeting cases (Ge et al. 2020).

16.4.4 Significance in Magnetic Resonance Imaging

It is observed that employing MRI, the anatomy and the different functions of the tissues are best monitored quantitatively as compared to other examining techniques

(Sprooten et al. 2019). It is a non-invasiveness mechanism without ionising radiation, which has been extensively employed. Compared with the optical and radionuclide imaging for improving, the T1 or T2 contrast in the observable water pool, it is observed that the brighter images of the T1 agents usually employed Gadolinium based composites (Clough et al. 2019), whereas for the T2 agents it employed for the composites which comprise iron oxide nanoparticles (Heckman et al. 2019). Gadolinium (Gd) and manganese (Mn) are generally toxic that are ions of paramagnetic in nature (García-Hevia et al. 2019). The intercalation of such toxic ions within the layers of Graphene layers minimises the toxicity response of the ions by coordinating with the available functional groups and moieties of the graphene architecture (Si et al. 2020). Such molecular coordinated architectured system enables to understand and enable to apply in the enhanced MRI relaxivity ($r1 = 70 \pm 6\ \mathrm{mM}^{-1}\ \mathrm{s}^{-1}$ and $r2 = 108 \pm 9\ \mathrm{mM}^{-1}\ \mathrm{s}^{-1}$) phenomenon, which forms the 16 and 21 times greater than the current clinically available Gd 3^+ based T1 agents which are chelated using $Gd3^+$ ions with the carboxyphenylated graphene nanoribbons (GNRs) (Li et al. 2020b).

16.4.5 Effect in the Photoacoustic Imaging

Imaging technique which comprises the conversion of short pulsed electromagnetic energy (non-ionising laser pulses) into heat production is categorised into the class of imaging technique known as *Photoacoustic Imaging,* which is based upon the photoacoustic effect (PA effect) (Liu et al. 2019b). Such observations resulted into the acoustic emission attributes because of the transient thermoeleastic expansion phenomenon (Fu et al. 2019a). In other words, the lower range electromagnetic waves have a potentiality to penetrate deeper into the tissues and cells as compared to the shorter wavelength. The radio frequency waves have the property of lower scattering nature in the biological specimens which seems to be more favourable in the measurement in the biological systems (Hariri et al. 2019). The mechanism of lower scattering phenomenon could be associated with the localised thermoelastic expansion, which in return produces wide-band acoustic waves. The sound waves from the biological specimens produce a deep-tissue imaging which is recorded with an interplay of ultra sound transducers (Moore et al. 2019). The significance of Photo Acoustic Imaging lies with the fact that PAI gives an optical absorption contrast agent along with the resolution at the ultrasound magnitude level. Such response of the optical contrasting nature of the Graphene sheet is because of the fact that Graphene bears sp2 domain architecture. In the larger view, among the graphene family nanomaterials, RGO sheets are potential PA contrast agents, which can absorb NIR light more efficiently than the native Gos (Jun et al. 2019). Such differing nature of GO based platform for the contrast agent lies in the fact that GO are hydrophilic whereas RGO sheets upon further reduction from GO sheets with an interplay of reducing agents, resulted into poor water solubility and more hydrophobicity nature. In one of the previous study, in order to obtain lesser oxygenated Graphene, one research group hase produced microwave assisted

lower oxygen content Graphene layer which has the potentiality to generate photoacoustic signals with the NIR excitation (Li et al. 2020c).

16.4.6 Multimodal Imaging Applications

Biomedical applications has gained popularity, the idea of using multiple imaging modalities in conjunction for bringing the significance of multiple imaging modalities at one place thereby harnessing the valuable properties of different imaging techniques in a comprehensive manner (Rouffiac et al. 2020). The mechanism of the multimodal imaging applications comprises the comprehensive integration of different detectability parameters at one place for detection process of the different dosages in the body system (Wang et al. 2019a). Graphene owing to its unique physico-chemical properties and enhanced multifunctional chemistry, the material has been find application in diverse multimodal imaging contrast agents (Chawda et al. 2019). The structural configuration of such multimodal contrast agents was exploited based on its RGO-IONP for triple modal Fluorescence, Photoacoustic (PA) and MR (Magnetic Resonance) imaging, respectively (Qian et al. 2019).

16.5 Conclusion

The revolution of the nanomaterials breakthrough has resulted into the widespread application in different domains of scientific arenas. Owing to the associated demerits of the available tagging agents and imaging applications in engineering and biomedical fields, the need of a more robust imaging agents with higher efficiency has become the need of the hour. The present study predominantly highlights the myriad types of the available nano-scaled materials and their different unique mechanism methodology in varieties of biological systems, which are employed in different bioimaging applications. The study focusses the significance of inorganic and organic based nanomaterials which are used in biomedical fields, which due to their unique physico-chemical properties and un-conventional electrochemical properties replace the already available conventional tagging agents in biomedical domain. The study in the nut shell opens up the new horizon in un-covering the different varieties of nanomaterials currently utilised in different types of imaging aspects from biomedical to bioengineering domain. The significance of the underlying electronical and other electromechanical, electrical properties of selected nano-scaled materials and their derivatives are the next choice in the intricate bioimaging applications, which this study will showcase for employing in different spheres of science and technological applications.

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