Design and Evaluation of Nanoparticulate Drug Delivery Systems for Imaging and Treatment of Malignant Brain Tumor

By Minyahil A. Woldu, Jimma Likisa Lenjissa & Gizaw Dabessa Satessa

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Keywords: nanoparticulate, nanoparticle, nanovectors, nanomedicine, nanoparticulate drug delivery system.

GJSFR-G Classification : FOR Code: 320206

Strictly as per the compliance and regulations of:
Design and Evaluation of Nanoparticulate Drug Delivery Systems for Imaging and Treatment of Malignant Brain Tumor

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Abstract - Malignant brain tumours are one of the most devastating human cancers associated with high mortality and morbidity rates. The median survival of malignant glioma patients ranges between 3 and 16 months and has virtually remained unchanged during the last 3 decades. Difficulties in early detection, local recurrence, and resistance to conventional therapies are the major reasons for failure in malignant brain tumour treatment. The therapy of malignant gliomas is further limited by the inadequate delivery of therapeutic agents to the brain due to the presence of the blood-brain barrier, blood-brain–tumor barrier as well as non-specificity targeting. Nanoparticles (NPs) have drawn increased interest in treating malignant brain tumours due to their potential to act as a vector for brain delivery and to provide tumour-specific detection and treatment. If designed appropriately, NPs may act as a drug vehicle able to target tumor tissues or cells, and protect the drug from inactivation during its transport. The aim of this article was to provide brief overview of nanoparticulate drug delivery systems for imaging and treatment of brain cancer and to evaluate their safety in clinical use. Besides invasive physical methods to bypass or disrupt the BBB and/or BBBT, other methods like pharmacological and physiologic approach are possible. Different manufacturing methods of nano-formulation have been investigated and these include nano-precipitation, emulsion polymerization, emulsion solvent evaporation, supercritical fluid expansion method, complex coacervation, salting out method, and denaturation. Liposomes can serve as a controlled release carrier or simply as a biocompatible solubilizing vehicle for poorly soluble agents. Dendrimers are organic NPs capable of crossing the BBB to deliver therapeutics to tumors. Most inorganic NPs employ an organic polymer as a protective layer so as to increase circulation, half-life and to protect both the particle from the body and the body from the particle. The magnetic NPs can be coupled with diagnostic and therapeutic agents to provide cellular targeting. Quantum dots, Fe3O4 NPs, gold NPs and polymers have all demonstrated levels of success as theranostic NPs. The NPs may be especially helpful for the treatment of the disseminated and very aggressive brain tumors. Unlike biodegradable particles such as liposomes and polymeric-based nanoparticles, metallic NPs are relative newcomers to the field and thus the available toxicology data for each NPs system are limited. In medicine, greater understanding of the origin of diseases on the nanometre is being derived, and drug delivery through function-alised nanostructures may result in improved pharmacokinetic and targeting properties.

Keywords: nanoparticulate, nanoparticle, nanovectors, nanomedicine, nanoparticulate drug delivery system.

I. Introduction

Cancer is currently the second leading cause of death in Europe, while it shows probably the highest clinical complexity [1]. Malignant brain tumours (gliomas) are one of the most common, aggressive and devastating human cancers associated with high mortality and morbidity rates. Clinical management of these tumours remains challenging despite recent advances in current treatment strategies [2,3]. The median survival of malignant glioma patients ranges between 3 and 16 months and has virtually remained unchanged during the last 3 decades [2]. Difficulties in early detection, local recurrence, and resistance to conventional therapies are the major reasons for failure in malignant brain tumour treatment [2]. Conventional anticancer drugs also exhibit a lack of specificity, poor solubility and distribution, unfavorable pharmacokinetics and high tissue damage or toxicity [4]. The therapy of malignant gliomas is further limited by the inadequate delivery of therapeutic agents to the brain due to the presence of the Blood-Brain Barrier (BBB), blood-brain–tumor barrier (BBBT) as well as non-specificity targeting [2,5,6].

Nano-Particles (NPs) have drawn increased interest in treating malignant brain tumours due to their potential to act as a vector for brain delivery and to provide tumour-specific detection and treatment [2,7]. The development of a drug delivery strategy which can mediate efficient tumor targeting together with high cellular internalization and extensive vascular extravasation is essential and important for glioma treatment [8]. Nanomedicine bears the potential to provide an effective answer to the complexity of the disease as it offers more therapeutic options compared to present conventional therapy [1]. The development of BBB targeting technologies is a very active field of research and development [9]. And therefore, nanoscale technologies are beginning to change the foundations of disease diagnosis, treatment, and prevention [10].

The majority of nanotechnology-based devices useful for cancer therapeutics have been defined as...
nano vectors, which are injectable nanoscale delivery systems [7]. Current progress in nanotechnology and nanomedicine has exploited the possibility of designing tumor-targeted nanocarriers able to deliver radionuclide payloads in a selective manner to improve the efficacy and safety of cancer imaging and therapy [4].

Nanoparticulate technology is of particular use in developing a new generation of more effective cancer therapies capable of overcoming the many biological, biophysical, and biomedical barriers that the body stages against a standard intervention [8]. Furthermore, there is a vast array of intriguing nanoscale particulate technologies capable of targeting different cells and extracellular elements in the body to deliver drugs, genetic materials, and diagnostic agents specifically to these locations [10]. Targeted Drug Delivery Systems (DDS) such as passive and active targeting nanocarriers, with diameters ranging from 10-100 nm have been developed to improve the biodistribution, pharmacological, therapeutic and toxicity properties of agents used in cancer diagnostics and therapeutics [4].

Nanoparticles show much promise in cancer therapy by selectively gaining access to tumor due to their small size and modifiability and also due to their ability of taking advantage of fundamental cancer morphology and modes of development such as rapid proliferation of cells, antigen expression, and leaky tumor vasculature. Hence, the application of novel therapeutic agents for the treatment of malignant brain tumours is a timely forwarded request and an urgently needed remedy [8].

The goal of any cancer therapeutics is to preferentially achieve high concentrations of a specific chemotherapeutic agent, a tumor imaging agent, and/or gene therapies at the site(s) of tumors and associated vasculature. Hence, nanovectors must be able to deliver an active agent to achieve effective anti-tumor treatment, or tumor imaging, which is essential for tumor diagnosis and for monitoring the extent and timing of an individual patient’s response to anti-tumor therapy [7]. If designed appropriately, NPs may act as a drug vehicle able to target tumor tissues or cells, and protect the drug from inactivation during its transport [11].

The aim of this article is to provide a brief overview of Nanoparticulate Drug Delivery System (NPDDS) for the treatment of malignant brain cancer and to evaluate its safety in clinical usage.

II. Design and Formulation

a) Design

NPs are, in general, colloidal particles, less than 1000 nm, that can be used for better drug delivery and prepared either by encapsulating the drug within a vesicle and or by dispersing the drug molecules within a matrix [12]. The primary consideration when designing any drug delivery system is to achieve more effective therapies by controlling the drug concentration in the therapeutic window, reducing cytotoxic effects, and improving patient compliance [13]. It is also true that effectiveness of the chemotherapy of brain pathologies is often impeded by insufficient drug delivery across the BBB [14] and/or BBTB [6]. The BBB is highly permeable to water, CO₂, oxygen and lipid-soluble substances like alcohol [15]. Many medicines including anticancer drugs are not able to reach the brain due to the lack of drug-specific transport systems through the BBB. Therefore, the development of new strategies based on NPs to enhance the brain drug delivery is of great importance in the therapy and diagnosis of Central Nervous System (CNS) diseases and it is based on the interactions between NPs and the BBB and on their intracellular traffic pathways that the reach of drugs to this system depends. NPs designed to cross the BBB, therefore will be affected by factors like diffusion inside the brain parenchyma, effect of protein corona, BBB alterations in neurological diseases and drug particle size[16].

Small-molecule drugs can be chemically designed or modified (e.g., by prodrug synthesis) to be adequately lipophilic for passive diffusion through the BBB. However, it is important to note that the presence of a brain tumor by itself also disrupts this very selective BBB, and creates an opportunity for the improved delivery of therapeutic agents [17]. Furthermore, drug lipidization results in increased metabolism and peripheral distribution, which necessitates higher doses, potentially at the cost of more frequent adverse reactions. In such cases, or when small drug molecules undergo metabolism in brain endothelial cells, NPDDS formulations should be considered as a means for improving brain delivery [18].

Besides invasive physical methods to bypass or disrupt the BBB and/or BBTB, other methods like pharmacological and physiologic approach are possible. For example, in a number of pharmacological approaches attempt were taken to reduce the relative number of polar groups on the compound of interest in order to enhance BBB and/or BBTB penetration however these approach were ended up with the loss of the activity of the drugs. Similar attempt were also taken to increase the lipophilicity of a molecule, but these trials also ended up with drug susceptible to efflux systems. In general, NPs research takes the advantage of invasive, pharmacological and physiological methods to enhance brain cancer therapy [6].

b) Formulation

Nanostructures and NPs can be used for drug delivery purposes, either as the drug formulation itself or as the drug delivery carrier [19]. Many liposomal, polymer–drug conjugates, and micellar formulations are part of the state of the art in the clinics, and an even
greater number of nanoparticle (NP) platforms are currently in the preclinical stages of development [13].

The formulation of NPs and physicochemical parameters such as pH, monomer concentration, added stabilizer and ionic strength as well as surface charge, particle size and molecular weight are important for drug delivery [11]. Many different formulations involving NPs have been used for drug delivery purposes, including albumin, poly(D,L-lactic-co-glycolide)acid (PLGA), solid lipid formulations, cetyl alcohol/polysorbate NPs, hydrogels, gold, poly alkyl cyanoacrylate composites, magnetic iron oxide, methoxy poly (ethylene-glycol)/poly(ε-caprolactone), and gelatin [19]. The characteristics of NPs are critically dependent upon the materials used to prepare the NPs [7].

NPDDS are especially important to formulate large-molecule therapeutics potentially efficient to target CNS using peptides, proteins, such as neurotrophic factors, antisense drugs, or genes (plasmids). Owing to their poor stability in biological fluids, rapid enzymatic degradation, unfavorable pharmacokinetic properties, and lack of diffusion towards the CNS [18].

The rapidly advancing field of cancer nanotechnology has generated several innovative DDSs, such as liposomes, dendrimers, quantum dots, iron oxide and carbon nanotubes, to improve and enhance targeted transport of cytotoxic drugs and radionuclides to tumor lesions. In year 2006 only, there were approximately 240 nano-enabled products entered in to the pharmaceutical research pipelines. These nanocarrier systems could provide the delivery platforms needed for improving the delivery of radionuclides to tumor sites [4]. One of the most promising aspects of NP-based cancer therapy is its multifunctionality (Figure 1). NPs can be attached to different types of small molecules such as targeting ligands, imaging, and therapeutic agents to serve as diagnostic and therapeutic agents simultaneously [2].

Different manufacturing methods of nano-formulation have been investigated and these include nano-precipitation, emulsion polymerization, emulsion solvent evaporation, supercritical fluid expansion method, complex co-acervation, salting out method, and denaturation [20].

![Figure 1](image_url): Multifunctionalized NPs (NPs). A single drug payload can be used as a carrier for multiple molecules with different functionality. Adapted from Reference [16].

**III. Lipidic NPDDS**

a) Liposomes

Liposomes, or phospholipid vesicles [21] are type of nanovector made of lipids surrounding a water core. Liposomes are the simplest form of nanovector and their utility is based on the significant difference in endothelial structures-defined as fenestrations-between normal vasculature and tumor-associated vessels[7]. liposomes can serve as a controlled release carrier or simply as a biocompatible solubilizing vehicle for poorly soluble agents [21].

A variety of therapeutic agents have been incorporated into liposomes. Several have reached clinical use. These include liposomal doxorubicin, daunorubicin, amphotericin, cytarabine and verteporfin. Numerous liposomal formulations are in clinical trial, including those for vincristine, all-transretinoic acid, topotecan, and cationic liposome-based therapeutic gene transfer vectors. Many more are in preclinical
evaluation including liposomal formulations of
chemotherapeutics, neuron capture agents, oligonu-
cleotides, plasmid DNA, photosensitizers, antibiotics,
and vaccines [22].

The free doxorubicin drug does not cross the BBB. But, it is known to bind to DNA-associated enzymes, intercalate with DNA base pairs, and target multiple molecular targets to produce a range of cytotoxic effects by inducing apoptosis and necrosis in healthy tissue while causing toxicity in the brain, liver, kidney and heart. Over the years, many studies have been conducted to devise a drug delivery system that would eliminate these adverse effects of doxorubicin [23].

Study in rats showed that, the employment of poly(butyl cyanoacrylate) NPs result in high efficacy of NPs-bound doxorubicin in intracranial glioblastoma [14]. This result identified that the nano formulations of doxorubicin exhibit favorable pharmacokinetics when compared with the free drug, for example the area under the curve after a dose of 50 mg/m² doxorubicin encapsulated in stealth liposomes is 300-fold greater than that of free doxorubicin. Similarly, clearance and volume of distribution can be reduced by at least 250- and 60-fold, respectively by using the nano-formulation [10].

The rate of CNS absorption will also be hastened by using the nano-formulations compared to the free anticancer drugs. For example one study showed that the intravenous injection of doxorubicin with polyfunctional liposomes in rats has shown that the brain of the animals contained the drug already within 15 minutes from injection time [24]. Intravenously injected doxorubicin-loaded polysorbate 80-coated NPs were able to lead to a 40% cure in rats with intracranially transplanted glioblastomas [25,26].

Some key limitations of liposomes include: their propensity to burst release cargo in vivo, a lack of compatibility with various active agents, a limited drug loading volume, the oxidation of liposomal phospholipids, and poor shelf-life stability [27]. “PEGylation,” of liposomes using Poly-Ethylene Glycol (PEG) , resulting in “sterically stabilized liposomes” could be helpful for protection against uptake by resident macrophages within the Reticulo-Endothelial System (RES) biobarrier, increasing the circulation time of liposome-encapsulated antitumor agent, resulting in significantly increased therapeutic efficacy [7]. However some studies reported that, the administration of PEGylated liposomes has led to the production of PEG-specific antibodies (immunoglobulin M, IgM), causing the rapid clearance of a further administered dose-leading to an Accelerated Blood Clearance (ABC) phenomena-which further diminishes effective drug concentrations at tumour sites. Fortunately this problem can be rectified by careful tuning of doses [27].

IV. Polymer-based NPDDS

a) Polymeric NPs

Polymeric NPs are either nanosized solid particles or capsules which consist of natural or synthetic polymers and to which the drug is attached. They are investigated as drug delivery systems for site-specific targeting of tumours and for the transport of drugs across biological barriers, particularly the BBB [28]. Non-biodegradable polymeric carriers have traditionally been successfully employed in clinically and commercially viable anticancer products. PEG has found a favorite among polymer-protein and polymer-aptamer conjugates, while N-2-Hydroxy-Propyl Methacryl Amide (HPMA) and Poly-Glutamic Acid (PGA) have been used in anti-cancer agents [11,29]. It is generally accepted that for a non biodegradable polymer NP to be able to be excreted it must have a diameter less than the renal filtration cutoff of approximately 5–6 nm [30].

The NPs may offer some advantages such as protection of drugs against degradation, targeting the drugs to specific sites of action, organ or tissues, and delivery of biological molecules such as proteins, peptides, and oligonucleotides [31]. For instance, Poly-Acryl Amide (PAA) nanocapsules, due to their polymeric nature, are stable in biological fluids and during storage, and can entrap various agents in a stable and reproducible way but, since they are not lysed by lysosomal enzymes, their clinical application is restricted [11]. The anticancer drug Abraxane™, the substance paclitaxel stabilised by albumine is one of the drug on the market that uses a (bio)polymeric NPDDS [28]. Nanoparticles may consist of either a polymeric matrix (nanospheres) or of a reservoir system in which an oily or aqueous core is surrounded by a thin polymeric wall (nanocapsules) [11].

The limitation of PNPs include: PNPs do have bioadhesive properties, which may cause them to be immobilized within the mucus or, when in contact with the epithelial cells resulting in a slower clearance from the gastrointestinal tract [11]. There is still very little data available on the long-term fate of polymers and possible toxicity they may generate in neuronal cells [32].

b) Dendrimers -Based DDS

Dendrimers are organic NPs capable of crossing the BBB to deliver therapeutics to tumors [33]. Dendrimers are globular macromolecules (5–10 nm) with well-defined tree-like branching architectures and surface functional groups available for further modification [13,28]. Cavities in the core structure and folding of the branches create cages and channels. The surface groups of dendrimers are amenable to modification and can be tailored for specific applications [10]. Dendrimers have remarkable molecular monodispersity and suitable pharmacokinetic properties.
for systemic drug delivery with cleavable chemistry for drug dissociation [13]. Therapeutic and diagnostic agents are usually attached to surface groups on dendrimers by chemical modification [10].

Poly (amidoamine), or PAMAM, is perhaps the most well-known molecule for synthesis of dendrimers. The core of PAMAM is a diamine (commonly ethylenediamine), which is reacted with methyl acrylate and then with another ethylenediamine to make the generation-0 PAMAM. Successive reactions create higher generations of PAMAMs. Functionalization of PAMAMs dendrimers has a dramatic effect on their ability to diffuse in the CNS tissue in vivo and penetrate living neurons following intra-parenchymal or intraventricular injections [16].

Dendrimers, like most other organic NPs, exhibit a tunable circulation lifetime and tolerable toxicity [34].

V. INORGANIC NPS FOR TREATMENT

Studies on Fe₃O₄ NPs have shown success with antibody treatments as well as with thermotherapy induced by an alternating magnetic field. Gold nanoparticles (AuNPs) also offer the ability to achieve noncovalent drug delivery, which allows drugs to be delivered in vivo without needing the AuNPs to be taken up into tumor cells. AuNPs can also utilize thermotherapy by heating gold with visible, infrared, or radiofrequency pulses to cause localized tumor damage [6,35,36].

VI. INORGANIC NPS FOR BIOIMAGING

Most inorganic NPs employ an organic polymer as a protective layer so as to increase circulation, half-life and to protect both the particle from the body and the body from the particle [6,37].

a) Quantum dots

Quantum dots (QDs) are nano-scale crystalline structures made from a variety of different compounds, such as cadmium selenide, that can transform the colour of light. QDs absorb white light and then re-emit it a couple of nanoseconds later at a specific wavelength. By varying the size and composition of quantum dots, the emission wavelength can be tuned from blue to near infrared. For example, 2nm quantum dots luminesce bright green, while 5nm quantum dots luminesce red [10]. QDs are the most prolific nanotechnology-based optical contrast agents which are coated with inorganic materials[28].

QDs are useful for studying genes, proteins and drug targets in single cells, tissue specimens, and living animals. QDs are being investigated as chemical sensors, for cancer cell detection, gene expression studies, gene mapping and DNA microarray analysis, immunocytochemical probes, intracellular organelle markers, live cell labeling, medical diagnostics and drug screening [38].

QDs have greater flexibility, when compared to other fluorescent materials, and this makes them suitable for use in building nano-scale computing applications where light is used to process information. These structures offer new capabilities for multicolour optical coding in gene expression studies, high throughput screening, and in vivo imaging [10].

QDs are highly advantageous as they can be tailored for fluorescence emission spectra from 400 to 2000 nm. However, because of their heavy metal content, QDs can potentially be toxic if accumulated in normal tissues without organic polymer protection [39].

b) Magnetic NPs

These entities are usually prepared by the alkaline co-precipitation of appropriate ratios of Fe and Fe salts in water in the presence of a suitable hydrophilic polymer such as dextran or polyethylene glycol. These superparamagnetic NPs possess large magnetic moments when brought into a magnetic field, thus producing a localized disturbance in magnetic field homogeneity, but the magnetic memory is lost when the field is removed [Figure 2]. Superparamagnetic NPs can serve as contrast agents in MR imaging to scan tumors, even micro-metastases, as well as in tumor angiogenesis, cell tracking, and gene expression [5,10].

Gadolinium chelates are currently the standard of MRI contrast agents because the gadolinium (III) ion is the best known T₁ contrast agent due to its large magnetic moment [40].

The magnetic NPs can be coupled with diagnostic and therapeutic agents to provide cellular targeting. Stealth NPs can act as pharmaceutical drug delivery devices to penetrate the BBB. A multifunctional NPs polyethylene glycol-chloro-toxin-fluorophore (NPC-Cy5.5) is capable of targeting glioma cells and is detectable by both MR imaging and fluorescence microscopy [5].
Figure 2: Intratumoural thermotherapy of a malignant brain tumour with magnetic nanoparticles.

Adapted from Reference [2]. A patient who has undergone intratumoural implantation of magnetic nanoparticles is depicted undergoing an alternating magnetic field session for treatment of his malignant brain tumour by thermotherapy.

To synthesize this nano-probe, iron oxide NPs will be coated covalently with bound bifunctional polyethyleneglycol (PEG) with chlorotoxin, a peptide derived from scorpion venom, and the near-infrared fluorescing molecule Cy5.5. The chlorotoxin peptide binds with high affinity to the membrane-bound matrix metalloproteinase-two endopeptidase, which is preferentially up-regulated in gliomas, medulloblastomas, and other tumors of neuroectodermal origin [2,5].

The delivery of the epirubicin-conjugated iron particles was done by intravenous injection of the NPs into a vein, which was located contralateral to the tumor. At the same time, a magnetic field, ranging from 0.5 to 0.8 T, was established and maintained for 45 minutes around the site of the tumor. In both preclinical and clinical studies the magnetic particles were concentrated in the solid tumor and significantly improve the antitumor efficacy of epirubicin treatment [18].

Proteins, including antibodies, can be attached to these magnetic NPs [5]. Two types of iron oxide NPs have been used as imaging agents: superparamagnetic iron oxide (SPIO) and ultra-small superparamagnetic iron oxide (USPIO) NPs [18]. Most MNP formulations are comprised of iron-oxide NPs (IONPs). The major advantage of USPOIs, compared to conventional Gd-(gadolinium-) based contrast agents, is their prolonged MRI contrast effect due to uptake by tumour cells and microglia (reactive phagocytic cells in the brain) and retention within the brain. The route of administration may be oral, parental (subcutaneous, intramuscular, intra-arterial, intravenous) and via the skin [19].

Typically, these NPs are coated with a variety of stabilizing agents including dextran, albumin, starch, or silicones. The major difference between SPIOs and USPIOs relates to their size and circulatory half-life. Both particles may be used as contrasting agents to image the gastrointestinal tract, liver, spleen, and lymph nodes, although the USPIOs may be used to demonstrate blood pooling in diseases such as brain and myocardial ischemia [18].

A sampling of the literature from the past decade finds that magnetic Fe$_3$O$_4$ NPs are the most popular inorganic motif for imaging brain tumors [41]. Fe$_3$O$_4$ NPs have been shown to be relatively nontoxic with no evidence of tissue damage or pathologic changes in the brain. These particles are also biodegradable [42].

Today, nanocarriers are used in detecting cancer at an early stage, delivering anticancer drugs specifically to malignant cells, and determining if these drugs are killing malignant cells [4]. It has been observed that drug-loaded NPs can have selective distribution to organs/tissues using different types of and proportions of polymers [12]. Inorganic particles require further modification to improve water solubility and stability, with polyethylene glycol (PEG) being popular due to the ‘stealth’ character during blood circulation and low toxicity [43].

c) Gold Nanoparticles

It makes sense that choosing an inorganic material that is generally inert such as gold than choosing a material that has inherent side-effects such as unchelated gadolinium or QDs [39]. Au NPs can emit
light so strongly that it is readily possible to observe a single NPs at laser intensities lower than those commonly used for multi-photon absorption-induced luminescence. Au NPs do not blink or burn out, even after hours of observation. These observations suggest that metal NPs are a viable alternative to fluorophores or semiconductor NPs for biological labeling and imaging [18]. Au NPs are able to actively cross the BBB with diameters of up to 50 nm, making them suitable for increased delivery through the disrupted BBB[44].

Au NPs can be used to enhance contrast of computed tomography imaging [45] [Figure 3]. While inorganic NPs have seen some use in clinical applications for cancer, many still require a greater understanding of their clearance and safety. The inorganic NPs that have seen clinical use are mainly NPs used for MRI contrast agents [6].

![Figure 3](image)

Figure 3: A gold nanoparticle-based delivery system for identification of brain tumor margins and improved surgical resection. Adapted from Reference [6] [6].

MPR: MRI-photoacoustic-Raman.

VII. ORGANIC NPS FOR BIOIMAGING

Liposomes have been investigated for noninvasive real-time monitoring for detection and diagnosis of brain tumors by delivering gadolinium using convection-enhanced delivery. Dendrimers have similarly been used to deliver gadolinium for MRI contrast enhancement as well as fluorescent imaging probes for optical detection of tumors [6].
VIII. Theranostic NPs

QDs, Fe$_3$O$_4$ NPs, Au NPs and polymers have all demonstrated levels of success as theranostic NPs. They have all been used as delivery vehicles to deliver both drugs and imaging agents. However, Fe$_3$O$_4$ and AuNPs do have the ability to function as theranostic NPs completely on their own. This is because Fe$_3$O$_4$ NPs are magnetic resonance contrast agents, while Au NPs are able to function as computed tomography imaging contrast agents due to their density, and both can be used for thermotherapy [6,46].

IX. Evaluation

a) Merits of NPDDS

The NPs may be especially helpful for the treatment of the disseminated and very aggressive brain tumors [25,26]. Many drugs suffer from rapid breakdown and/or clearance in vivo. Encapsulating the drugs in a protective environment, NPDDSs increase their bioavailability, thereby allowing the clinicians to prescribe lower doses [31]. Nanoparticulate drug delivery system is more effective in delivering of compounds to the brain tumour site in comparison to conventional DDSs [2]. Because, NPs selectively increase the localization of drugs and radionuclides in the tumor through passive targeting or
active targeting, while sparing non-targeted tissue (the tendency of NPs to accumulate within the brain tumor site via the enhanced permeability and retention effect (EPR)), ensuring minimal drug or radionuclide leakage during circulation, and facilitating intracellular drug or radionuclide delivery and uptake for active targeting [2,4]. This is because the size of the NPs is significantly smaller than a cell; they can deliver a large payload of drugs, contrast agents or fluorescent probe onto the surface or interior of the cell, without disrupting its function [21].

NPs can enter the systemic blood circulation without forming blood platelet aggregates. Their reduced particle size entails high surface area and hence a strategy for faster drug release. Drug delivery rates and particle integrity can be modulated and controlled by engineering carriers in such a way that they can be activated by changes in the environmental pH, chemical stimuli by the application of a rapidly oscillating magnetic field, or by application of an external heat source [21]. As a drug carrier, NPs have significant advantages like better bioavailability, systemic stability, high drug loading, long blood circulation time and selective distribution in the organs/tissues with longer half life [12].

b) Safety and efficacy of nanomedicines

Materials at the nanometer scale often have different physical and biochemical properties from those of the same materials at bulk volume properties that make nanostructures attractive for diagnostic and therapy applications [21]. Reduction in size to the nanoscale level results in an enormous increase of surface to volume ratio, so relatively more molecules of the chemical are present on the surface, thus enhancing the intrinsic toxicity. This may be one of the reasons why NPs are generally more toxic than larger particles of the same insoluble material when compared on a mass dose base [19]. However, data concerning the behaviour and toxicity of particles mainly comes from studies on inhaled NPs [19].

In regards to treatment toxicity, the payload of the NPs can be isolated from the surrounding normal tissues by the addition of biocompatible polymers, preventing the release of the loaded agents within those normal tissues. The result is increased maximum tolerated dose of the therapeutic agent and reduced systemic toxicity. Moreover, targeted delivery of therapeutic agents encapsulated into NPs in conjunction with retention of NPs within the brain tumor site can lead to higher localized concentrations of the agents within the tumour mass, while preventing the undesired systemic consequences of the therapeutic agents [2].

Unlike biodegradable particles such as liposomes and polymeric-based nanoparticles, metallic NPs are relative newcomers to the field and thus the available toxicology data for each NPs system are limited [18]. Several possible mechanisms of action for the toxicity of particles in general have been postulated, including injury of epithelial tissue, inflammation, oxidative stress response, and allergy [19].

Although nanoscale formulation is aimed at enhancing drug delivery without loss of drug activity, a study comparing insulin-chitosan NPs to chitosan solution and chitosan powder formulations showed that the insulin-chitosan NPs were less effective in terms of bioavailability and lowering blood glucose level in both a rat and sheep model [47]. Data from preclinical studies revealed that the particles were cleared by the RES after removal of the magnetic field. Other healthy filtering organs such as the lung and the kidney did not show the presence of the NPs [18].

X. Conclusion and Recommendations

In medicine, greater understanding of the origin of diseases on the nanometre is being derived, and drug delivery through functionalised nanostructures may result in improved pharmacokinetic and targeting properties.

**Acronyms**

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<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ABC</td>
<td>Accelerated Blood Clearance</td>
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<td>Au NPs</td>
<td>Gold Nano-Particles</td>
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<td>BBB</td>
<td>Blood-Brain Barrier</td>
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<td>BBTB</td>
<td>blood–brain–tumor barrier</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>DDS</td>
<td>Drug Delivery Systems</td>
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<td>HPMA</td>
<td>Hydroxy-Propyl Methacryl Amide</td>
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<td>RES</td>
<td>Reticulo Endothelial System</td>
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Competing Interest
The Authors’ declare that there are no competing interests.

References Références Referencias
