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Review

# Nanotechnology based approaches in cancer therapeutics

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**Abstract**

The current decades are marked not by the development of new molecules for the cure of various diseases but rather the development of new delivery methods for optimum treatment outcome. Nanomedicine is perhaps playing the biggest role in this concern. Nanomedicine offers numerous advantages over conventional drug delivery approaches and is particularly the hot topic in anticancer research. Nanoparticles (NPs) have many unique criteria that enable them to be incorporated in anticancer therapy. This topical review aims to look at the properties and various forms of NPs and their use in anticancer treatment, recent development of the process of identifying new delivery approaches as well as progress in clinical trials with these newer approaches. Although the outcome of cancer therapy can be increased using nanomedicine there are still many disadvantages of using this approach. We aim to discuss all these issues in this review.

Keywords: cancer chemotherapy, nanotechnology, nanoparticle, drug delivery

Mathematics Subject Classification: 2.05, 4.00, 4.02, 5.08

## 1. Introduction

Nanotechnology is the study, design, creation, synthesis, manipulation, and application of materials, devices, and systems at the nanometer scale. The prefix nano is derived from the Greek word dwarf. One nanometer is equal to one billionth of a meter, that is, $10^{-9}$ m [1]. The importance of particles in this range is in the sense that they can have different and enhanced properties compared with the same material at a larger size. Increased surface area and quantum effects are two principal factors separating nanomaterials from other materials. These two factors can enhance properties such as reactivity, strength, electrical characteristics and *in vivo* behavior [2]. Nanotechnology and nanoscience are widely seen as having a great potential to bring benefits to many areas of research and applications [3]. The application of nanotechnology in the field of health care has come under great attention in recent times. There are many treatments today that take a lot of time and are also very expensive. Using nanotechnology, quicker and much cheaper treatments can be developed. Besides, there is another aspect to using nanotechnology in medicine. By using nanotechnology, the drug can be targeted to a precise location which would make the drug much more effective and reduce the chances of possible side-effects [3]. Cancer is one of the leading diseases and although there are many drugs available for treatment, using nanotech based approach increases the activity as well as reducing the side effects profile many fold [4]. In this review, we aim to discuss the nanotech based approach, especially the use of NPs and their various forms in anticancer drug delivery.

## 2. Definition of nanomedicine and applications

The definition of nanomedicine slightly differs between the US National Nanotech Initiative and the European Science Foundation and European Technology Platform. The former clearly

 

refers to the nanoscale but not the latter [5]. According to the US National Nanotech Initiative, 'Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometres, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modelling, and manipulating matter at this length scale. Nanomedicine is the application of nanotechnology to medicine'. However, the European Science Foundation states nanotechnology as 'The field of nanomedicine is the science and technology of diagnosing, treating and preventing disease and traumatic injury of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body'. The European Technology Platform on Nanomedicine describes nanomedicine as follows: 'Nanomedicine is defined as the application of nanotechnology to health. It exploits the improved and often novel physical, chemical, and biological properties of materials at the nanometric scale. Nanomedicine has potential impact on the prevention, early and reliable diagnosis and treatment of disease'. The main areas of nanomedicine are: delivery of pharmaceuticals; *in vitro*, *on vivo*, *in vivo* diagnostics including imaging; regenerative medicine; and implanted devices [5].

Nanomedicine has the ability to potentially revolutionize our ability to screen, diagnose and treat conditions ranging from cancer to cardiovascular disease to diabetes [6]. Some nanomedicine drug-delivery systems and anti-cancer drugs are already in use. Many other applications are in various phases of clinical or pre-clinical testing, and, if found safe and effective, may reach the market. More advanced nanomedicine products such as biocontainers for medical diagnostics and cell treatment are in earlier stages of development. Scientists are at work on the following projects, among many others [7]:

- injection and genetic testing tools, that are faster, more accurate and less invasive than conventional methods
- nanoneedle and pulsed laser surgery, that alters cell structures without damaging surrounding areas
- targeted drug-delivery systems, that transport the drug exactly where needed and monitor its effect
- nanotube-based biosensing devices, that provide *in vivo* diagnostic testing capabilities, such as tracking electrolyte and blood glucose levels
- gold-coated nanoparticles (NPs), that destroy individual tumor cells while leaving nearby healthy cells unharmed
- intelligent synthetic biomaterials, that mimic body tissues and may eventually enable organ regeneration

## 3. Nanoparticles: particles having unique properties to be considered as delivery vehicles

NP-based drug-delivery systems have made a remarkable difference in site-specific release of drugs especially chemotherapeutic agents, owing to their physical and chemical characteristics and biological attributes [8]. Various researches in this exciting area have been conducted, several of the formulations are released in the market and are now routinely used in clinics [9].

NPs are materials with overall dimensions in the nanoscale range. In the recent decades, several types of NPs and microparticles have been synthesized and proposed for use as contrast agents for diagnostics and imaging and for drug delivery; for example, in cancer therapy [10]. The mechanism by which NPs enter the cell has important implications not only for their fate but also for their impact on biological systems. Several papers in the literature discuss the potential risks related to NP exposure, and more recently the concept that even sub lethal doses of NPs may elicit a cell response has been proposed. The overall views of cell mechanisms that may be perturbed by cell–NP interaction are discussed here. NPs should no longer be viewed only as simple carriers for biomedical applications, as they can also play an active role in mediating biological effects [11].

NPs offer the unique possibility to overcome cellular barriers in order to improve the delivery of various drugs and drug candidates, including promising therapeutic biomacromolecules such as nucleic acids, antisense oligonucleotides, small interfering ribonucleic acid (siRNA), and plasmid DNA, that can only exert their function once inside the cells, and that otherwise may not be delivered [12]. As polar molecules, they cannot permeate the lipid bi-layer of plasma membrane or other biological membranes (blood brain, air blood, gastrointestinal barriers). By using NPs these therapeutic agents can not only be delivered site specifically but also there is the possibility to load NPs with a high concentration of the desired drug. In carrying a large payload, nanocarriers can favorably modulate bio-distribution and pharmacokinetic profiles of the drug formulations. They may be also used as carriers for contrast agents *in vivo* magnetic resonance imaging or, again, as an all-in-one system [13].

Nanocarrier cell internalization is highly influenced by NPs' physicochemical properties, such as size, shape, and chemistry [14]. The NPs, in fact, have to be soluble in physiological solutions, then, depending on the route of administration chosen (oral or intravenous), at a certain point they interact with the cell's plasma membrane and, eventually, gain access to the cells and to the appropriate organelle where the biological target is located [15].

Particle size can affect the bio-distribution, the efficiency (i.e., how many NPs are found inside the cell at a given time point), and the cellular uptake pathway for liposomes, polymeric, gold, and silica NPs by influencing their adhesion and interaction with cells [15]. In some NP applications, the first aim is to avoid clearance by the reticuloendothelial system, thus prolonging the circulation time in the blood and increasing the bioavailability at the target site. The clearance rate increases with increasing size of NPs: NPs in a range of 250 nm to 3 $\mu$m have been shown to have an optimal *in vitro* phagocytosis, while NPs with a size limit of around 200 nm preferentially involve other uptake routes, such as clathrin or caveolin mediated endocytosis. Apart from size, shape is one of the primary parameters that require special attention. The vast majority of NPs developed for drug delivery have a spherical shape, but other forms such as cube-shaped,

cylindrical, ellipsoids, and disks have recently been proposed as new drug nanocarriers [15]. Macrophages fail to internalize NPs when they present too large a surface area, as they are spread around because of the complexity of actin structure required to initiate the process of phagocytosis [16]. The shape of NPs also influences the trafficking of nanomaterial inside the cells: hexagonal shapes are retained in the cytoplasm, while the rod-like ones are moved towards the nucleus by microtubules [17].

NP rigidity is a significant factor that influences the entry pathway. Soft hydrogel NPs were also internalized via macropinocytosis and NPs with intermediate elasticity exhibited multiple uptake mechanisms [18].

Other characteristics show that interaction between NPs and serum protein induces the formation of a protein corona that can quickly cover the entire nanoparticle surface [19]. Mainly, these include poly(ethylene glycol), polysaccharides (such as dextran), 266 poly(N-vinylpyrrolidone), polyvinyl alcohol, poly(2-methyl-2-oxazoline), poly(2-ethyl-2-oxazoline), poly(2-methacryloyloxyethyl phosphorylcholine) and poly sulfobetaine methacrylate [20].

Characterization of NPs in terms of surface charge established that due to the negatively charged character of the cell plasma membrane, cationic NPs are internalized more efficient than neutral and anionic [21]. So it is quite clear now that surface chemistry properties critically affect the way NPs interact with each other, with their surrounding environment, and with cells. Despite the growing body of knowledge, an understanding of how all these factors can be combined to define the best characteristics for specific NP cell interaction remains a great challenge.

In this case of specific cellular target the functionalization of the NPs plays a central role in the redirection of the particle to specific cell sub compartments. The use of stimuli-responsive nanocarriers offers an interesting opportunity for drug and gene delivery in the optimization of therapies. An example of a biological stimulus that can be exploited to target drugs and genetic material is pH [22]. Cellular components such as the cytoplasm, endosomes, lysosomes, endoplasmic reticulum, golgi apparatus, mitochondria, and nuclei are known to maintain their own characteristic pH values, which range from 4.5 in the lysosome to about 8.0 in the mitochondria. Moreover, pH value is greatly affected by diseases: the hypoxic environment in cancer leads to an increase in production of lactic acid and hydrolysis of ATP, both contributing to acidification. In fact, most solid tumors have lower extracellular pH (pH 6.5) than the surrounding tissues (pH 7.5). By selecting the right material composition, it is possible to engineer nanocarriers that can exploit these pH differences and allow the release of the delivered drugs or genes to the selected target site. pH sensitive poly($\beta$-amino ester), a biodegradable cationic polymer, in acidic microenvironment undergoes rapid dissolution and releases its content all at once [23], thus it may represent a good scaffold to deliver anticancer drugs. Other strategies involve the presence of acid-sensitive spacers like poly (vinylpyrrolidone-*co*-dimethyl maleic anhydride) between the drug and the polymer that enable, after endocytosis, drug release in endosomes or lysosomes of tumor cells [24]. In this scenario, NPs are promising vehicles for antitumor drug delivery which are designed to be pH responsive, undergoing physicochemical changes to release enclosed drugs at acidic pH conditions [25]. If the target is not the lysosome or in general the acidic compartments of the cells, the low pH environment and various lysosomal enzymes result in the degradation of endocytosed components, thus the loss of the therapeutic effect. This happens unless there are specific mechanisms for the payload to escape out of the lysosomes and maximize the efficiency of various treatments [26].

## 4. Nanomedicine and background of nanomedicine for cancer treatment

Nanotechnology has very useful drug delivery approaches. In nanomedicine formulation research, developing nanodosage forms (polymeric NPs and nanocapsules, liposomes, solid lipid NPs, phytosomes and nanoemulsion etc) have a number of advantages for delivery system, including enhancement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation etc [27].

Scientific advances have significantly improved the basic understanding of biology of cancer. Due to the lack of drug availability, adverse side effects and drug resistance, the conventional therapy failed to achieve proper treatment [28]. During the past few years, nanomedicine has showed considerable progress in improving the cancer treatment, and this review highlights some of the recent advancements in this field of research. After the commencement of nanotechnology in 1959, the field of nanomedicine has developed quickly and we are now successfully approaching solutions to various challenges. The term liposome was described and the drug encapsulated liposome was developed before the 1970s. From there, the advancement of nanomedicine passed through various achievements, starting from gold NP, polymeric NPs, quantum dots, fullerenes etc, to the clinically approved nanomedicines for chemotherapy [29]. The priority of developing nanomaterial for cancer treatment includes [30]: (i) multifunctionality, (ii) increased potency and multivalency, (iii) increased selectivity for targets, (iv) theranostic potential, (v) altered pharmacokinetics, (vi) controlled synthesis, (vii) controlled agent release and kinetics, (viii) novel properties and interactions, (ix) lack of immunogenicity and (x) enhanced physical stability.

### *4.1. Various nanotechnology platforms for cancer therapeutics*

The most common examples of nanotechnology platforms for cancer therapy include polymeric NPs, liposomes, dendrimers, nanoshells, carbon nanotubes, and superparamagnetic NPs. With small size and various structural and physicochemical features, these nanotechnology platforms can enter tumor vasculature through enhanced permeability

and retention effect (EPR). The use of cancer specific targeting residues (e.g. antibodies, ligands, and lectins) can also achieve tumor cell targeting [31].

*4.1.1. Nanoshells.* As the layerbylayer assembly of NPs, polymeric nanoshells (20–60 nm) of di-block copolymers can be made by selfassembly of oppositely charged polymers forming a core/shell structure [32]. The most useful nanoshells are those that have a silica core diameter of 120 nm with a 10 nm layer of gold shell, because these strongly absorb near infrared (NIR) light 800 nm and can create intense heat that is lethal to cells. This NIR light can penetrate several centimeters of human tissue without causing harm, because tissue chromophores do not absorb much energy in the NIR range 1. The benefit of the nanoshell mediated approach is that the energy can pass through the healthy tissue and leave the neighboring cells intact, while killing only the tumor cells that have been targeted by the nanoshells [33].

*4.1.2. Carbon nanotubes.* Carbon nanotubes are a distinct molecular form of carbon atoms that was discovered in the late 1980s [34]. There has been tremendous enthusiasm over carbon nanotube applications in many industrial sectors, in part because they have been actively promoted as possessing the advantages of being 100 times stronger than steel with only one-sixth of its weight, and with unusual heat and conductivity properties. In the area of cancer therapeutics, carbon nanotubes have primarily been used for transporting DNA cargoes into the cell and for thermal ablation therapy, in much the same way as the nanoshells described above [35].

*4.1.3. Dendrimers.* Dendrimers are extensively studied nanocarriers, they are uniformly distributed complex molecules with branched architecture [36]. Dendrimers are able to carry hydrophobic as well as hydrophilic drugs due to the presence in them of hydrophobic core and hydrophilic surface. The size, shape and pharmacokinetics of dendrimers depend on the generation number, chemical composition of core and branches as well as surface function group. Chemical modification also can significantly alter the pharmacokinetics and bio-distribution of dendrimers. Dendrimers have been used for various applications such as solubility enhancement, photodynamic therapy, drug delivery, bio imaging, cancer treatment and 3D nanoscale core–shell structures [37]. Polyvalent dendrimers interact simultaneously with multiple drug targets. Dendrimers are spherical polymers that are normally less than 5 nm in diameter. Their key useful feature is the polymer branches that provide vast amounts of surface area into which therapeutic agents and targeting molecules could be attached [38, 39]. The prototypical dendrimer starts with an ammonia ($NH_3$) core that is reacted with acrylic acid to produce a tri-acid molecule. They synthesized from an ethylenediamine core a G5 poly (amidoamine) dendrimer whose primary amino groups on the surface were first neutralized through partial acetylation to provide enhanced solubility of the dendrimer and prevent nonspecific targeting interactions during delivery. The application of dendrimers is to conjugate different biofunctional moieties, such as folic acid, using complementary DNA (cDNA) oligonucleotides to produce clustered molecules, which target cancer cells that over express the high affinity folate receptor. Linked with multiple types of molecules, which bind selectively to cancer cells, chemotherapy agent can be conjugated with antibodies that act as recognition sites to kill cancer cells. Targeted delivery of small molecular drugs, proteins/peptides and genes can be obtained through this process [40].

*4.1.4. Magneto-fluorescent NPs.* These NPs are usually magnetic and fluorescent applied to *in vivo* imaging rapid screening [41] in hermotherapy and locoregional delivery of chemotherapeutic agents in cancer treatment [42].

*4.1.5. Ceramic NPs.* These materials can be synthesized readily at ambient temperatures with the desired size, shape and porosity and used as drug delivery system for photodynamic cancer therapy [43].

*4.1.6. Quantum dots.* Quantum dots (QDs) are nanometer-scale semiconductor crystals composed of groups II–VI or III–V elements, and are defined as particles with physical dimensions smaller than the exciton Bohr radius [44]. Quantum dots are frequently referred to as nano crystals in the lay press, although the term nano crystal is not restricted to quantum dots. They range from 2 to 10 nm in diameter and are made of semiconductors and they are currently being used as probes for high resolution molecular imaging of cellular components and for tracking a cell's activities and movements inside the body. Because semiconductors are poisonous heavy metals, toxicity is a huge obstacle to clinical application of quantum dots for humans. Currently, their application is restricted to *in vitro* or animal studies, and researchers are actively trying to develop different ways to coat them so that they would be safe for use in people [45].

*4.1.7. Superparamagnetic NPs.* Superparamagnetic NPs refer to iron oxide particles or magnetite ($Fe_3O_4$) particles that are less than 10 nm in diameter. They have been around for years as contrasting agents for magnetic resonance imaging (MRI). Many groups have explored the use of magnetic fields to localize magnetic NPs to targeted sites, a system known as magnetic drug targeting. As with other NPs, these superparamagnetic NPs are getting functionalized so as to permit specific tumor targeting. Such as iron oxide NPs can also be made by coating with aliphatic surfactants or liposomes resulting in magnetoliposomes [46]. Magnetic NPs can be remotely activated using electromagnetic fields, and they can also be used to thermally treat cancers [47]. Most recently, superparamagnetic NPs have been used in clinical thermotherapy of locally recurrent prostate cancer [47].

*4.1.8. Liposomes.* Liposomes are self-assembled phospholipid membranes with an inner core where drugs can be entrapped. Liposomes are relatively stable,

biodegradable, and do not elicit any immune response. They are efficient vehicles for targeted delivery of hydrophobic drugs [48]. Liposomes are vesicular formulations of lipid bilayers prepared synthetically. The water-soluble drugs are present in aqueous compartments while lipid-soluble drugs and amphiphilic drugs insert themselves in the phospholipid bilayer. Liposomes have been in vogue for varied applications such as DNA delivery in gene therapy and genetic engineering, drug delivery in nutrition and dietary supplements, or cosmetics. Liposomes may be synthesized in various sizes and shapes, however, nanoscale liposomes called nanosomes are of specific interest in targeting cancer. Such nanosomes are several nanometers in size and most commonly contain anticancer drug [48, 49]. Since nanosomes are soluble in aqueous solvents (such as blood), they can carry hydrophilic as well as hydrophobic molecules, thus allowing administration of anticancer drugs that showed poor efficacy due to their limited solubility. A nanosome is essentially a vesicular lipid bilayer with the polar heads facing the solvent and the tail regions facing each other. The anticancer drug, if hydrophobic, can thus be contained in the tail region, and if hydrophilic, solubilized in the liposomal core. Surface modification of liposomes using polyethylene glycol (PEG) confers the liposomes stealth property, from being destroyed by the reticuloendothelial system. Liposomal doxorubicin (doxil, caelyx, Schering-Plough pharmaceuticals) was the first liposomal anticancer drug for the treatment of ovarian cancers. Several lipid-based formulations such as liposomes have been synthesized and characterized. Newer generations of liposomes containing two anticancer agents within a single liposome are under development [50].

*4.1.9. Polymeric NPs.* These are prepared easily and have no or low toxicity. These polymers can be degradable or non degradable, synthetic or natural. They are used for targeted treatment of cancer cell delivery, which can be achieved avoiding the reticuloendothelial system, antibody targeted therapies and thus cause fewer side effects [51].

### *4.2. Practical applications of NPs in cancer therapy*

The fate of a drug after administration *in vivo* is determined by a combination of several processes such as distribution, metabolism and elimination when given intravenously [52] or absorption, distribution, metabolism and elimination when an extravascular route is used [53], which depends mainly on the physicochemical properties of the drug and therefore on its chemical structure. NPs loaded with anticancer agents can be used successfully to increase drug concentration in cancer tissues and also act at cellular levels, enhancing antitumor efficacy [54]. They can be endocytosed or phagocytosed by cells, with resulting cell internalization of the encapsulated drug. NPs of biodegradable polymers can provide controlled and targeted delivery of the drug with better efficacy and fewer side effects [55]. Lipophilic drugs, which have some solubility either in the polymer matrix or in the oily core of nanocapsules, are more readily incorporated than hydrophilic compounds, although the latter may be adsorbed onto the particle surface. Nanospheres can also be formed from natural macromolecules such as proteins and polysaccharides, from non polar lipids, and from inorganic materials such as metal oxides and silica [56].

Prostate cancer is the most common cancer in men and is the sixth leading cause of cancer mortality in men [57]. In human prostate cancer, a multistage process involves progression from small latent carcinomas of low histological grade to high-grade metastatic cancer [58]. To enhance the therapeutic efficacy of anticancer agents in general, polymeric-, misceller- and liposome-based delivery systems conjugated to tumor-specific ligands have been studied [59–61]. NPs conjugated ligand can enhance the therapeutic efficacy of the encapsulated drug and thus could be more effective in promoting tumor regression than the drug dissolved in the cremophor el (CrEL) formulation [62].

Nanomedicine can be used to design artificial red and white blood cells successfully [63]. Cancer patients are now treated by injecting artificial red blood cells to balance the human body blood level. Artificial antibodies, white and red blood cells and antiviral nanorobots could be considered as successful applications of nanomedicine [64].

Paclitaxel is one of the best antineoplastic drugs found in nature in the past decades [65]. It is effective in treating a wide spectrum of cancers including breast cancer, ovarian cancer, lung cancer, Kaposi's sarcoma [66], colon cancer, bladder cancer, head and neck cancer, multiple myeloma and melanoma. Its poor solubility in water creates difficulties in clinical administration and can create many serious side effects [67]. NPs of biodegradable polymers can be considered to counteract the side effects and achieve controlled and targeted delivery of the drug [68]. By optimization of particle size and surface coating, NPs formulation of paclitaxel could improve the efficacy and quality of chemotherapy, making possible personalized chemotherapy, local chemotherapies, sustained chemotherapy, oral chemotherapy, and chemotherapy across the blood–brain barrier [69], chemotherapy across the microcirculation barrier, and other advancements.

The hydrophobic cytotoxic drug camptothecin [70] incorporated into fluorescent mesoporous silica NPs can be delivered to various cancer cells to induce cell death. This can also be a method to overcome the insolubility problem of many anticancer drugs, which is considered to be one of the major challenges in cancer therapy [71].

NPs are useful delivery vehicles for promising drug candidates that face obstacles for clinical applicability. Sirolimus, an inhibitor of mammalian target of rapamycin has gained attention for targeted anticancer therapy, but its clinical application has been limited by its poor solubility [72]. Polymeric nanoparticle (PNP)–sirolimus was developed as an injectable formulation and has been characterized by transmission electron microscopy and dynamic light scattering. Pharmacokinetic analysis revealed that PNP–sirolimus has prolonged circulation in the blood [73]. PNP–sirolimus preserved the *in vitro* killing effect of free sirolimus against cancer cells, and intravenous administration displayed its potent *in vivo* anticancer efficacy in xenograft tumor mice. In

**Table 1.** Nanomedicine for anti cancer therapy.

| Trade name | Compound | Nanocarrier |
|---|---|---|
| Abraxane | Paclitaxel | Albumin bound paclitaxel |
| DaunoXome | Daunorubicin | Pegylated Liposome |
| Doxil | Doxorubicin | Pegylated Liposome |
| Bexxar | Anti-CD20 conjugated to idodine131 | Radioimmunoconjugate |
| Zevalin | Anti CD 20 conjugated to yittrium-90 | Radioimmunoconjugate |
| Zeladex | Goserelin | Acetate Polymer rods |
| Myoset | Doxorubicin | Non-pegylated liposome |
| Oncasper | PEG-L-asparaginase | Polymer-protein conjugate |
| Ontak | IL 2 fused to diphtheria toxin | Immuno toxin fusion protein |
| SMANCS | Zinostatin | Polymer protein conjugate |

addition, PNP–sirolimus enhanced the radiotherapeutic efficacy of sirolimus both *in vitro* and *in vivo*. Clinical application of PNP–sirolimus is a promising strategy for human cancer treatment [72].

NPs can also be used in hyperthermia therapy of tumors [74]. Hyperthermia refers to localized heating of tumours to a temperature of 41–43 °C or whole-body heating to 40–42 °C [75]. The exact target for heat-induced cell death is debateable [76]. Unlike radiotherapy where the cells die during their attempt to divide after irradiation, cell death in hyperthermia occurs faster and at all stages of the cell cycle. The potential mechanisms proposed are denaturation of membrane proteins, repair enzymes and even chromosomal proteins-apoptotic death [75]. At temperatures between 50–60 °C the tissues show coagulative necrosis [77]. In terms of classification, nanomedicine is classified as first and second generation nanomedicine.

*4.2.1. First generation cancer nanomedicine.* US food and drug administration (FDA) approved nanomedicine for anti cancer therapy [78] is shown in table 1.

*4.2.2. Second generation nanomedicine.* Second generation nanomedicine primarily focused on the development of new nanocarriers, which were specifically targeted at cancer cells, without affecting the function normal cells [79]. New generation nanomedicine comprises nanocarrier loaded with one or more cancer therapeutics, chemosensitizer, imaging components and an active targeting element such as folate receptor [80]. Albumin-based nanoparticle carriers have been extensively studied by various groups [81–83]. Pegylated liposome encapsulated doxorubicin, carbon nanotubes, micellar NPs etc are also extensively studied nanoformulations for targeted delivery. A combination of cancer diagnostic aid and therapeutic agent loaded onto same NP system called theragnostic NPs are also studied [84].

### *4.3. Routes of NPs anticancer drug administration*

The most convenient route for drug administration is oral, but this has several barriers to the use of colloidal carrier owing to conditions within the gastrointestinal tract [85]. Duodenal enzymes and bile salts destroy the lipid bilayers of most types of liposome, releasing the drug. Polymeric NPs are more stable, although there is some evidence that polyesters can be degraded by pancreatic lipases [86]. They may be able to improve bioavailability, particularly for highly insoluble drugs, by increasing the surface area for dissolution and as a result of bioadhesion. However, NPs can be used to protect a labile drug from degradation in the gastrointestinal tract or to protect it from toxicity due to the drug. Polymeric NPs, due to their bioadhesive properties [87], may be immobilized within the mucus or, when in contact with the epithelial cells, show a slower clearance from the gastrointestinal tract [88]. NPs of biodegradable polymers containing alpha-tocopheryl PEG 1000 succinate (vitamin E-TPGS) have been proposed to replace the current method of clinical administration and to provide an innovative solution for oral chemotherapy. Vitamin E TPGS could be a novel surfactant as well as a matrix material when blended with other biodegradable polymers [89] and has great advantages for the manufacture of polymeric NPs for controlled release of paclitaxel and other anticancer drugs [90]. Subcutaneously or locally injected (in the peri tumoral region) NPs can be used for lymphatic targeting as a tool for chemotherapy against lymphatic tumors or metastases since they penetrate the interstitial space around the injection site and are gradually absorbed by the lymphatic capillaries into the lymphatic system.

### *4.4. Recent progress of nanomedicine in clinical trials of anticancer drugs*

The FDA has approved the first clinical trial in humans of brightly glowing NPs to light up cancer cells to aid in diagnosing and treating cancer. The trial with five melanoma patients at Memorial Sloan-Kettering Cancer Center (MSKCC) will test if the technology is safe and effective in humans. The NPs, called cornell dots for the university that conducted the research, are silica spheres less than 8 nanometers in diameter that enclose several dye molecules. The silica shell, essentially glass, is chemically inert and small enough to pass through the body and out in the urine. For clinical applications, the dots are coated with polyethylene glycol so the body will not recognize them as foreign substances. To make the dots stick to tumor cells, organic molecules that bind to tumor surfaces or specific locations

within tumors can be attached to the shell. When exposed to near-infrared light, the dots glow much brighter than the unencapsulated dye, which serves as a beacon to identify the target cells. For the human trials, the dots will be labeled with radioactive iodine, which makes them visible in PET scans to show how many dots are taken up by tumors and where else in the body they go and for how long. The researchers say this technology can show the extent of a tumor's blood vessels, cell death, treatment response, and invasive or metastatic spread to lymph nodes and distant organs [91].

Targeted therapeutic NPs that accumulate in tumors while bypassing healthy cells have shown promising results in an ongoing clinical trial. The NPs feature a homing molecule that allows them to specifically attack cancer cells, and are the first such targeted particles to enter human clinical studies. Originally developed by researchers at MIT and Brigham and Women's Hospital in Boston, the particles are designed to carry the chemotherapy of drug docetaxel, used to treat lung, prostate and breast cancers, among others. The particles were also shown to be safe and effective: many of the patients' tumors shrank as a result of the treatment, even when they received lower doses than those usually administered [92].

### *4.5. Recent developments of NPs based anticancer drug*

Nanoscale drug devices are currently being developed to deliver anticancer therapeutics specifically to tumors [93]. But most of the existing anticancer agents cannot distinguish between cancerous and healthy cells, leading to toxic actions and side effects. To further improve drug delivery efficiency and cancer specificity, tumor-targeting strategies have recently received significant attention [94, 95]. NPs and liposomes are the first generation of these devices. Some of them have already reached clinical practice, such as liposomal doxorubicin used to treat specific forms of cancer, or liposomal amphotericin B used to treat fungal infections often associated with aggressive anticancer treatment [96]. Recently, a nanoparticulate formulation of the well-known anticancer compound taxol was submitted as a new treatment for advanced stage breast cancer [97].

One of the most promising tumor targeting approaches is the investigation of pH-sensitive drug delivery systems [98], as the existing pH of tumor tissue is generally considered an ideal trigger for the selective release of anticancer drugs [99, 100]. Compared to normal tissue pH 7.4, the average extracellular pH value in tumor tissues is 6.8, and the pH values of intracellular components such as endosomes and lysosomes are 4.5–6.5, which is caused by hypoxia in poorly perfused regions due to the high metabolic rate required for tumor growth [101]. The specificity of lower pH levels within the tumor region can be a strategy for acid-sensitive drug delivery at local microenvironments for not only improving the efficacy of chemotherapy, but also for reducing the level of cytotoxicity [102]. Recent studies have highlighted the development of some drug carriers with pH-sensitive, and therefore tumor-selective, drug delivery. Strontium carbonate NPs (SCNs), a novel biodegradable nanosystem for the pH-sensitive release of anticancer drugs, were developed via a facile mixed solvent method aimed at creating smart drug delivery in acidic conditions, particularly in tumor environments [103]. Structural characterization of SCNs revealed that the engineered nanocarriers were uniform in size and presented a dumbbell-shaped morphology with a dense mass of a scale-like spine coating, which could serve as the storage structure for hydrophobic drugs. Chosen as a model anticancer agent, etoposide was effectively loaded into SCNs based on a simultaneous process that allowed for the formation of the nanocarriers and for drug storage to be accomplished in a single step. The etoposide loaded SCNs (ESCNs) possess both a high loading capacity and efficient encapsulation. It was found that the cumulative release of etoposide from ESCNs is acid-dependent, and that the release rate is slow at a pH of 7.4; this rate increases significantly at low pH levels 5.8 and 3.0. Meanwhile, it was also found that the blank SCNs were almost nontoxic to normal cells, and ESCN systems were evidently more potent in antitumor activity compared with free etoposide, as confirmed by a cytotoxicity test using an MTT assay and an apoptosis test with fluorescence-activated cell sorter (FACS) analysis. These findings suggest that SCNs hold tremendous promise in the areas of controlled drug delivery and targeted cancer therapy [103].

Oral chemotherapy is attractive because of its convenience and ease of administration, particularly in a palliative setting [104]. In addition, the oral route facilitates the use of more chronic treatment regimens, which result in prolonged exposure to anticancer drugs. However, most anticancer drugs such as taxoids (paclitaxel and docetaxel) are not orally bioavailable i.e., not absorbable in the gastrointestinal (GI) tract [105], because taxoids have a very low level of oral bioavailability at less than 10% [106, 107]. The low systemic exposure of taxoids after oral drug administration is, at least in part, due to their high affinity for the multidrug efflux pump P glycoprotein (P-gp) [108, 109]. P-gp in the mucosa of the GI tract limits the absorption of the orally administered taxoids and mediates their direct excretion into the gut lumen [108]. In addition, first pass elimination by cytochrome P450 (CYP) isoenzymes in the liver and/or gut wall may also contribute to the low oral bioavailability of taxoids [110, 111].

Possible solutions for oral delivery of taxoids and other anticancer drugs are currently under extensive investigation [107]. In this study a novel nanoparticle formulation was proposed, i.e., biodegradable PLGA-TP.GS NPs modified with a cationic surfactant, didodecyldimethylammonium bromide (DMAB), for oral chemotherapy using docetaxel as a therapeutic drug due to its excellent therapeutic effects against a wide spectrum of cancers and its commercial success as one of the top-selling anticancer agents. DMAB is capable of producing small and highly stable NPs at 1% w/v concentration [112]. The superior anticancer efficacy of TPGS is associated with its increasing ability to induce apoptosis and not due to its increased cell uptake into cells [113, 114]. In addition, TPGS-emulsified NPs have been shown higher drug encapsulation and cellular uptake, longer half-life and higher therapeutic effects of the formulated drug than those

emulsified by polyvinyl alcohol (PVA), a widely used emulsifier in nanoparticle technology [115]. We were thus inspired to synthesize a novel biodegradable poly (lactide-co-glycolide)-D-a-tocopheryl polyethylene glycol 1000 succinate (PLGATPGS) random copolymer for nanoparticle formulation of small molecule drug chemotherapy [115].

Combined chemotherapy and photothermal therapy *in vitro* testing has been achieved by means of multifunctional NPs formed by plasmonic gold nanoclusters with a protecting shell of porous silica that contains an antitumor drug [116]. It proposed a therapeutic nanoplatform that associates the optical activity of small gold NPs aggregates with the cytotoxic activity of 20s-camptothecin simultaneously released for the efficient destruction of cancer cells. For this purpose, a method was used for the controlled assembly of gold NPs into stable clusters with a tailored absorption cross-section in the visible NIR spectrum, which involves aggregation in alkaline medium of 15 nm diameter gold colloids protected with a thin silica layer. Clusters were further encapsulated in an ordered homogeneous mesoporous silica coating that provides biocompatibility and stability in physiological fluids. After internalization in 42-MG-BA human glioma cells, these protected gold nanoclusters were able to produce effective photothermolysis under femtosecond pulse laser irradiation of 790 nm. Cell death occurred by combination of a thermal mechanism and mechanical disruption of the membrane cell due to induced generation of micrometer-scale bubbles by vaporizing the water inside the channels of the mesoporous silica coating. Moreover, the incorporation of 20s-camptothecin within the pores of the external shell, which was released during the process, provoked significant cell death increase. This therapeutic model could be of interest for application in the treatment and suppression of non-solid tumors [117].

### *4.6. Benefits of NPs for the treatment of cancer*

Conventional chemotherapy employs drugs that are known to kill cancer cells effectively [118]. But these cytotoxic drugs kill healthy cells in addition to tumor cells, leading to adverse side effects such as nausea, neuropathy, hair loss, fatigue, and compromised immune function. NPs can be used as drug carriers for chemotherapeutics to deliver medication directly to the tumor while sparing healthy tissue [119]. Nanocarriers present several advantages over conventional chemotherapy. They can be:

(i) Nanoparticle-based drug-delivery systems have made a remarkable difference in site-specific release of chemotherapeutic agents, owing to their physical and chemical characteristics and biological attributes [9, 120].
(ii) The size and surface properties of nanomaterials can cause them to selectively accumulate in tumor tissue via what is termed the enhanced permeability and retention (EPR) effect [121, 122] making them potentially useful tumor delivery vectors.
(iii) NPs have shown many implications for the development and success of new therapeutic strategies for anticancer drug delivery, peptide and protein delivery and gene therapy. Furthermore, NPs and other colloidal drug-delivery systems modify the kinetics, body distribution and drug release of an associated drug [123].
(iv) The most important categories of nanocarriers showing the highest clinical and commercial interest for anticancer drugs are: a) liposomes [124] (small spherical lipid vesicles with size typically 25–200 nm), b) the polymeric micelles [125] (spherical colloidal particles with a size typically 20–100 nm) c) dendrimers (branched polymeric macromolecules with size 10–100 nm), d) quantum dots (semiconductor nanocrystals with a diameter of 2–10 nm), e) biodegradable polymeric NPs (solid spherical NPs of biocompatible polymers with sizes <1000 nm) the water-soluble polymer-drug conjugates (macromolecular drugs) and g) hybrid inorganic/organic NPs [126].
(v) Conjugation or encapsulation of drugs in PLGA nanocarriers reduces the undesirable shortcomings of these therapeutic agents, such as short circulation half-life and non-site-specific targeting [127].
(vi) Increasing experience in the field of preparation, characterization and *in vivo* application of PLGA NPs has provided the necessary momentum for promising future use of these agents in cancer treatment, with higher efficacy and fewer side effects [128].
(vii) The folate receptor is over-expressed on the cell membrane of cancer cells in the brain, kidney, breast, ovarian and lung, whereas it is absent from normal cells. This has led recently to the use of folic acid molecule as a guide for targeting tumor cells [129].

However, according to the above-mentioned safe use of NPs based anticancer drug, it seems that NPs can be safely used as anticancer drug nanocarriers without the risk of materials cytotoxicity.

### *4.7. Limitations to the efficacy of NPs based anticancer drug*

Although NPs have tremendous potential for a host of applications, their adverse effects on living cells have raised serious concerns recently for their use in the healthcare and consumer sectors [130]. The behavior of NPs is relatively different from larger particles of the identical material. NPs have shown biological functions such as killing pathogenic bacteria and viruses (e.g. flu), but research has also shown that NPs may produce adverse effects (dose related) in human cells on contact [131]. There is a correlation between a decrease in particle size and an increase in toxicity, because of larger surface area. The high surface area and high local charge densities generate a large area which can interact with surrounding biological molecules. *In vitro* cytotoxicity studies of NPs using different cell lines, incubation times, and colorimetric assays are increasingly being published [132]. Diffusion of macromolecules, as well as that of NPs, is a

critical issue in drug delivery. The diffusion of microscopic objects through tissues is a multifactorial process, depending on tissue type, anatomical location, extracellular matrix composition and many other parameters [133]. With each of these NPs, different data have been published about their cytotoxicity due to varying experimental conditions as well as differing nanoparticle physiochemical properties. The safe use of inorganic NPs in biomedical applications remains an unresolved issue. To date, the question remains whether inorganic NPs are safe to be used for biomedical purposes. More and more data are becoming available regarding NP toxicity, but a lot of effort is still required in order to truly advance our knowledge in this field [134].

### *4.8. Future perspective for nanotechnology based cancer therapy*

Currently, psoriatic arthritis (PA) diagnosis and platinum based cancer therapy demonstrate a potential future scope for human use. In the future, nanotechnology-based cancer therapy will face many challenges, such as surface modification, multireceptor cancer targeting, and drug loading for therapy, toxicology and relevant regulations, including stability testing [135–137]. The emerging nanomedicine techniques will be theranostic in nature, with a multifunctional platform capable of simultaneous diagnosis and therapy [136]. The future development may encompass multifunctional properties in nanomedicine developed for cancer therapy. A multidisciplinary approach on the development of the nanocarrier will bring valuable products for cancer therapy.

The future of nanomedicine and the opportunity to eliminate the suffering and death due to cancer will hinge on our ability to confront cancer at its molecular level [138]. Nevertheless, there are many outstanding questions that remain unanswered. A revolution in NPs based anticancer medicine that now heralds a long-awaited era of personalized medicine that is delivery of the right drug to the right patient at the right time is now much closer than ever before. Personalized medicine will ensure that such drugs are given only to patients who stand to benefit from them. If that happens, nanobased drugs will be at least less toxic than today's armamentarium for cancer. If these medicines work as intended, they should also prove to be far more effective [139].

Nanotechnology is also opening up new opportunities in implantable delivery systems [140], which are often preferable to the use of injectable drugs, because the latter frequently display first-order kinetics. This rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as the drug concentration falls below the targeted range. In contrast, implantable time release systems may help minimize peak plasma levels and reduce the risk of adverse reactions, allow for more predictable and extended duration of action, reduce the frequency of re-dosing and improve patient acceptance and compliance. Nano-implants will also be used in the not-too distant future for treating cancer [141]. Among the first nanoscale devices to show promise in anti-cancer therapeutics and drug delivery are structures called nanoshells, which nanomarkets believes may afford a degree of control never before seen in implantable drug delivery products. Despite these advances, the vast majority of consumers prefer an oral drug delivery system to implantables or injectables. With this in mind, various development groups are working to enhance traditional oral delivery systems with nanoengineered improvements. There are some areas where nano-enhanced drugs could make a big difference in increasing oral bioavailability and reducing undesirable side effects. By increasing bioavailability, NPs can increase the yield in drug development and more importantly may help treat previously untreatable conditions [2].

## 5. Conclusion

Anti-cancer drug delivery specifically to cancer cells remains a major challenge. Due to the lack of drug availability, adverse side effects and drug resistance, the conventional therapy failed to achieve proper treatment of cancer. Nanotechnology has great potential to radically improve current approaches to the diagnosis and treatment of patients with various types of cancer. Nanotechnology has already begun to have a significant impact on the treatment of patients by improving major challenges for the future including optimization of design and engineering of cancer targeted materials. In order to realize the potential of nanoparticle strategies, an improved understanding of the tumor specific, tumor site, and host factors which influence the delivery of nanomaterials specifically to sites of cancer causing cell will be necessary. Because of appropriate size and surface chemistry, allowing conjugation to biologically active molecule, several NPs are being investigated for more efficient targeted delivery of chemotherapeutic agents. Protein and liposome based nanomedicine formulation is already in clinical use, and many new formulations are in the phase 2 and phase 3 stages of evaluation. The future of nanomedicine will no doubt yield innovative platforms for cancer treatment, and the study presented herein may improve the general consideration of anticancer treatment with NPs.

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