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# Innovative nano-carriers in anticancer drug delivery-a comprehensive review

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ABSTRACT

In the scientific field, nanotechnology has offered multipurpose and designated functional nanoparticles (NPs) for the development of applications in nano-medicine. This present review focuses on cutting edge of nano-technology in biomedical applications as drug carries in cancer treatment. The nanotechnology overcomes several limitations of drug delivery systems used in distinct therapeutic approaches of cancer treatment. The serious effect of conventional chemotherapeutics by nonspecific targeting, the lack of solubility, and the inability of chemotherapeutics entry to cancer cells which, offers a great opportunity for nanotechnology to play significant roles in cancer biology. The selective delivery of nano-drugs to the targeted cancer cells by the programmed way and avoiding nonspecific interactions to the healthy cells. The present review focuses on the methods of improving the size, shape and characteristics of nanomaterials which can be exploited for cancer therapy. The successful designing of nanocarriers can be tailored for cancer treatment for upcoming future as nano-medicines.

## 1. Introduction

The Nano particle research is a fascinating branch of Science having a lot of potential applications. Their preparation with exclusive results in modern research is not restricted to man-made materials. There are various approaches have been used for the synthesis of NPs from naturally organic compounds (proteins, polysaccharides, lipids, bacteria, fungi, and viruses), inorganic materials (Ag, Au, Ti, Zn, Co, etc.) and also by volcano eruptions and weathering [1,2].The NPs are synthesized through physical, chemical and biological methods. The physical and chemical methods are extremely pricey. The biological methods of NPs synthesis would assist to remove ruthless processing conditions, by allowing the synthesis at physiological pH, temperature, pressure, and at the same time, at negligible cost. Huge number of microorganisms has been found competent of synthesizing inorganic NPs composite, either intra or extracellularly [3–5].

Nanotechnology is an emerging field which exploits the current and upcoming application of science and technology using NPs in the range of 100 nm (nm) or less, with completely improved and novel qualities, which distinguishes it from larger particles characteristics. They are normally produced on specific characteristics that include size, shape, distribution, and surface morphology [6]. The NPs showed characteristic colors and properties with the variation of size and shape, which can be utilized in bioimaging applications [1,2,6–8].

Nanotechnology is involved in the manipulation of materials and the creation of structures and systems at the atomic and molecular scale. These methods controls matter at near-atomic scales to produce unique or enhanced materials, products and devices [9–12].

The field of nanotechnology existed for the centuries, but applications were limited until they were introduced by modern laboratories. The quantum size effect inspired researchers and motivated their performance to work on NPs because metal and semiconducting NPs

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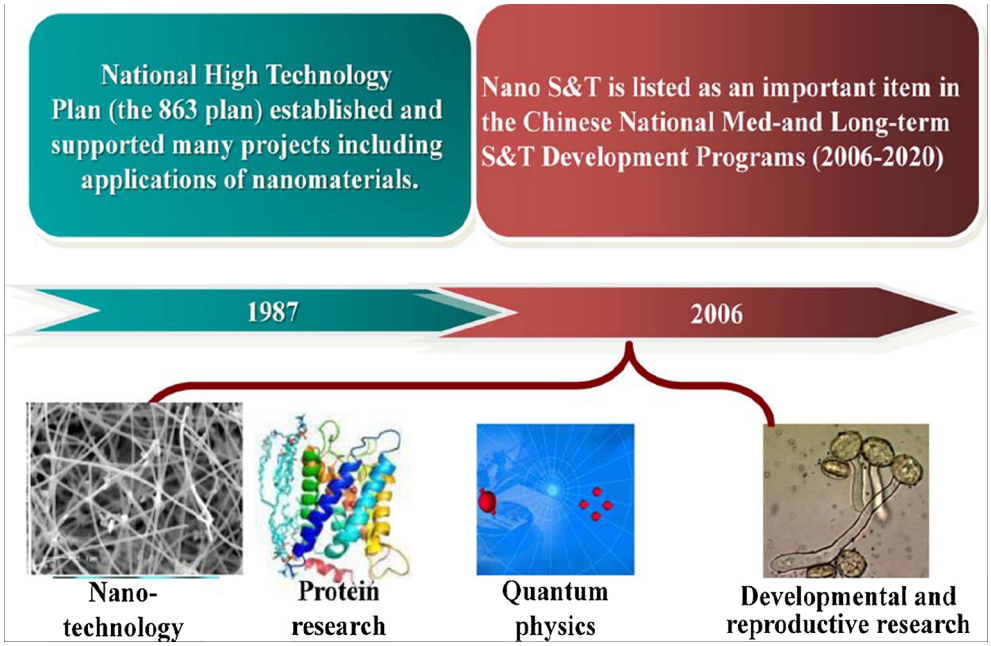


**Fig. 1.** The Chinese government standing to support nanotechnology R&D programs.

nanometers in diameters and size between single atom/molecules with a distinct shape have size-dependent optical and electrical properties. These observations were explored for the expectations of superior performance compared to bulky materials for possible applications, the size and shape of the NPs are optimized in a lucid way [13–15]. These important matters have opened new exhilarating possibilities to tailor the physical and chemical properties of NPs to create a novel material for new controlled applications rather altering the composition [15,16–18].

In addition to this newer synthesis routes paved for its numerous applications to develop interesting material rather than traditional bulk synthesis. NPs having a particle size of less than 100 nm tremendously attracted many scientific domains due to their fascinating properties with multiple applications than their bulk counterparts [19,20]. The research on particle size, shape, material surface properties is one of the prime important areas of NPs properties for targeted applications in vast areas of science.

Nature has provided ways and insights into the synthesis of advanced nanomaterials. It has been reported in the literature that biological systems can act as the 'bio-laboratory' to produce pure metal and metal oxide particles at the nanometer scale using biomimetic approach [21]. Various microorganisms, such as bacteria, fungi, yeast, plant extracts and waste materials have acted as eco-friendly precursors for the synthesis of NPs with potential applications. Also NPs synthesis by the green route has become the latest development, because of the bioavailability of sources like plants or microorganisms, and it also reduces the utilization of toxic chemicals. This microorganism involved in the synthesis of these NPs also elucidate the size, shape and functional groups involved in the synthesis of NPs and its application [22,23].

The biological approach which includes different types of microorganisms has been used for the synthesis of different metallic NPs and for the coating of biological molecules on the surface of NPs, which has advantages over other chemical methods as this is greener, energy saving and cost-effective. The biocompatibility of bio-inspired NPs offers very interesting applications in biomedicine and related fields [24]. These biomolecules are exploited for the treatment of cancer, diabetes, thrombosis, obesity, and other degenerative diseases and act as reducing as well as capping agents. Many previous reports are demonstrating that biosynthesized NPs effectively controlled oxidative stress, genotoxicity and apoptosis related changes. Sigma Aldrich is currently the leading supplier of nanomaterials [25,26].

## 2. Competition for the nano-area

In the 21st century, nanotechnology is one of the key rolling transformative technologies, and many industries are revolutionized. Among which, the improvement of the diseases diagnosis and the better treatment intern are recognized as a national technological competence. Numerous developed and developing countries are facing serious competition which leads those governments to make strategies for the development of advanced technologies including nanotechnology to lift the countries status [27–29].

Therefore, trillions of dollars of money has been invested in the area of nanotechnology to use innovative nanotechnology for the manufacture of first-class materials from raw materials with low cost, non-hazardous from green efficient energy to come back from hazardous to nature. More than 60 leading countries started nanotechnology programs to create a new avenue through re-engineered nonmaterials for diverse fields such as energy efficiency, environmental protection, and health care system [30].

China started nanotechnology research in the mid-1980s and supported research to tune ultra-fine materials to solve the issues in the scientific field with the help of the Chinese Academy of Science (CAS) and National Science Foundation Committee (NSFC). The National Steering Committee for Nanotechnology Development initiated in October 2000 established to manage nationwide efforts on nanotechnology research and development (R&D). This committee contains 21 high-class scientists from different institutes, universities, industries and 7 government agencies which are responsible and contributed their expertise to start nanotechnology R&D. To the success of this initiative, around 863 well-planned ideas are executed string projects to support nanotechnology for NPs and their applications in engineering, food, medicine, healthcare and many more areas (Fig. 1) [31]. Then afterwards, nanotechnology has grown as a high-priority by the Chinese government, for example, Shanghai Municipal Government supported by the Shanghai Nanotechnology Promotion Center (SNPC; www.snpc.org.cn) with an annual budget estimated to be 100 M RMB (~$14.7 M) for nanotechnology R&D established in 2001 to carry out engineering, technology and nanoscience through substantially increased the

investments for possible extended collaborations with different sectors for nano-era for future world [32–34].

With the vision in 1987, establish ultrafine material research and from 2006 to 2020, the motivational research in nanotechnology as one of the four most prioritized programs (bottom panel). The figure is adapted from Ref. [31]. Copyright from Elsevier publishers

### 2.1. Functionalization of NPs for high output biomedical applications

The advanced nanotechnology field of science attracted a number of researchers due to its tremendous advantages in many fields, especially as biomedical materials for possible applications. The unique chemical and physical properties and their growing interest in the field of nano science have motivated the synthesis of NPs from different materials including noble metals such as Ag [35], Au [36], Pd [37], Pt [38], magnetic materials (e.g. Co [39], CoPt [40], $CoFe_2O_4$ [41], $Fe_3O_4$ [42], FePt [43]) and semiconductors (e.g. CdSCdSe, ZnS [44], InP [45], PbS [46], Si [47], $TiO_2$ [48]) and their possible combinations. The NPs are widely used in biomedical applications of labeling, drug carriers, tracking agents [36], gene delivery [49], diabetes [50], cancer [51], hyperthermia treatments, and magnetic resonance imaging (MRI) contrast agents [52] and many other applications (Fig. 2**A**) [53]. If the designed NPs have been used as biomedicine (Fig. 2**B**) they should have certain criteria such as fluorescent staining, minimal cytotoxicity, less non-specific interactions to plasma proteins, evade the reticuloendothelial system (RES) depending on the application, under physiological condition, they should also have good colloidal stability in a wide range of pH, and carriers should avoid remove to release of the drug at a wrong site will be highlight of the events.

The ionic ligands are primary pre-requisite to allow NPs to proceed conjugation. The physiological salt concentration should be around 100 mM and the synthesized NPs with ionic species such as citric acid/citrate or orthophosphoric acid/phosphate can lose protons easily and exhibit highly pH sensitive property such as protonation/deprotonation which intern affects the surface charge which leads to the salting out of the NPs. This type of nanomaterials is unfortunately unsuitable for any type of biomedical applications [54–57]. It is an alternative strategy to ionic stabilization of NPs to prevent aggregation by giving physical barrier for superior NPs. This type of performance can be achieved by coating ligand shell on NPs or embedding NPs within the suitable polymer or inorganic matrixes. This allows NPs to come in contact and aggregation which helps in increasing the hydrodynamic radius of the NPs and therefore make them suitable for *in vivo* applications with a longer circulation time in the blood stream. To attain the NPs for the desired applications, considerations should be taken for many important characteristics of the synthesized NPs s such as,

1. Ionic stabilization
2. Steric stabilization
3. Polymeric ligands
4. Small-molecule ligands
5. Phase transfer (PT)
6. Ligand exchange
7. Ligand addition
8. Effects of the ligand shell
9. Type of biofunctionalization
10. Type of coupling strategies for biofunctionalization.

NPs were synthesized in many ways and they offer many pre-requisite advantages over larger particles such as increased surface to volume ratio and increased magnetic properties and they are classified into different nanosystems engineered for many cellular targets, medical research and other interesting applications [58–63].

The NPs were synthesized as discussed above and they were attracted due to unique optical, magnetic, drug delivery properties that can be further tuned depending upon their size, shape, and surface functionalization [64–66]. For biomedical applications, if material is water soluble it attracts for many interesting applications. This can be possible by designing NPs with small molecules such as polymers, lipids, proteins, and coating other organic materials to assemble into predetermined to provide desirable properties for many biomedical applications such as tracking, drug delivery, cellular labeling, therapies for cancer, microbial infections, and other therapeutics to perform complex desirable functions in a controlled physiological system [67–72] (Fig. 3).

### 2.2. First class magnetic NPs (MNPs) in cancer therapy

The current hot topic of research in the biomedical application for cancer is synthesizing NPs having magnetic properties with well-defined specifically triggering biological response and received a great attention as a unique proposal for biomedical systems. Their inclusion in the treatment pathways of various pathologies highlights a growing trend towards the integration of novel biotechnologies in healthcare

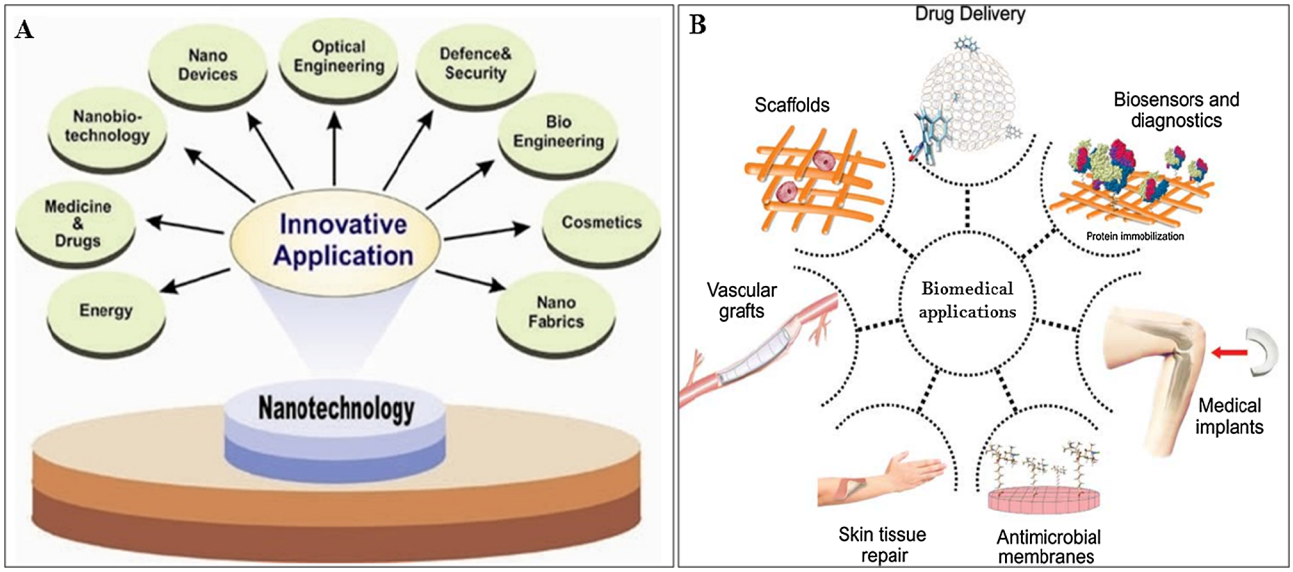


**Fig. 2.** Nanotechnology research proved its strength through many applications in different fields of sciences. A. Various applications of nanotechnology and new hot areas in the upcoming years. B. Application of nanomaterials in the field of biomedical science, Adapted from Ref. [53]. Open access article, with permission.

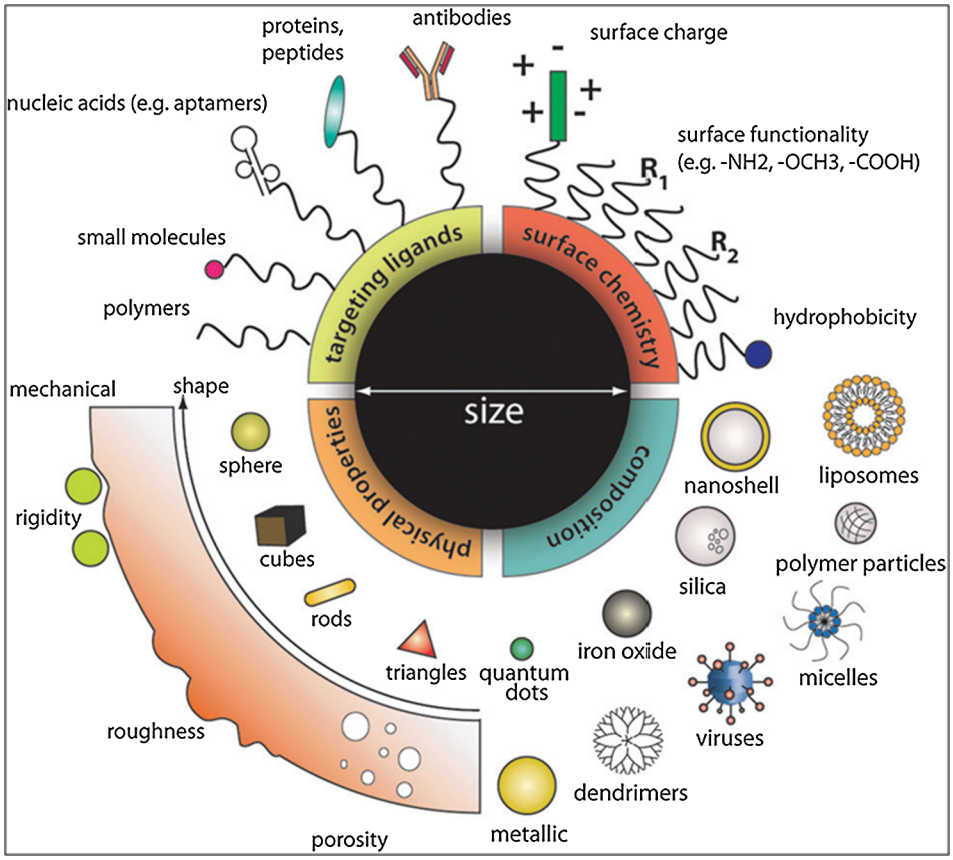


**Fig. 3.** The different types of NPs and intracellular applications. The NPs can be synthesized in different ways from different materials suitable for desired applications for biological targets using pre-determined strategies. The figure is adapted from Ref. [70], with permission.

and therapeutic settings. Superparamagnetic NPs (SPNs) allow clinicians to produce a localized thermo-ablative effect leading to the destruction of bacterial biofilms and cancer cells. In addition, through the physical disruption of bacterial membranes, SPNs can sensitize resistant bacterial cells to antibacterial compounds [73,74].

The ferromagnetic magnetic NPs are superior compared to light, and the MNPs can convert external electromagnetic energy (i.e., alternating magnetic field, AMF) into heat applied in the vast area of biology and medicine due property to control the local temperature at the nanoscale in a remote-controlled manner [75,76]. This is because the biological molecules such as DNA and membrane proteins had similar dimensions influence the MNPs to specifically stimulate or activate target molecules in a fastidiousness way at the molecular level. The MNPs extensively studied specifically for the type of cancer using thermal treatment. The tumor cells are damaged by excess heat released by MNPs which leads to series of shock response and generated heat can stop cancerous cells and return to state for anti-cancer activities. This remarkable potential has made it a potent candidate for clinical applications specifically for prostate cancer and gliomas without considerable side effects. Recently, researchers in biomedical applications, spontaneously MNPs are begun to utilize as stimulating components for various biological systems such as cell signal trafficking, cargo delivery by magnetically triggered NPs, for the activation of membrane receptors by heat-sensitivity by NPs, and production of proteins by gene expression studies [77–81] (Fig. 4**a–d**).

### 2.3. Magneto thermal NPs in drug delivery

Many decades ago, by trial and error various strategies have been employed to trigger and release loaded particles under controlled physiological conditions, including pH, ionic conditions, varying glucose levels, altering enzyme levels, different thiol states, and highly sensitive response immune stimuli's or different intermolecular associations. Under these conditions, MNPs induce effective targeted drug delivery through modulating bimolecular interactions such as dissociations, shrinkage, and cleavage of the targeted molecules. With this new interesting approach, many novel molecules such as siRNA, aptamers, chemotherapy agents, antibodies, and interesting cell-membrane escaping peptides can be used for various applications and have the future for remote-controlled cellular activities through designing MNPs with new characteristic properties to extend its potentiality to whole body for providing suitable therapy for various biological systems accurate therapy for biological system [82,83].

In terms of therapeutics NPs play a potentially large role [84,85]. NPs can be also engineered for selective drug and gene delivery to targeted organs or tissues, minimizing exposure of healthy tissue to drugs or genes [86–90]. Furthermore, some nanomaterials are used for thermal therapy. Several classes of NPs, namely liposomes, magnetic and metallic, are currently in clinical trials for cancer thermal therapy [91]. Magnetic NPs (MNPs), are designed to heat under a high frequency magnetic field to induce cancer cell death [92,93]. Research progresses even further in the cancer fight by targeting cancer stem cells (CSCs). Infact, the CSCs not only can play a major role in cancer initiation, progression and drug resistance, but chemotherapeutic drugs may increase the CSCs fraction in the tumour, allowing these cells to survive and evade to distant sites [94]. In this battle against CSCs, MNPs have shown encouraging results. For example, the magnetic hyperthermia transduced by superparamagnetic iron oxide NPs (SPION) in the alternating current magnetic field reduced or eliminated CSC population [95]. The combination therapy of monoclonal antibody and paclitaxel loaded iron oxide magnetic NPs against cancer stem-like cell activity in multiple myeloma, led to significant reduction of tumor

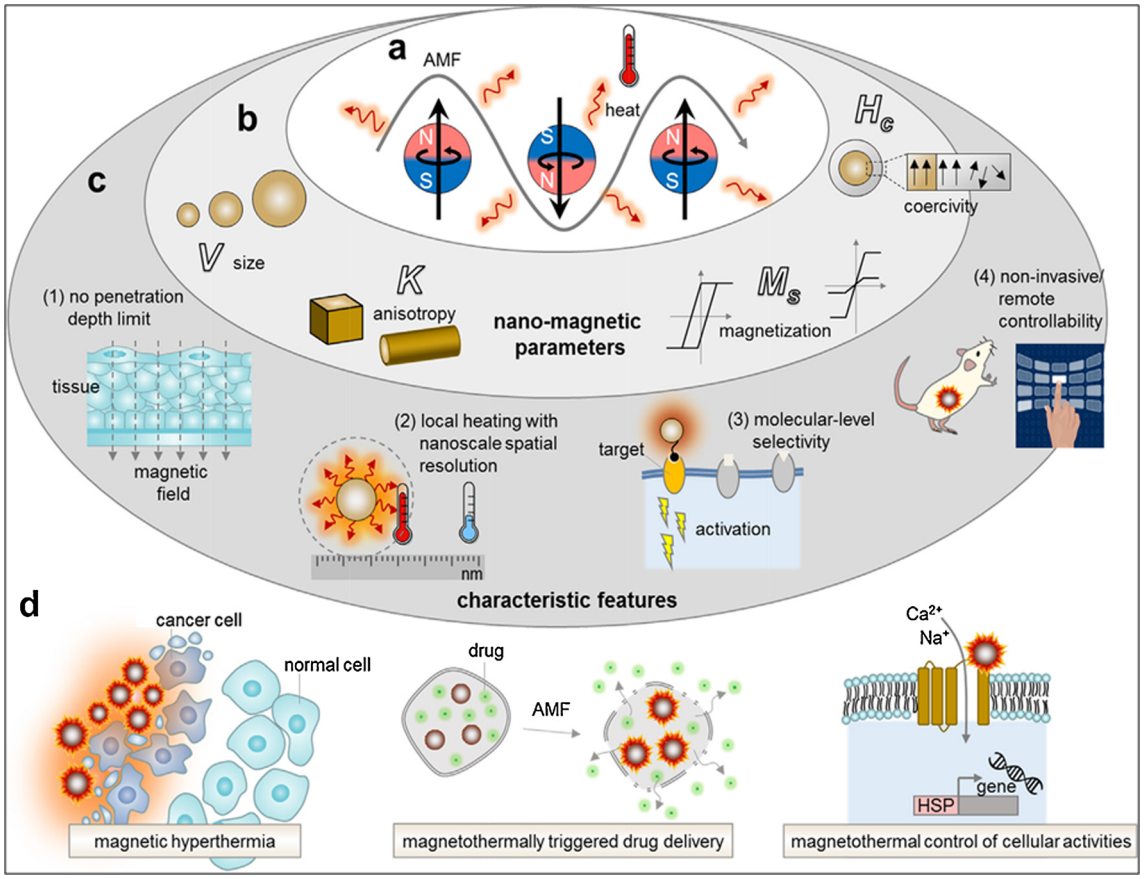


**Fig. 4.** Magnetothermal triggered NPs are the multipurpose podium for hyperthermia therapy and other biomedical applications. (a) MNPs exchange energy in the form of heat as an alternative to magnetic field (AMF). (b) Nano-magnetic parameters controlling generated heat through K-anisotropy, V-size, and MS-saturation magnetization. (c and d) The illustrations showing for penetration with no limit into the tissues in future biomedical applications with molecular specificity, nanoscale resolution and remote controllability without heating (c) and heating by the magnet can be utilized for hyperthermia, drug delivery through magnetically triggered NPs, other different cellular functions (d). The figure is adapted from Ref. [77]. Copyright from Elsevier publishers.

growth in a preclinical study [96].

The aim of theranostic nanomedicine is not only to improve the detection and to increase the efficacy of the treatment of cancers but also reduce the systemic toxicity associated with this treatment. It is important that the therapeutic agents reach and can concentrate in the target sites. One more advantage of the nanomedicine in the treatment of cancer is personalised medicine where we can review the outcome of a treatment in individual patient and plan the next therapy or to decide to repeat the same therapeutic session (personalized medicine) [97]. These innovative multifunctional hybrid NPs combine therapeutic and visualization capabilities for the future use in simultaneous magnetic resonance imaging and therapy strategies based on targeted drug delivery, magnetic hyperthermia or magneto-mechanical actuation [98].

SPIONs are multifunctional and they can be exploited for medical imaging, tumor targeting, drug delivery and cancer therapy. Sizes, shapes and surface properties of SPIONs can be engineered to improve their targeting efficiency, drug delivery, contrast in MRI, responses to external magnetic fields and reduce their toxicity as well as nonspecific cellular uptake. The success in MRI application and some clinical outcomes of SPIONs can pave the way for advanced theranostic utilization in clinical applications [99].

The role of NPs in breast cancer nanotherapy is not yet fully explored. SIONPs, have great potential to enhance treatment of breast cancer. They increase the sensitivity of breast cancer cells to MRI detection, hyperthermia, chemotherapy, radiotherapy and photodynamic therapy. IONPs with this important feature can act as diagnostic and a therapeutic agent simultaneously and this needs to be exploited further to develop low cost drugs. IONPs can be developed as an important thernostic tool for early detection which is the mainstay of prevention and better patient survival in breast cancer. Therefore, more of thernostics multifunctional IONPs with very high saturation magnetization and ability to incorporate biological ligands need to be developed in the future. Successful clinical translation of these IONPs formulations is the most important challenge to overcome in nanotherapy [100].

### 2.3.1. *Self-immolative polymers (SIPs)*

The controlled release of therapeutics using drug delivery systems has been studied in depth over the last several decades [101,102]. Drug delivery systems can provide improved solubility or dispersibility of hydrophobic drugs, improved bioavailability, and more specific targeting, leading to fewer adverse side effects. Polymers have been widely explored for drug delivery, as they can be engineered to assemble into a variety of nanostructures such as vesicles, micelles, and solid core particles by tuning both their chemical structures and their processing conditions [103,104]. Over the past decade, a new class of stimuli-responsive polymers was introduced. Often termed self-immolative polymers (SIPs), these polymers undergo complete end-to end depolymerization in response to stimuli-mediated cleavage of end-caps from the polymer termini [105,106]. This offers the potential to amplify responses to stimuli, making SIPs of significant interest for a wide range of applications such as sensors [107], responsive plastics and coatings [108], lithography [109], and drug delivery [110]. Only a few studies thus far have explored the potential of SIPs for drug delivery. To address this, recently reported the study of micelles based on poly(ethyl glyoxylate) (PEtG)-PEG block copolymers. PEtG depolymerizes to ethyl glyoxylate, which is subsequently hydrolyzed to generate ethanol and

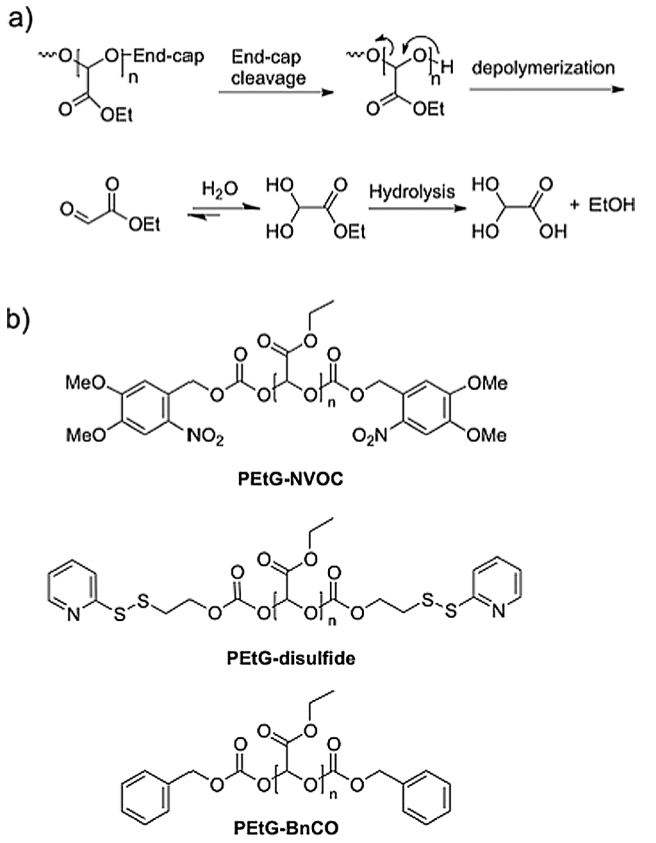


**Fig. 5.** (a) Depolymerization scheme for PEtG. (b) Chemical structures of the stimuli-responsive and control PEtGs.

glyoxylic acid **(**Fig. 5**)** [111,112]. Glyoxylic acid is a metabolic intermediate that can be processed in the liver and should be nontoxic in low concentrations. It was envisioned that triggering of PEtG degradation would result in erosion and rapid drug release from the PEtG domains, leaving drug-loaded PLA for a sustained drug release. 6-Nitroveratryl carbonate capped PEtG was selected for its rapid responsiveness to UV light and served as an ideal model system [113].

### 2.3.2. Zwitterionic polymers

Nanoparticles have also been designed to demonstrate a pH-dependent change in surface charge. One of the most commonly investigated systems is based on zwitterionic polymers, as they have cationic and anionic groups that control surface charge in response to pH. In acidic pH, these zwitterionic polymers have a positive charge, and in basic pH, they have a negative charge. However, when these zwitterionic polymers are in neutral pH, they are overall neutral with balanced populations of positive and negative components and they become more hydrophobic. However, upon entering tumor cells, the balance between positive and negative charges will be broken and thereby cause conformational changes, facilitating drug release in tumor cells. Kang et al. [114] have reported the fabrication of tumor microenvironment responsive theragnostic with a pH-dependent fluorescence turn on/off property. The nanoparticles were constructed by encapsulating a photothermal dye (IR 825) in the carbonized zwitterionic polymer. Before accumulating in the tumor site, these nanoparticles displayed quenching of fluorescence due to the hydrophobic interaction with neutral pH and π-π stacking. The slight change in the pH in TME enabled the charge of the nanoparticles to be altered, leading to the release of IR 825 and recovered fluorescence. These types of nanoparticles can simultaneously be used for diagnosis and photothermal therapy.

### 2.3.3. Electrochemical potential-responsive nanoparticles

In the recent years, electrically triggered drug delivery systems gained more attention towards the cancer therapy. This can be achieved by using materials which spontaneously changes its dipole moment or molecules which can shows redox property in the external applied current. Electro-responsive drug delivery system achieve through different electro-responsive materials such as conducting polymers, metal nanoparticles and nanocomposites etc., and the rate of deliver of drugs is based on the applied filed and conductive materials [115]. These electric signals can be generated and controlled easy and also to trigger the molecules in pulse, sustained or on demand release to target site. The electro-responsiveness affected by different parameters such as, charge density, electrodes, concentration of electrolyte, hydrophilicity of electro-responsive material, presence of ionisable molecule in system, *in-vivo* pH, and composition of aqueous medium, etc [116]. Ge et al., described the daunorubicin loaded in conducting polypyrrole nanoparticles which releases with weak and external electric field and approached for *in vivo* model [117]. The amount of loaded drugs varies with the variation in the thickness of thin film. If the thickness of film was thin then, the release of drug is more effective, but amount of holding of drug in film is less. If the film thickness is more the capacity of loaded drug will also increase but the release of drug from inner film is difficult so, high applied electric current is required [118]. Thin film incorporated nanomaterials enhances the loading drug capacity due to its volume to surface ratio property [119]. Weaver et al., designed graphene oxide nanocomposites incorporated polypyrrole loaded with dexamethasone. The graphene oxide acts as nanocarrirer due to high stability and improves the amount of drug loaded into nanocomposite film. The drug releases from thin nanocomposite film by the electrical response [120]. Rodzinski et al., paclitaxel loaded magentoelectric nanoparticle ($CoFe_2O_4$@$BaTiO_3$) was treated to ovarian cancer. He demonstrated that on applying d.c current some of the nanoparticles found in the target site compare to a.c current [121]. Redox potential gradients are already present in intracellular and extracellular environment in many biological systems so if we choose a weak redox conductive material as a nanocarrier as DDS the efficiency in release of drug in target site is decreased [121].

### 2.3.4. NIR light-based photo-responsive materials

Light is used as external stimuli in a various field in biomedical applications like drug deliver, imaging etc., [122] due to its various advantages such as non-invasive, high spatial resolution, temperature control, convenience and easy to handle. NIR based drug deliver based systems are more advantage compare to other stimuli responsive system [123]. NIR –stimulus drug delivers are potential carrier for drug deliver to target site because NIR (750–1200 nm) are good tissue penetration and safe for cells and tissues compared to UV light. NIR light induces different types of photoreactions like photo isomerisation, photolysis, photocoupling, photo polymerisation, photothermal in drug delivery systems [124]. These photoreactions are mainly worked on two photon absorption, upconverting nanoparticles and photothermal mechanism [125]. Photochemically drug delivery (PCDD) depends on the rate of covalent cleavage by irradiation of NIR. PCDD requires sufficient energy to cleave the covalent bonds, so this strategy should contain moieties like ester, aldehydes, and carboxylic acid etc., which readily cleavable upon irradiation of NIR. The photo-thermal responsive is mainly conversion of light energy to thermal energy due to the vibrational motion. There are several nano-materials like carbon-based nanomaterial, metal oxide nanoparticles, grapheme-based nanomaterials, NIR absorbing dyes were used in the photo-thermal drug delivery system. Liu et al., synthesized gold nanoshell-coated betulinic acid liposomes (AuNS-BA-Lips) which shows controlled drug release with synergetic effect of chemio-therapy and thermal-therapy and inhibits tumour upto 83.02% in mice model [126]. Xu et al., synthesized gold nanoparticles decorated with catechol and then loaded with doxorubicin conjugated hyaluronic acid (GNRs-HA-FA-DOX) and

demonstrated great potential against breast cancer [127]. Chen et al., prepared nanocomposite decorated with spiropyran-functionalized amphiphilic polymers and upconversion nanoparticles (UCNPs) loaded with doxorubicin and tested against U-87 MG cancer cells which killed 60% of cancer cells [128]. Jonas et al., reported two photon fluorophores with two photon absorption which is suitable for FRET to photoisomerize azobenzene and mesoporous nanosilica and loaded with anticancer drug captothecin which shows controlled release by two photon trigerred photoisomerzation and kills the cancer cells [129].

### 2.4. Nanotechnology: Smart ligands and antibodies targets in cancer biology

Recent current World population is faced with the threat of the most serious disease-cancer which is the leading cause of death Worldwide. Cancer is the uncontrolled proliferation of active cells where apoptosis is dysregulated and thereby complicates the treatment processes. The diversity in the cancer genetics, cancer types become resistance to several chemotherapies and require varieties of new strategies to treat or eliminate cancer. The treatments for cancer currently employed are chemotherapy, hormone therapy, surgical removal, and radiation therapy. Generally, the chemotherapy delivers anticancer drugs to quench the active cancer cell proliferation. But, the nonspecific delivery of anticancer agents may lead to side effects due to nonspecific interactions with the normal body cells which avoid desired outcome in most of the cases. Also, many side effects issues including organ damage and results in impaired treatment at the low dose, ultimately less chance of survival rate. At this stage, modifications of NPs in shape, size, physical and chemical properties and the developments of cancer drug delivery system play an important function in cancer biology by targeting neoplastic cells in active or passive targeting way [130–133] (Fig. 6**A and B**) (Table 1).

Folate tagged IONPs have also been used for targeted delivery to folate receptors overexpressing breast cancer cells for similar applications. Targeted delivery affects only cancer cells expressing the targeted molecule, thereby decreasing the systemic toxicity and the side effects, some of which could be life threatening. AntiHer2 antibodies tagged IONPs have also been used as immunosensor to detect Her2 in serum samples as breast cancer biomarkers with excellent sensitivity. Phosphatidylserine (PS) targeting monoclonal antibodies (MAb) have been tagged to SPIONPs to help target and bind to PS exposed tumor vessels to increase accumulation of SPIONPs in breast tumors and enhance tumor contrast. This increases sensitivity and specificity of detection of breast cancer at an early stage. Endoglin/CD105 MAb tagged-IONPs loaded single wall carbon nanotubes (SWCNTs) allowed enhanced targeting to 4T1 breast tumors, increasing sensitivity of MRI detection and delivery of higher doses of thernosticsnano-carrier SWCNTs. IONPs tagged with EGFR-MAb have been used for dual imaging i.e. fluorescence molecular tomography (FMT) and MRI (both non-radiative and non-invasive) to enhance breast cancer detection [134–136]. One major challenge in nanomedicine is how to selectively deliver NPs to diseased tissues. Nanoparticle delivery system requires targeting for specific delivery to pathogenic sites when enhanced permeability and retention (EPR) is not suitable or inefficient. The ideal nanoparticle-based therapeutics should have specific targeting to pathologic tissues, which minimizes or avoids off-target effects of the active therapeutic agents on healthy tissues. Much research has conjugated targeting ligands specific to cell surface components that are unique to, or upregulated in, dysplastic and pathologic tissues to nanoparticle surfaces. These targeting ligands fall into several general classes: small molecules, polypeptide-based peptides, protein domains, antibodies, and nucleic acid-based aptamers.

#### 2.4.1. Active targeting

Here, the desired NPs are used as chemotherapeutic agents and designed in such a way that the surfaces of the NPs have been modified with specific agent interact directly with defective cells based on molecular recognition of target cancer cells. The interaction of NPs will be either antigen-antibody interaction or ligand-receptor recognition in which drug delivered in three ways, (i) targeting moiety-as a penetration enhancer (ii) apoptosis-induced by the anticancer drug, and (iii) using carrier using lipids, metals, and ceramic in NPs. The mechanism in cancer therapy here is NPs having active agent engulfed by phagocytes then cleared by reticuloendothelial systems (RES). The designed NPs should sustain in the blood stream for which hydrophilic polymers have been coated to remain in the bloodstream for a longer time to target cancer cells efficiently, and escapes NPs from opsonization and clearance; this is called as “cloud” effect. Once the NPs involved in receptor-mediated endocytosis by cells, which results in internalization of drug carried NPs [137–140] (Fig. 6**A**).

#### 2.4.2. Precise receptor targeting

There are many cell membrane receptors for targeting cancer cells in which specifically targeted NPs can be designed in to bind to interact and release the anticancer drugs at the target site. They include (i) Folate Receptor-expressed more in neoplastic cells for targeting certain cancer therapies [141], (ii) Transferrin Receptor-investigated and over expressed by certain types of tumor cells to help in increasing the iron uptake. The transferrin can be engineered to different materials for cancer therapy includes Tf-toxic protein, Tf-antibody, Tf-chemotherapeutic agent, Tf-RNase, and Tf-peptide [142–145] (Fig. 6**B**). One of the commonly prevalent targeting ligands conjugated to NPs are small molecules. The advantage of using them is for their stability, ease of conjugation with NPs at a low cost. Vitamin B9 (folic acid) is a small molecule ligand that has been intensively used and investigated. Benzamides can target sigma receptor-positive tissues. Carbohydrates which interact weakly with some cell surface receptors can be used for small molecule targeting ligands.

#### 2.4.3. Asialoglycoprotein

The Asialoglycoprotein (ASGP) is a type of overexpressed receptor in hepatoma, and NPs are used in the treatment of cancer by targeting anticancer drug delivery system [146,147]. The biodegradable NPs with size of 140 nm targeted to hepatoma cells by preparing poly(β-glutamic acid)-poly (lactide) block copolymers loaded with paclitaxel in a technique called emulsion solvent evaporation and its NPs were linked with galactosamine (GAL) in amide linkage to increase the hepatoma HepG2 cell opsonization through ASGP membrane receptors [148].

### 2.5. Luteinizing hormone-releasing hormone receptor (LHRHR)

It is an ongoing research interestingly nowadays, targeting ligand to LHRH receptor over expressed in the various plasma membrane in cancer cells like prostate, breast, and ovarian cancer [149–152].

#### 2.5.1. Nanoparticles-vehicles to target angiogenesis

It deals with the growth of new blood vessels from preexisting vessels. It is a special nature of some tumor types, without angiogenesis, the tumor will not grow even not more than 2 mm in diameter. It is due to overexpression of angiogenic growth factors of abnormal state and limitation of angiogenic inhibitors leading to leaky and tortuous vessels induce an inflammation, reoccurrence of the tumor, high degree of metastasis, and shorten lifespan correlated to angiogenesis. Development of anti-angiogenesis therapy is based on either using drugs that will prevent formation of new blood vessels supplying to the tumor or the drugs that will damage the existing tumor [153–157]. The NPs directed antiangiogenesis chemotherapy mechanism based on delivered NPs must involve in preventing the steps involved in blood vessel formation for tumor growth (e.g., endostatin, angiostatin, and TNP-470) or NPs coated drugs must involve in the destruction of existing blood vessels (e.g., combretastain) [158–160].

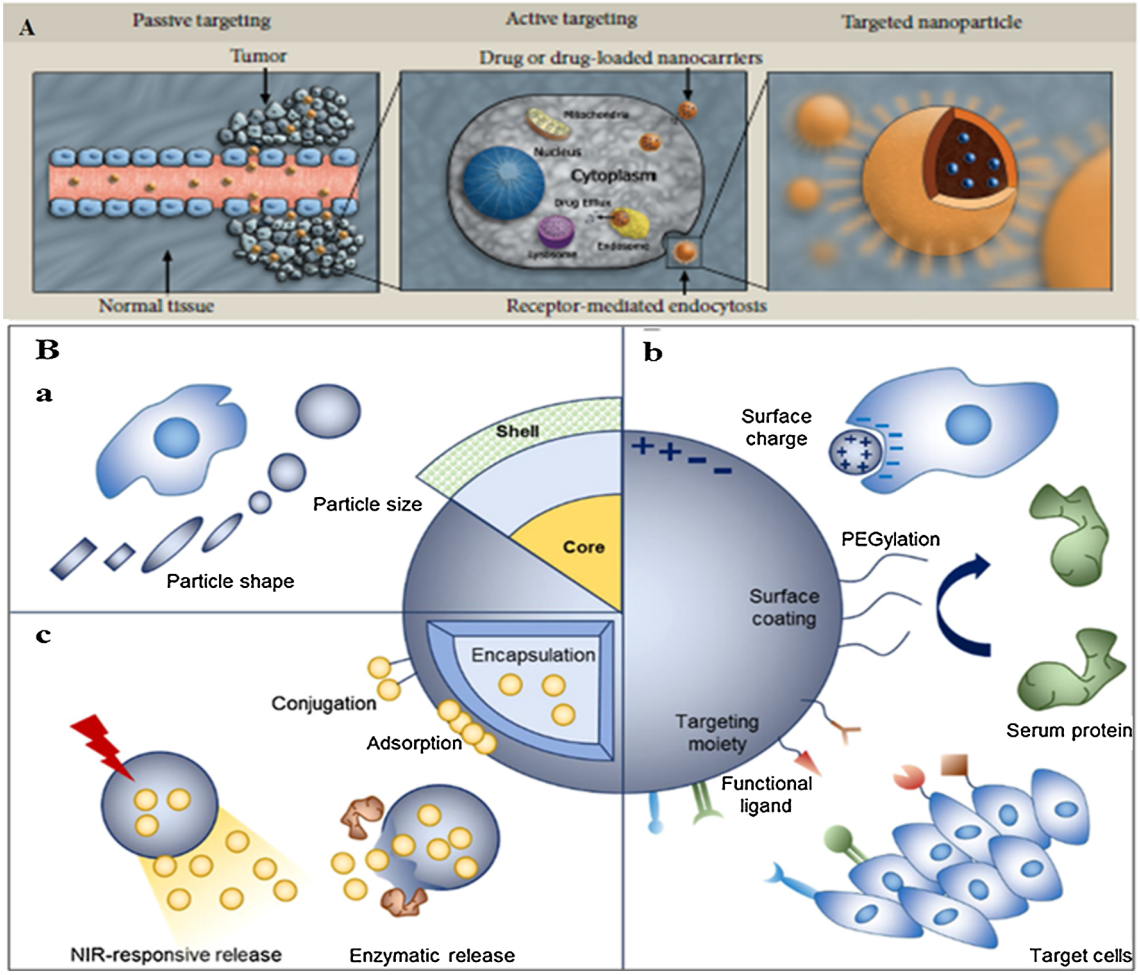


**Fig. 6.** NPs in drug delivery system. A. Active and passive targeting of NPs. B. The engineering NPs for cancer immunotherapy through (a) particle size & shape control, (b) surface modification, and (c) spatiotemporal drug release. The figure is adapted from Ref. [103]. Open access article, with permission.

*2.5.2. Antibody mediated targeting*

Many cancer cells show different antigens of unusual function due to genetic defects occurred for environmental alterations, cell type, and developmental state of an organism and their cells are unrecognized due to own cells. To activate the immune system to destroy the tumor cells, highly specific monoclonal antibodies (mAbs) are designed for NPs to delivery at target specific cancer cells [161–163].

## 3. Overcoming limitation of conventional chemotherapy

Cancer is one of the major causes of death worldwide and chemotherapy is a major therapeutic approach for the treatment which may be used alone or combined with other forms of therapy. However, conventional chemotherapy suffers lack of aqueous solubility, lack of selectivity and multidrug resistance. The chemotherapeutic agents have cannot be efficiently delivered to the exact site of tumor for the treatment of cancer. This problem can be overcome using NPs in drug delivery system by encapsulating hydrophobic drugs in micelles to become soluble. Also, the dendrimers have binding sites for both hydrophilic and hydrophobic molecules to bind. Hydrophobic nature of chemotherapeutics leads to poor aqueous solubility and low bioavailability which can be overcome by nanocrystals, albumin-based nanoparticles, liposomal formulation, polymeric micelles, cyclodextrin and chitosan-based nanoparticles. The liposomes mediated drug delivery system can be efficiently used in cancer treatment to transport active molecule to the desired site of release. The NPs drug delivery method has been efficiently adopted to solve the P-glycoprotein mediated drug resistance. Generally, the drugs are localized to plasma membrane only. The problem will be solved using cyclosporine or verapamil agents and administered with a cytotoxic drug to restrain the P-glycoprotein. In this way, chemotherapeutic and inhibiting agents are used in one formulated NPs form to overcome the P-glycoprotein associated problem [164,165].

Some important technological advantages of nanotherapeutic drug delivery systems (NDDS) are (a) NDDS provides longer shelf life, (b) Both hydrophilic and hydrophobic substances can be incorporated in NDDS. (c) NDDS can be administrated through oral, nasal, parenteral, intraocular etc. (d) NDDS improve the biodistribution of cancer drugs. Whereas optimal size and surface characteristics of nanoparticles increases the circulation time of the drug, (e) NDDS provides control and sustain release of the drug both during the transportation and at the site of action and (f) NDDS increases the intercellular concentration of drug either by enhanced permeability and retention effect (EPR) or by endocytosis mechanism [166,167]. The role of nanotherapeutics to overcome lack of selectivity, multidrug resistance and lack of aqueous solubility of conventional cancer chemotherapy. However, due to lack of selectivity these drugs cause significant damage to rapidly proliferating normal cells. The major goal of targeted therapies is to target the chemotherapeutics to cancer cell which ultimately reduce the side effects. Strategies continuously assessing for the safe delivery of the targeted drugs for the cancer therapies such as,

***A.*** *Nanoparticle drug delivery system to overcome lack of selectivity of anticancer drugs can be achieved through*: passive targeting [168], active targeting [169], folate-mediated targeting [170], and transferrin-

**Table 1**
The recent development is NPs research and positive results.

| Type of nanoparticle | Name of the polymers used | Anticancer drug | Targeting agent | Outcome | Ref. |
|---|---|---|---|---|---|
| Dendrimer | Poly(propyleneimine) and polyethylene glycol | Small interfering RNA (siRNA) | Luteinizing hormone-releasing hormone (LHRH) peptide | High specificity | [164] |
| Dendrimer | Polyamidoamine | | Folic acid | Increased cellular uptake | [165] |
| Nanoparticle | Poly(D,L-lactidecoglycolide) | Paclitaxel | Folic acid | Inhibition of P-glycoprotein | [197] |
| Nanoshell | Biodegradable polymer | Doxorubicin | Folic acid | Sustainable, controlled, and targeted delivery | [198] |
| Polymeric nanoparticle | Poly(D,L-lactidecoglycolide) and polyethylene glycol | Cystatin | Cytokeratin specific monoclonal antibody | Prevent metastasis | [199] |
| Polymer micelle | PEG-poly(aspartate hydrazone doxorubicin) | Doxorubicin | Folic acid | Increased endocytotic cellular uptake | [200] |
| Polymer micelle | PEG-co-poly(lactic-coglycolic acid) | Doxorubicin | Folic acid | Increased cellular uptake and cytotoxicity | [201] |
| Polymeric nanoparticle | Polylactic acid and polyethylene glycol | Paclitaxel | Folic acid | Enhanced drug accumulation in tumor | [202] |
| Polymeric nanoparticle | Poly(D,L-lactic acid) | Paclitaxel | Monoclonal antibodies (antiHER2) | Selective targeting | [203] |

mediated targeting [171] etc.

***B.*** *Nanoparticle drug delivery system to overcome multidrug resistance:* A major problem in cancer chemotherapy is multidrug resistance. Cancers such as non-small cancer, lung cancer, and rectal cancer may not respond to standard chemotherapy from the beginning which is called primary resistance or natural resistance. The cell membrane, cytoplasm, and nuclear protein participate in resistance mechanisms. The mechanisms with known clinical significance are: (a) activation of transmembrane proteins effluxing different chemical substances from the cells; (b) activation of the enzymes of the glutathione detoxification system; (c) alterations of the genes and the proteins involved into the control of apoptosis (especially p53 and Bcl-2). However, multidrug resistance is mostly due to increased efflux pumps in the cell membrane. The most common efflux pump in the cell membrane is Pglycoprotein (Pgp) and it transports various anticancer out of cells by using ATP [172–174]. Various nanoparticluate drug delivery systems to overcome multidrug resistance are Chemosensitizers through NDDS [175], Mesoporous Silica Nanoparticles [176], Solid lipid nanoparticles (SLN) [177], Polymeric nanoparticles [178], Poloxamers, and Magnetic nanoparticles (MNPs) [179–181].

***C.*** *Nanoparticle drug delivery system to overcome aqueous solubility*: Drug substances are considered highly soluble when the largest dose of drug is soluble in < 250 mL water throughout the physiological pH range from 1 to 8 but most of the anticancer drugs show poor aqueous solubility. Poor aqueous solubility chemotherapeutics both from plant source and synthetic often demonstrate decreased bioavailability, increased chance of food effect, more frequent incomplete release from the dosage form and higher interpatient variability. There are two basic approaches to overcome the poor water solubility and poor bioavailability problems (a) Increase of saturation solubility (by complex formation) and (b) Increase of dissolution velocity (Dissolution velocity can be increased by increasing the surface area of the drug powder, i.e. nanonisation) [182] through Nanocrystals [183], Albumin based nanoparticles [184], Liposomal formulation [185], Polymeric micelles [186], Cyclodextrin based nanoparticles [187], and Chitosan based nanoparticles [188]. Poor aqueous solubility and low bioavailability of cancer chemotherapeutic can be effectively overcome by nanocrystals, albumin-based nanoparticles, liposomal formulation, Polymeric micelles, cyclodextrin and chitosan-based nanoparticles.

Attempts have been made to circumvent the mechanisms that cancer cells use to avoid cell death using chemotherapy. A polymeric NP was created to deliver ceramide, which triggers resistant cells to apoptosis under paclitaxel treatment. Another option is to treat with the multifunctional nanoparticle which resulted in 100% mortality among cultured cells. To overcome MDR in a human ovarian cancer cell line, modified poly(epsiloncaprolactone) (PEO-PCL) NPs were used to encapsulate and deliver therapeutic agents for enhanced efficacy. With nanoparticle drug delivery, the resistant cells can be sensitized to paclitaxel. Chemotherapy enhanced via nanoparticle delivery has a promising potential as a strategy to overcome multidrug resistance [189–195].

An alternative new approach was evaluated to inhibit the P-glycoprotein- mediated efflux of vincristine loaded to lipid NPs, which are conjugated to anti-P-glycoprotein mAb (MRK-16). This shows the greater cytotoxicity of resistant human myelogenous leukemia cells than another nonspecific particle [196].

## 4. Conclusions and future perspectives

NPs based cancer therapy is still in its infancy and holding considerable potential. Nanotechnology has been revolutionized for cancer therapy by changing the strategy of many biomedical applications. This made a remarkable importance for specifically recognizing cancer types through tagging active molecules and delivering of safe and efficient systems. Some of the nanotechnology-based formulations have been launched in the market and many are in clinical trials to overcome the

limitations of conventional chemotherapies. The most chemotherapies side effects can be eliminated by active or passive drug delivery systems to extend the survival rate of a human being. In addition, the detailed information of NPs mediated lingering safety issues such as toxicity and immune response lead a nanotechnology to get into deep in nanomedicine. The successful development of NPs-based therapies requires a lot of research in cutting edge of scientific fields including immunology, tumor biology, and in nanotechnology. The life-threatening disease cancer can be effectively treated through new nanotechnology approaches in the future to make an enormous clinical impact that will ultimately improve public health.

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## Contribution

The work designed and manuscript was written by MHM and KPR; suggestions were given by HLQ and PM; and corrections were edited by CSK, PD, YHEM, and SS.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.01.019.

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