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Cancer Nanotechnology: Hopes and Hurdles

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ABSTRACT

Nanotechnology has opened a new era for the treatment and diagnosis of cancer, which is one of the leading causes of death in the 21st century. Using nanotechnology different engineered particles, known as naoparticles has born. Nanoparticles have provided several opportunities to deal with cancer in a more convenient way which are useful to overcome the drawbacks of the conventional cancer treating and diagnosing method. This article is an overview of the opportunities provided by nanotechnology, especially nanoparticles such as, liposomes, dendrimers, fullerenes, carbon nanotubes, solid lipid, paramagnetic and super paramagnetic, ceramic, gold, quantum dots, polymers to deal with cancer and the challenges needed to overcome for proper utilization of them.

KEYWORDS
Nanoparticle, Nanotechnology, Opportunities, Challenges, Conventional.

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Introduction

Cancer came from the Greek words carcinos and carcinoma (represents crab), used by a Greek physician Hippocrates (460-370 B.C.) to describe about ulcer forming and non-ulcer forming tumors (Sehdev et al., 2013). Arguably cancer is the most complex disease, and still it is one of the principal health problems of the 21st century, since after cardiovascular diseases it is the second leading cause of death in developing countries (Fang, Peng, Pang, & Li, 2012),(Bikiaris, 2012),(Nagahara et al., 2010). Almost all cancers (stomach, liver, colon, breast etc) are genetically rooted disease which involves the concurrent

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occurrence of cellular malfunctions (Sehdev et al., 2013), (Yun-Peng Zhang, 2013). Usually cancer forms as a solid tumor, which may or may not be cancerous (benign) (Sudhakar, 2009). Thus cancerous state is a consequence of some chronological matters stimulated by factors like genetic predispositions, transformation by viruses, radiation or certain chemicals (Yan et al., 2016). When the tumor expands big enough, some of its cells may find their pathway into the bloodstream, configuring tumors in different parts of the body, known as metastasis, which effectually increases the cancer and its effects (Sehdev et al., 2013). In bulk tumors greater number of cells may be non-tumorigenic end cells, and within tumors a small population of cells is liable for tumor initiation, growth, and repetition, which are called "cancer stem cells" (CSCs) (K. Wang, Wu, Wang, & Huang, 2013).

The prefix "nano" obtains from the Greek word "nanos" (dwarf) means one-billionth (10-9) of something (QING LI, 2001), (Datta & Jaitawat, 2006). In 1974, Norio Taniguchi defined the term nanotechnology (Stefan Peinert, 2010) but the concept was predicted by Richard Feynman (Physicist) in 1959 (Asiyanbola & Soboyejo, 2008), (Leary, 2010), who gave a lecture entitled as "There's plenty of room at the bottom" (Safari & Zarnegar, 2014), (Al Saghie, 2013). Nanotechnology covers the development and use of materials, devices and techniques at the atomic, molecular or supramolecular level, by using two philosophies, known as "top down"(photolithography, deposition, and etching) and "bottom up" (chemical synthesis, nano-manipulation, and atomic control) manufacturing techniques (Kostoff, Koytcheff, & Lau, 2007), (Panchapakesan & Wickstrom, 2007). According to National Nanotechnology Initiative (NNI) nanotechnology defined as, the knowledge and management of matter at dimensions of roughly 1-100 nm, where noble applications are enabled by unique phenomena (Sudhakar, 2009) or, it may defined as, study and application of technology encompassing nanoparticles (particles less than 1 micrometer) (Asiyanbola & Soboyejo, 2008). Combination of biology and nanotechnology known as nano-biotechnology, and application of this technology in medicine termed as nanomedicine (Stefan Peinert, 2010), (Chang, Zhang, Xia, Zhang, & Xing, 2012), which is applicable to deliver pharmaceuticals, in vitro and in vivo diagnostics, tissue engineering, implant device etc (Jin & Labhasetwar, 2009), (Boisseau & Loubaton, 2011). Nanomedicine may use to maximize the health condition and to minimize the harmful effects of conventional medicine, as it is designed by nanoscale structured materials (Pautler & Brenner, 2010), (Akash Yadav, 2011).

Conventional detection and treatment of cancer

Detection of cancer is completed by remarking the physical changes in the body part using X-rays or CT scans and is later justified by biopsy through cell culture. But this method is not very responsive, and the detection is possible after considerable growth of the cancerous cells (Chandrasekhar P & M, 2013).

The treatment options are chemotherapy (Gorka Orive, 2005) surgery (Jabir et al., 2012), irradiation therapy (C. Moorthi, 2011), or a combination approach (Jabir et al., 2012), (Birendra Kumar, 2009). Surgery means removal of

cancerous part. When the cancerous cells (CC) are burnt by specific frequency radiation, it is called radiation therapy and when those (CC) are killed by drugs toxic to cells, is termed as chemotherapy (Jabir et al., 2012).

Conventional treatment method has several limitations like, systemic toxicity (chemotherapy) (Vergaro et al., 2011), the treatment may not possible for all types of cancer cases (surgery) (Jabir et al., 2012), radiation therapy may cause toxicity (Gunasekera, Pankhurst, & Douek, 2009), gross approach and may unsuccessful in case of advanced stage of the cancer (chemotherapy) (Vergaro et al., 2011). Until now, chemotherapy is the widely used method to treat localized and metastasized cancer. But because of its several limitations (limited aqueous solubility, lack of selectivity of anticancer drugs, multidrug resistance etc) it is not very effective (Vergaro et al., 2011), (Jones & Saba, 2011).

Cancer nanotechnology

Cancer nanotechnology is the medical application of nanotechnology, which is a new interdisciplinary field where prevention, diagnosis and treatment of cancer have done with the help of nanotechnology (Santos, Ponte, Boonme, Silva, & Souto, 2013),(Misra, Acharya, & Sahoo, 2010),(Cai, Gao, Hong, & Sun, 2008). In comparison with the traditional way this new technology, also known as "nanooncology" holds much promise (Meng et al., 2012), (K. K. Jain, 2010) that shows scientist new hope to deal with cancer (Patra, Bhattacharya, Mukhopadhyay, & Mukherjee, 2010).

Hopes

Cancer nanotechnology provides several opportunities over the conventional method of cancer diagnosis and treatment (R. Wang, Billone, & Mullett, 2013), (P. S. Kim, Djazayeri, & Zeineldin, 2011). Such as, it helps to detect cancer at an early stage (Carolina Salvador Morales, 2012), minimize side effects of small molecules (Thomas, Pappu, & Baker, 2011), helps to diagnose, image and treat cancer more effectively (Kalevi Kairemo, 2008) and helps to overcome the conventional treatment problems (lack of early disease detection, non specific systematic distribution, inadequate drug concentrations reaching the tumor etc.) by using nanomaterials or nanoparticles, which may used as a drug, imaging agents or both (multifunctional nanoparticle) with the help of a delivery system known as "nanocarrier" (Thomas et al., 2011), (S. Jiang, Gnanasammandhan, & Zhang, 2010). Nanoparticles may classified as one dimensional (i.e., thin films), two dimensional (i.e., nanotubes, nanowires, nanofibers) or three dimensional (i.e., fullerenes, dendrimers, quantum dots). These nanoparticles provide several benefits, such as, greater bioavailability, low toxicity, stable dosage form, equivalent dose etc (Navedul haque & M. S. Al-Sharif, 2010). Nanomaterials are decent delivery vectors for tumors (Stern et al., 2010). Nanocarriers, also known as nanovectors are hollow or solid structured nanoparticles constitute of a core constituent material, imaging or therapeutic payload, and targeting moieties (Mody, 2011), (Ferrari, 2005) and have the capability to access through biological barriers with extended efficacy (W. Zhang, Zhang, & Zhang, 2011), (Siddiqui, Adhami, Chamcheu, & Mukhtar, 2012).

Different nanoparticle based systems used in cancer therapy

Liposomes

Liposomes (biocompatible lipid based carrier)(A. Sharma, Jain, & Sareen, 2013), discovered by Bangham, are small closed spherical vesicles or colloidal structures consist of cholesterol and phospholipid (natural or synthetic) bilayer (Can Wang, 2014), (Istvan J. Majoros, Brent B.Ward, Lee, Huang, & Baker, 2010) having a central aqueous space (Chen et al., 2013), (X. Wang, Yang, Chen, & Shin, 2008) and can capture both hydrophilic and hydrophobic drugs (Park et al., 2008), imaging agent and others (Alexander-Bryant, Vanden Berg-Foels, & Wen, 2013), (Mohs & Provenzale, 2010). Size of the liposomes (25 nm to 10µm) may vary depending on their preparation method (X. Wang, Wang, Chen, & Shin, 2009). Depending on the formation of lipid bilayers and size liposomes may classified as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles, where unilamellar vesicles carry water soluble drugs and multilamellar vesicles carry lipid soluble drugs (A. Sharma et al., 2013), (Alexander-Bryant et al., 2013). As liposomes are biocompatible and easy to formulate they have wide range of application for therapeutic or imaging agent delivery (X. Wang et al., 2009). For example, there are different liposome basis formulated drugs like Stealth liposomal doxorubicin Doxil, liposomal doxorubicin Myocet, and liposomal daunorubicin DaunoXome (Hu et al., 2014), (McNeil, 2005). Stealth liposomes are long circulatory liposomes developed for better response (M.-H. Lee et al., 2010). These drugs are approved by FDA (US Food and Drug Administration), and used for the treatment of different types of human cancer (i.e. ovarian cancer (Alexis et al., 2008), Kaposi's sarcoma (Sengupta & Sasisekharan, 2007), prostate cancer) (Parhi, Mohanty, & Sahoo, 2012), (Veiseh, Kievit, Ellenbogen, & Zhang, 2011). While developing targeted drug delivery therapies liposomes have both advantages (i.e. capsulate hydrophilic and hydrophobic drugs, capability to treat multidrug resistant cancers) and disadvantages (poor control over drug release, useful for potent drugs only, physically unstable, may cause severe side effects)(Alexander-Bryant et al., 2013). Thus, efforts have been emphasized on the development of liposomes to overcome its drawbacks (Alexis et al., 2008).

Dendrimers

Dendrimers (non-linear polymers) (Khemtong, Kessinger, & Gao, 2009) came from the Greek word “dendron” (tree) (Tokuhara et al., 2008), are highly branched 3D structured complex macromolecules (Mei et al., 2013), (Sahoo, Parveen, & Panda, 2007), consists of a central core (Qiao et al., 2010), building pieces with a number of internal layers composed of repeating units and various peripheral functional groups (Boulaiz et al., 2011), (Kateb et al., 2011). They have well defined branching shape that provides them large amounts of surface area where therapeutic agents and other biologically active molecules may engage (Koo, Rubinstein, & Onyuksel, 2005), (Deepak Godara & Kheman, 2012).

Synthesis of dendrimers incorporated by two principal schemes, they are the divergent method and the convergent method. Divergent method (outward from the core) was first discovered by Tomalia and his groups in 1980's and the convergent method (inwardly toward the core) was discovered by Hawker and Frechet. Polyamindoamine (PAMAM) and polypropylenemine (PPI) are the example of dendrimers synthesized by using divergent method and convergent method, respectively (Bharali, Khalil, Gurbuz, Simone, & Mousa, 2009). Dendrimes possess several applications, such as, solubility enhancement, gene therapy, drug delivery, nanocomposites, photodynamic therapy etc. Dendrimers may used in cancer therapeutic agents and in imaging techniques (i.e. magnetic resonance imaging) as contrast agents (Kateb et al., 2011). "Avidemers", developed by Baker are dendrimers used to target tumor vasculature (Alexis, Pridgen, Langer, & Farokhzad, 2010). For example, generation 5 polyamidoamine (G5 PAMAM) dendrimers conjugated to fluorescein and folic acid, prepared by Choi and his groups, may used as therapeutic and imaging agents in cancer therapy (Qiao et al., 2010).

Fullerenes

Fullerenes, discovered in 1985 (Chetan C. Anajwala, 2010), are large hollow sphere, ellipsoid or tube shaped (Siddiqui et al., 2012) carbon cage molecules consist of 28 to more than 100 carbon atoms (Navedul haque & M. S. Al-Sharif, 2010). The most common form of fullerene is C60. Because of its soccer ball like structure it is also known as buckyball or buckminster which is 7Å in diameters with 60 carbon atoms (Chetan C. Anajwala, 2010). Other common forms of fullerenes are C40, C70, C76 and C84. Because of their stability, fullerenes are relatively safe to deliver highly toxic substances to tumors and it has several applications in cancer therapy. For example use of hydrated fullerene (HyFn) for the prevention of cancer (Sehdev et al., 2013). Fullerene compounds may also be used as antiviral agents, antibacterial agents, antioxidants etc (Akash Yadav, 2011).

Carobon nanotubes

Carbon nanotubes (CNTs), member of fullerene family (W. Zhang et al., 2011), discovered by Iijima in 1991 (Safari & Zarnegar, 2014), are large cylindrical carbon graphitic molecules with a hexagonal arrangement (W. Zhang et al., 2011). It may be single walled (single cylindrical carbon layer), or multi walled (multiple cylindrical carbon layers) (Chetan C. Anajwala, 2010). According to the arrangement of the graphite sheets single walled carbon nanotubes (SWCNTs) can be categorized as armchair, zigzag, chiral or helical and multi walled carbon nanotubes (MWCNTs) can be categorized as "Russian doll" like structure and parchment like model (Madani, Naderi, Dissanayake, Tan, & Seifalian, 2011). Because of their distinctive features they have wide applications in cancer therapy (Chetan C. Anajwala, 2010). For example, chemotherapeutic agent, paclitaxel, widely used in cancer therapy, is a poorly water soluble molecule and has short circulation time, which minimizes its efficacy as an anticancer agent. To solve this problem it can be conjugated with functionalized SWCNT, which is more effective in cancer treatment rather than single paclitaxel. A protein named streptavidin which has anticancer activity

can't penetrate the tumor cell because of its large molecular weight. Using a complex of streptavidin with SWNTs-biotin Kam and coworkers solved this problem (Elhissi, Ahmed, Hassan, Dhanak, & D'Emanuele, 2012). CNTs can also eliminate cancer cells as they are able to absorb near infrared region (NIR) light. This method is known as local hypothermia (Chetan C. Anajwala, 2010). CNTs have other therapeutic applications rather than cancer (i.e. antifungal, antibacterial etc) (Elhissi et al., 2012).

Solid lipid nanoparticles

To overcome the difficulties (physical stability, degradation of labile drugs, difficult preparation procedure, toxicity level etc) of existing carriers (i.e. lyposomes, polymeric nanoparticles) solid lipid nanoparticles (SLNs) have been developed as a substitute system (Jabir et al., 2012).They are lipid originated submicron sized (50 to 1000nm) particles and remain in a solid state at room and body temperature (Can Wang, 2014), (Chetan C. Anajwala, 2010). They are spherical in shape and merge the benefits of lipid emulsion and polymeric systems 80(E. K. Lim, Jang, Lee, Haam, & Huh, 2013) and may administered via different routes (i.e. intravenous, intramascular, oral, rectal, topical) (C. Moorthi, 2011). By using two different methods, known as hot homogenization and cold homogenization SLNs are manufactured. Because of its several advantages (i.e. increased bioavailability, controlled release of drugs) (Koo et al., 2005) it plays a significant role in cancer treatment (Can Wang, 2014). For example, anticancer drug doxorubicin loaded with SLN is much more efficient rather than single doxorubicin, which is used to treat breast cancer (C. Moorthi, 2011), (E. K. Lim et al., 2013). By using this method other anticancer agents (i.e. daunorubicin, idarubicin, pacltitaxel etc.) may also be encapsulated to improve their efficacy (Can Wang, 2014), (Chetan C. Anajwala, 2010).

Paramagnetic and Super paramagnetic Nanoparticles

Paramagnetic and Super paramagnetic nanoparticles are uniformly sized, highly paramagnetic, functionalizable nanoparticles and have a size range of 10 to 100nm (Sudhakar, 2009). They are made with various compositions (i.e. iron oxide) and are pulled by a magnetic field (Hobson, 2011). On the basis of their size they may classified into two groups, known as, SPIOs (super paramagnetic iron oxides) and USPIOs (ultra small paramagnetic iron oxides). SPIOs have a size greater than 50nm and USPIOs have a size lower than 50nm (Kalevi Kairemo, 2008). These nanoparticles can be used in diagnosis and treatment of cancer (Chen et al., 2013). For example, super paramagnetic nanoparticles can be used in the treatment of prostate cancer (K. Y. Kim, 2007), killing cancer cells by producing heat. Conjugated with antibodies paramagnetic nanoparticles are used to detect breast cancer cells in vitro (Chetan C. Anajwala, 2010).

Ceramic nanoparticles

Ceramic nanoparticles are made from silica, alumina, and titania and have a size of less than 50 nm. They have various advantages. Such as, they are easy to prepare which is similar to sol-gel process; surface of these particles can be modified easily by adding various functional groups to target them to

required sites; they are biocompatible, extremely inert and are not susceptible to microbial attack; with the change of pH it doesn't undergo any porosity change (Sudhakar, 2009), (Koo et al., 2005). Because of its advantages it can be used in photodynamic therapy as photosensitizing drug carrier (Koo et al., 2005). Ultra fine ceramic nanoparticles (silica based) help to release anticancer drugs which are water (Gorka Orive, 2005).

Gold nanoparticles

Gold nanoparticles (AuNPs or GNPs), also known as metal and/or inorganic nanoparticles, are biologically compatible and inert materials which are clusters of gold atoms which are prepared from the gold salts by using suitable agents (i.e. citric acid) (Mohs & Provenzale, 2010). AuNPs have some unique physicochemical, optical, magnetic or thermal properties (Shenoi, Shah, Griffin, Vercellotti, & Bischof, 2011), (Dreaden, Austin, Mackey, & El-Sayed, 2012) which make them pretty useful for medicinal applications (i.e. delivery of proteins, peptides, genes, low molecular weight drugs) (Arvizo, Bhattacharya, & Mukherjee, 2010). AuNPs can be prepared via three different ways; known as, physical, chemical and biological methods (Bhattacharyya, Kudgus, Bhattacharya, & Mukherjee, 2011) and in 19th century, Michael Faraday was the first who synthesized gold colloidal by using phosphorous, a reducing agent (S. Jain, Hirst, & O'Sullivan, 2012). In ancient time (2500–2600 BC) Au compounds were used to treat male impotency, to increase necessary power and various diseases by the people of China and India (Bhattacharyya et al., 2011). Later in 19th and 20th century, Au compounds were used to treat rheumatoid arthritis (Singhal, Nie, & Wang, 2010), tuberculosis, inflammatory skin diseases etc (Bhattacharyya et al., 2011). AuNPs have myriad application in cancer therapy and diagnosis (Arvizo et al., 2010), (Nadine Schulte, 2014). For example, to improve the detection of cancer by imaging modalities (i.e. radiography, computed tomography, magnetic resonance imaging, ultrasound etc.)(Ryvolova et al., 2012), (K. K. Jain, 2005), gold nanoparticles are used as contrast agents (Nadine Schulte, 2014). Conjugation of AuNP with CPG (cytosine-phosphate-guanine), which is an ODN (synthetic oligodeoxynucleotide) is used in the treatment of cancer, as a vaccine (Lin et al., 2013). Nanoconjugate products, such as, folate-4 ATP (4-aminothiophenol)-AuNP, folate-MH (6-mercapto-1-hexanol) are used to target folate receptor positive cancer cells (G. A. Mansoori, Brandenburg, & Shakeri-Zadeh, 2010). AuNP conjugated with anti-EGFR (epidermal growth factor receptor) used to target cancer cells (El-Sayed and coworkers) (Dreaden et al., 2012), and for drug delivery (Master & Sen Gupta, 2012). Cetuximab (C225), is an anti-EGFR monoclonal antibody, approved by FDA is used to treat colorectal cancer (Jameel Ahmad Khan., 2011). Cytokine based immunotherapy with the help of AuNPs used in the treatment of cancer (Almeida, Figueroa, & Drezek, 2014). AuNPs are also used in cancer thermal therapy, known as hyperthermia (Manthe, Foy, Krishnamurthy, Sharma, & Labhasetwar, 2010), (Arruebo et al., 2011).

Quantum dots

Quantum dots (QDs), also known as Q-Dots are almost spherical shaped (Gunasekera et al., 2009) inorganic semiconductor (Maehara, 2003) fluorescent

nanoparticles (Hong, Zhang, Sun, & Cai, 2009), have a size range of 2 to 100nm (Juzenas et al., 2008). They are composed mainly of inorganic metals such as, cadmium selenide (CdSe), cadmium telluride (CdTe) etc.(Mousa & Bharali, 2011) and can be synthesized by heating organic solvents containing the parent constituents at a high temperature (about 300^0C) (S. Jiang et al., 2010). They have some distinct physico-chemical and optical properties which make them a versatile candidate for imaging and therapeutic application at molecular level (G. Ali Mansoori, Mohazzabi, McCormack, & Jabbari, 2007), (Misra et al., 2010). QDs can be used as a multifunctional nanoparticle by attaching more than one type of molecule with it (Maehara, 2003). In cancer research, management and treatment they have various applications (Birendra Kumar, 2009). For example, conjugation of QDs with an antibody helps to detect human prostate cancer (Fang et al., 2012). QDs conjugated with anti-EGFR antibody used to image breast cancer cells (McCarthy, Bhaumik, Karver, Sibel Erdem, & Weissleder, 2010) and ovarian cancer (Fang et al., 2012). QDs having polyacrylate coat with antibody link may also be used for the labeling of breast cancer marker (Retel, Hummel, & van Harten, 2009). It has also been used for the detection of gastrointestinal cancer, pancreatic cancer (Fang et al., 2012), and prostate cancer (Misra et al., 2010). For the detection of supersensitive biomarker of cancer, QDs can be used as signal amplifying agent (Choi, Kwak, & Park, 2010). Although QDs have some distinct advantages over other fluorescent techniques (Silva, 2006), such as, high signal intensity (Kawasaki & Player, 2005), low photobleaching (Hong et al., 2009), highly stable (Laroui, Rakhya, Xiao, Viennois, & Merlin, 2013), long period of in-vivo tracking (S. Jiang et al., 2010) etc. they have some drawbacks. For example, water insolubility (S. Jiang et al., 2010), heavy metal toxicity (G. Ali Mansoori et al., 2007), and low penetration power (Gunasekera et al., 2009). Encapsulated QDs with polymer may helpful to reduce toxicity (Johnson, Charles-Edwards, & Douek, 2010), surface modification (i.e. ligand exchange) of QDs help to make them water soluble (S. Jiang et al., 2010) and to improve QDs penetration power, it may coupled with paramagnetic gadolinium (Gunasekera et al., 2009). Still more research is needed for the proper use QDs (G. Ali Mansoori et al., 2007).

Polymer nanoparticles

Polymer nanoparticles (PNPs) either natural such as chitosan (Sudhakar, 2009), gelatin (Thakor & Gambhir, 2013), alginates (Amiji, 2011), heparin (Julien, Behnke, Wang, Murdoch, & Hill, 2011), dextran (Nie, 2010) or synthetic such as poly lactic acid (PLA) (Yallapu, Jaggi, & Chauhan, 2011), poly glycolic acid (PGA) (Mulens, Morales, & Barber, 2013), poly lactic glycolic acid (PLGA) (Prasad et al., 2011), poly caprolactone (PCL) (Jakel, Vogt, Gonzalez-Carmona, & Schmidt-Wolf, 2014) are spherical shaped (Julien et al., 2011) nanostructures have a diameter range within 10-100 nm (Gannon, Patra, Bhattacharya, Mukherjee, & Curley, 2008), consist of a hydrophobic core and a hydrophilic shell (M.-H. Lee et al., 2010) and can play significant role as delivery system (Liechty, Kryscio, Slaughter, & Peppas, 2010) by carrying drugs, proteins and DNA to target cells and organs successfully (Kateb et al., 2011). They can be also categorized as biodegradable e.g., poly alkyl cyanoacrylate (Thakor & Gambhir, 2013) or non-biodegradable e.g., polyurethane (Gannon et al., 2008). Preparation method of polymer based nanoparticles may divide into two categories (Thakor

& Gambhir, 2013). They are polymerization of monomers e.g. emulsion polymerization and dispersion of preformed polymers e.g. salting out (Koo et al., 2005). In formulation, hydrophilic cores are loaded with therapeutic or imaging agents and are coated by stealth materials such as PEG (Poly Ethylene Glycol) to confirm stability (Luk, Fang, & Zhang, 2012). To overcome the drawbacks of conventional cancer therapy PNPs play a significant role (Liechty & Peppas, 2012) as they offer several advantages, such as, improved pharmacokinetic properties (S. M. Lee et al., 2010), non toxic (biodegradable polymer) (Gannon et al., 2008), targeted delivery of drugs (Liechty et al., 2010). For example, an anticancer drug paclitaxel, bound to albumin based PNP may used in the treatment of metastatic breast cancer which increases its efficacy, and has already been approved by FDA (Thakor & Gambhir, 2013). Polymersome (polymer based nanovesicle) (Levine et al., 2008) loaded with porphyrins can create fluorescent imaging agents which are highly capable of detecting cancer cells (Cheng et al., 2011). PNPs are also used in targeting of cancer cells selectively (S. Kim, Kim, Jeon, Kwon, & Park, 2009) that can be either active (C. W. Liu & Lin, 2012) or passive (Liechty & Peppas, 2012). Anticancer drug doxorubicin conjugated with PEG modified liposomes is an EPR (Enhanced Permeation and Retention Effect) based cancer therapy, which is an example of passive targeting (S. Kim et al., 2009). Table 1 comprised of various types of nanoparticles and their application.

Table2: Various Nanoparticle Based Systems & Their Application in Cancer Therapy

Name of Nanoparticles	Use	References
Liposomes	Targeted drug & gene delivery	(X. Wang et al., 2009)
Gold Nanoparticles	Targeted delivery & imaging agent	(Arvizo et al., 2010), (Nadine Schulte, 2014)
Quantum Dots	Targeting & imaging agent	(G. Ali Mansoori et al., 2007), (Misra et al., 2010)
Dendrimers	Targeted drug delivery	(Kateb et al., 2011)
Carbon Nanotubes	Drug, gene & DNA delivery, tumor targeting	(Can Wang, 2014)
Magnetic Nanoparticles	Targeting & imaging agent	(McNeil, 2005)
Paramagnetic nanoparticles	Imaging agent	(Chetan C. Anajwala, 2010)
Ceramic nanoparticles	Targeting agent	(Gorka Orive, 2005)
Fullerene	Targeting & imaging agent	(Can Wang, 2014)
Solid Lipid Nanoparticles	Targeted drug delivery	(Chetan C. Anajwala, 2010)
Polymer nanoparticles	Targeted drug delivery	(Liechty et al., 2010)

Nanowires	Targeting & imaging agent	(Chetan C. Anajwala, 2010)
Nanoshells	Tumor targeting	(Can Wang, 2014)

Chitosan nanoparticles

Chitosan, discovered in 19th century (Xin, 2015), is a biocompatible (Lemke et al., 2011), cationic (Schoffski, 2002), biodegradable (Li et al., 2013), natural (Yan et al., 2016) mucoadhesive polysaccharide (Santos et al., 2013) which is soluble in dilute acids (J. J. Wang et al., 2011). It's a derivative of chitin which is a long chain polymer of N-acetyglucosamine (Li et al., 2013) and is the main component of the shells of crab, krill etc (Schoffski, 2002). Synthesis of chitosan from chitin is done by a process called deacetylation, using sodium hydroxide as a reagent and water as a solvent (Li et al., 2013). Chitosan based nanoparticles can be prepared by using different methods such as, ionic cross link (Xin, 2015), covalent cross link (Yan et al., 2016), complex coacervation , precipitation (desolvation and diffusion of emulsified solvent) (J. J. Wang et al., 2011), reverse micellar method (Yan et al., 2016), polymerization (J. J. Wang et al., 2011). Because of their various advantages such as, improved biodistribution, high specificity and sensitivity, low pharmacological toxicity (Li et al., 2013) and their various biological activities such as, antitumor activity, immune-enhancing effect, antimicrobial and antifungal properties (Santos et al., 2013) it have been extensively applied in medicine and pharmacy. For example, super paramagnetic iron oxide nanocrystals (SPION) coated with chitosan nanoparticles (CNPs) are used as MRI contrast agent, that is highly efficient to detect cancer cells. In-vivo intratumoral injection composed of CNPs conjugated with gadolinium exhibit prolonged retention in tumor tissue. 5-fluororouracil which is used in the treatment of colon cancer conjugated with CNPs provides excellent antitumor activity, having 19% loading capacity and 61% release in 24 hr. Heparin, an anticoagulant conjugated with chitosan and PEG may used to kill cancer cells effectively. To detect colorectal cancer at an early stage, which have a short survival time 5-aminolaevullinic acid (5-ALA) conjugated with CNPs may used. Arginine rich hexapeptide coated by chitosan-dextran sulphate nanoparticles may used to block the growth and metastasis of VEGF that is responsible to produce human carcinoma cells. Tamoxifen, used in breast cancer treatment may conjugate with CNPs to reduce its toxic effect (Yan et al., 2016). Gemcitabine, an analog of deoxycytidine which is used in the treatment of locally advanced and metastatic cases of cancer may conjugate with chitosan and glyceryl monooleate (GMO) nanostructures to increase its therapeutic efficacy (Trickler, Khurana, Nagvekar, & Dash, 2010). Paclitaxel is one of the extensively used anticancer drugs but is not very useful against brain tumors treatment because of its restricted access to tumor site across the blood brain barrier (BBB). Conjugation of CNPs and paclitaxel may provide useful result to overcome this limitation (Schoffski, 2002). Doxorubicin-CNPs complex helps to inhibit tumor cell proliferation successfully (J. J. Wang et al., 2011). Thiolated chitosan modified PLA-PCL-TPGS nanoparticle formulation can be used in the

treatment of lung cancer (L. Jiang, Li, Liu, & Zhang, 2013). Chitosan may also be used in the formulation of cancer vaccines (Lemke et al., 2011) where it works as an adjuvant (compounds that trigger the immune system and increase vaccine responsiveness) (Li et al., 2013) but it is still experimental.

Curcumin nanoparticles

Curcumin, discovered by Vogel and Pelletier (Gupta, Patchva, Koh, & Aggarwal, 2012) is a polyphenolic compound found in the dried ground rhizome of the perennial herb *Curcuma longa* Linn., known as turmeric (R. A. Sharma, Gescher, & Steward, 2005), which is a member of the Zingiberacae family and is available in Southeast Asia (Wilken, Veena, Wang, & Srivatsan, 2011). Curcumin is yellow in color, molecular weight is 368.37, melting point is 183°c (R. A. Sharma et al., 2005), insoluble in water and ether but soluble in organic solvents like acetone, dimethylsulfoxide, and ethanol (Z. Zhang et al., 2014). Chemically it is known as diferuloylmethane, or 1, 6-heptadiene-3, 5- dione-1,7-bis (4-hydroxy-3-methoxyphenyl)-(1E, 6E) which was identified by Milobedzka and Lampe in 1910 (Gupta et al., 2012). At basic pH it is unstable (R. A. Sharma et al., 2005) but can be in neutral condition at a pH range of 1 to 7. Ferulic acid and feruloylmethane are the chief degradation products of curcumin which was found by Tonnesen and Karlsen (Z. Zhang et al., 2014). Curcumin is biologically active in case of both animal and human (Gupta et al., 2012). It can be used as dietary supplement (Wilken et al., 2011), in skin and eye disorder (Gupta et al., 2012), as anti-inflammatory agent (R. A. Sharma et al., 2005), as coloring agent (Bisht et al., 2007), in Parkinson's and Alzheimer's disease (Mimeault & Batra, 2011), as antioxidant (Rath et al., 2013), as antimicrobials (Teiten, Gaascht, Eifes, Dicato, & Diederich, 2010) etc. Recently several experiments proved that curcumin has also anti cancer properties and may used in the treatment of various cancers such as, head and neck cancer (Wilken et al., 2011), ovarian cancer (Yallapu et al., 2010), pancreatic cancer (Bisht et al., 2010), prostate cancer (Qu et al., 2013), (Ying Wu, 2010), breast cancer (Cridge, Larsen, & Rosengren, 2013), (D. Liu & Chen, 2013), lung cancer (Ye, Li, Yin, & Zhang, 2012), (Rigas, 2013), brain tumor (K. J. Lim, Bisht, Bar, Maitra, & Eberhart, 2014). For example, it has been shown that while inducing apoptosis in medulloblastomas and malignant glioma cells curcumin helps to suppress the proliferation of brain tumor by arresting the G2/M phase and this apoptotic effect of curcumin can be enhanced by using piperine, an alkaloid from black pepper. Evidence have found that curcumin is useful to counteract prostate cancer cells by down regulating the circulation and activity of various oncogenic and survival indicating components such as EGFR, androgen receptor (AR), hedgehog. By up regulating various pro-apoptotic factors such as p53 tumor suppressor protein, Noxa curcumin can also cause DNA damage of prostate cancer cells. Down regulating different over expressed transcription factors such as Sp1, Sp2 and Sp3 and NF-kB gene transactivation curcumin helps to inhibit the proliferation of pancreatic cancer cells Panc28 and L3.6pL. It has been proved that a combination of curcumin with gemcitabine, a first line chemotherapeutic drug is more effective to treat pancreatic cancer. A combination of low doses of curcumin, COX-2 (cyclooxygenase) inhibitor, and other dietary agents such as resveratrol, isoflavone show synergistic apoptotic effect on prostate cancer which has also been experimented. It has also been

reported that development of colorectal cancer may prevented by administrating 0.6% of curcumin in the diet. Curcumin combined with resveratrol, pan-erbB inhibitor, Src inhibitor dasatinib, 5-fluorouracil and oxaaliplatin may also be used to treat colorectal cancer (Mimeault & Batra, 2011). Though free curcumin have diverse therapeutic effects, it has some crucial disadvantages such as poor water solubility, low bioavailability (Teiten, Eifes, Dicato, & Diederich, 2010), and instability (K. Wang et al., 2012). To overcome these limitations several approaches have been taken such as using combination of curcumin with other naturally derived compounds (Cridge et al., 2013), synthetic derivatives of curcumin (Teiten, Gaascht, et al., 2010), and formulation of curcumin nanoparticles (Vladimir N. Anisimov & Zabezhinski, 2012) by using liposomes, solid lipid nanoparticles etc (Bansal, Goel, Aqil, Vadhanam, & Gupta, 2011). Curcumin encapsulated by PLGA has shown enhanced cytotoxic effect on metastatic and prostate cancer cells. Conjugation of specific monoclonal antibody for ovarian cancer cells and PLGA formulated curcumin nananoparticle show enhanced activity to treat ovarian cancer. Conjugation of curcumin with poly-ß-cyclodextrin (PCD) has been shown more effective to treat prostate cancer rather than free curcumin. Curcumin encapsulated by polymeric micelle has shown greater bioavailability in the treatment of pancreatic cancer when it is combined with gemcitabine. Though curcumin nanoparticles have helped to overcome the drawbacks of free curcumin more studies and trials are needed to use it successfully (Mimeault & Batra, 2011).

Hybrid nanoparticles

These are nanoparticles consist of more than one nanoparticle and used to enhance the activity of a single nanoparticle, which is known as non-hybrid nanoparticle. In cancer therapy hybrid nanoparticles may used to overcome the limitations of single or multifunctional nanoparticles such as multidrug resistance which is a major barrier to treat cancer effectively (Carolina Salvador Morales, 2012). For example, bi-phospholipid with combrestatin encapsulated PLGA nanoparticle with doxorubicin developed by Sasisekharan and co-workers has shown more effectiveness to treat lung cancer (Alexis et al., 2010). Different types of nanoparticles are shown in figure 1.

Others

There are some other nanomaterials which can be used for effective cancer therapy such as nanobarcodes (A. Sharma et al., 2013), nanobodies (Alexis et al., 2008), nanoshells (Mousa & Bharali, 2011), nanowires (Choi et al., 2010), nanospheres (Juzenas et al., 2008), nanocapsules (Thakor & Gambhir, 2013) etc.

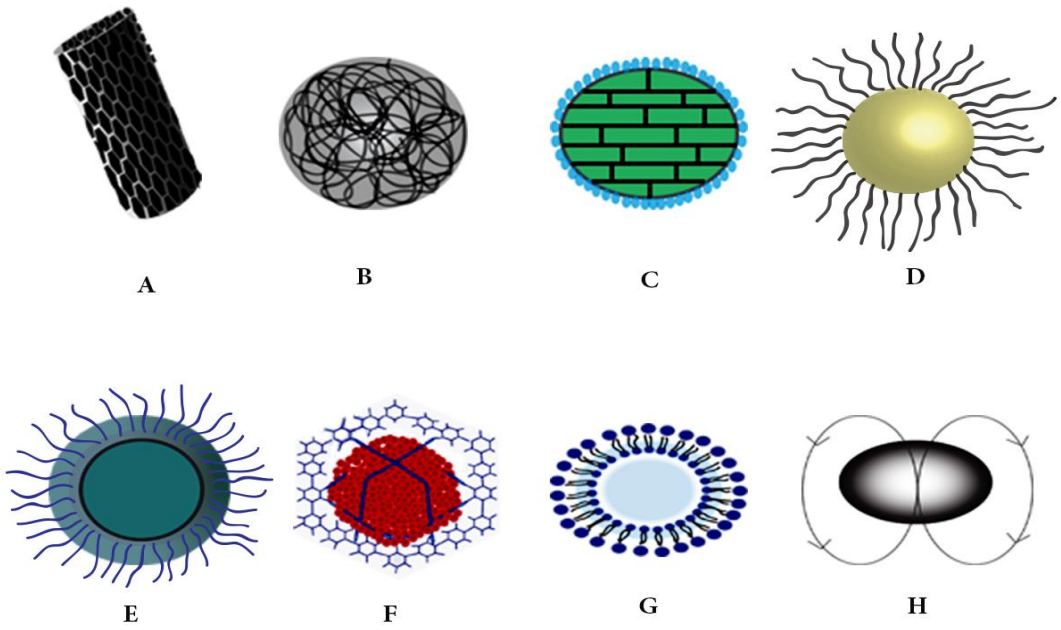

Figure 1: Different types of nanoparticles: (A) carbon nanotube (B) Polymeric (C) Solid Lipid (D) Gold (E) Nanoemulsion (F) Silica (G) Liposome (H) Magnetic nanoparticle

Hurdles

Though cancer nanotechnology is an ongoing developing sector by which cancer can be treated in a more convenient way by using nanoparticles, it has several drawbacks or challenges needed to overcome to be more effective. These include surface opsonization of nanoparticles (Nie, 2010), cellular uptake of nanoparticle (Mody, 2011), difficulties in solid tumor targeting (Li-Feng Qi, 2005), toxicity concern of nanoparticles (Nadine Schulte, 2014), etc.

Opsonization

When a foreign particle or organism is shielded by nonspecific protein and makes it visible to phagocytic cell the process is called opsonization. This helps to induce the phagocytosis process which then engulf the foreign particle (e.g. nanoparticles) from the bloodstream and stop the activity of the particle. To overcome this particle size reduction may helpful (Nie, 2010).

Cellular uptake

Liver, spleen, lungs and different parts of the reticuloendothelial system (RES), which is a part of immune system usually grab up the opsonized

nanoparticles and stop the activity of it. Surface modification of nanoparticles can solve this problem (Nie, 2010), (Liechty & Peppas, 2012).

Tumor targeting

Tumor can be targeted by both active and passive mechanism. There is an ongoing debate that tumor targeting ligands do effect the accumulation of nanoparticle in a solid tumor or not (Nie, 2010).

Toxicity concerns

In the form of reducing agent or stabilizing agent several toxic chemicals is used to produce different nanoparticles. For example, sodium borohydride and hydrazine are used in the production of gold and other metallic nanoparticles, which are toxic to both living organism and the environment (Sironmani, 2016). Nontoxic and biodegradable materials can be used to overcome this problem (X. Wang et al., 2009).

Conclusion

Nanotechnology especially nanoparticles has made a crucial impact on the treatment, diagnosis and prevention of cancer, which has been regarded as an untreatable disease. Using nanoparticles formulation of anticancer drugs are possible which are more effective and selective rather than conventional drug with numerous advantages. Though it provides several promising opportunities to deal with various types of cancer it can be harmful because of our limitation of knowledge. Their misuse or toxicity may cause disorders like inflammation or even cancer. To use its full potential more studies and experiments need to be done while reducing the side effects.

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