Available online on 25.06.2014 at http://jddtonline.info
Journal of Drug Delivery and Therapeutics
Open access to Pharmaceutical and Medical research

REVIEW ARTICLE

A REVIEW ON CURRENT ADVANCES IN NANOTECHNOLOGY APPROACHES FOR THE EFFECTIVE DELIVERY OF ANTI-CANCER DRUGS

Sharma Deepak[1]*, Kumar Dinesh[2], Singh Gurmeet[3], Singh Mankaran[4], Rathore Mahendra Singh[5]

[1]Rayat Bahra Institute of Pharmacy, Hoshiarpur-146001, Punjab, India

[2]CSIR Institute of Microbial Technology, Sector 39A, Chandigarh 160036, India

[3]PDM School of Pharmacy, Karsindhu, Safidon Tehsil, Jind District, Haryana-126112, India

[4]Quantum Solutions, Chandigarh 160036, India

[5]Maharishi Markandeshwar University, Mullana- Ambala, 133207, Haryana, India

ABSTRACT

Nanotechnology has achieved the status as one of the vital research endeavors of 21[st]century, which may be called as "Nano-Century" with nanotechnology making its presence felt in different spheres of lives. Nanotechnology may be defined as the creation of materials, drugs and devices that are used to manipulate matter of size in the range of 1-100nm. Nanotechnology has found its applications in many fields related to medicine including novel drug delivery systems. Many different types of nanosystems have been utilized in diagnostics and therapeutics of various diseases. To subside the disadvantages of conventional cancer therapeutics, nanotechnology has been given considerable attention. The purpose of this expert review is to discuss the impact of nanotechnology in the treatment of the cancer. These have been applied to improve drug delivery and to overcome some of the problems of drug delivery in cancer. Current nanotechnology platforms for cancer therapeutics encompass a vast array of nanomaterials and nanodevices. This review will focus on seven of the most prominent and most widely studied: polymeric nanoparticles, nanoshells, carbon nanotubes, dendrimers, quantum dots, superparamagnetic nanoparticles, and liposomes. All of these nanotechnology platforms can be multifunctional, so they are frequently touted as "smart" or "intelligent." It is concluded how nanotechnology can help solve one of the most challenging and longstanding problems in medicine, which is how to eliminate cancer without harming normal body tissue.

Keywords: Nanotechnology, Cancer, Drug targeting, Nanoparticles, Quantum dots, Nanotubes.

INTRODUCTION

Nanotechnology is considered to be an emerging, disruptive technology that will have significant impact in all industrial sectors and across-the-board applications in cancer research. There has been tremendous investment in this area and an explosion of research and development efforts in recent years, particularly in the area of cancer research [1].Cancer remains one of the world's most devastating diseases, with more than 10 million new cases every year. However, mortality has decreased in the past two years owing to better understanding of tumour biology and improved diagnostic devices and treatments. Current cancer treatments include surgical intervention, radiation and chemotherapeutic drugs, which often also kill healthy cells and cause toxicity to the patient [2].

Breast cancer, colorectal cancer, lung cancer, liver cancer and stomach cancer are some of the major types of cancer existing today. Deaths from cancer are continuously rising worldwide with a projection of about 12 million deaths from cancer in 2030. Thereby, over the past few years, tremendous attention has been given to the cancer related research and developments. There has been an outstanding progress in the basic cancer biology. Many institutions, pharmaceutical and biotechnological industries have focused on cancer as their main target in their research and development departments[3]. The chemotherapeutic treatment of cancer has undergone revolution in the past 5-10 years with a variety of new drugs and regimens being either approved or under investigations. In the area of targeted delivery, the colonic region of GI tract is the one that has been embraced by scientists and is being extensively investigated over the past 2 decades. Targeting of drugs to specific sites of action provides several advantages over non-targeted drugs. A drugs needs to be protected from degradation, release and or absorption in the upper portion of GI tract and then to ensure abrupt or controlled release in the proximal colon while targeting drugs to colon [4].

**** Correspondence Address:***
Deepak Sharma
Assistant Professor,
Rayat Bahra Institute of Pharmacy, Hoshiarpur.
Street no 8, Mansa Devi Nagar,
Phagwara, District Kapurthala, Pin code: 144402
Email: deepakpharmacist89@yahoo.com
Mobile: 09988907446

Many developed innovative nanotechnology platforms, such as polymeric nanoparticles, liposomes, dendrimers, nanoshells, carbon nanotubes, quantum dots, nanowires, cantilevers, superparamagnetic nanoparticles, have been applied to the effective delivery of specific anticancer drugs , including small molecular weight drugs and macro molecules (protein, peptides or genes) [5]. Nanotechnology is defined as the study and use of structures between 1 nanometer and 100 nanometers in size. Nanotechnology is the combined effect of material sciences, microelectronics, mechanical, electrical, chemical engineering, and biological screening. Nanotechnologies are the design, production, characterization, and application of structures, devices and systems by controlling size and shape at nanometer scale. In modern scenario nanotechnology is used to provide more accurate and timely medical information for diagnosing disease, and miniature devices that can administer treatment automatically if required. It is used worldwide in the treatment of Cancer like precarious diseases. This article overviewed current nanotechnologies for cancer therapy, focusing on the wide variety of nano-technological platforms for anticancer drug delivery [6].

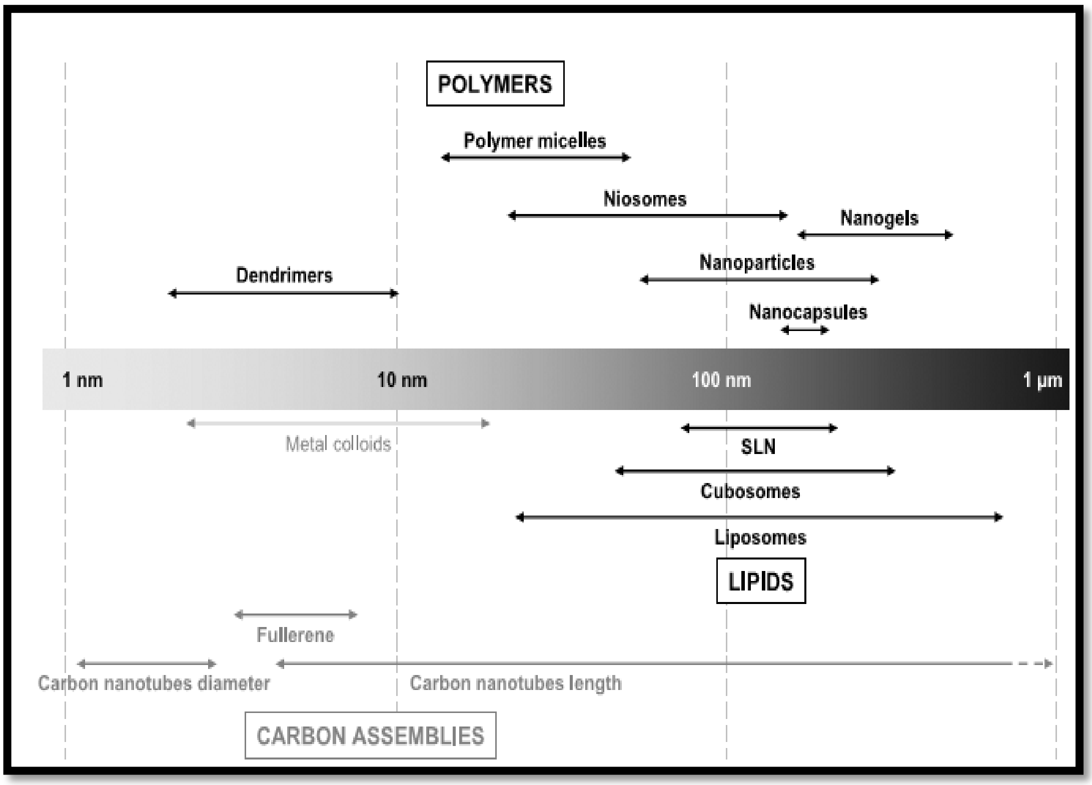

Figure 1: Types of nanotechnology used for drug delivery and targeting

NANO-TECHNOLOGICAL APPROACHES FOR TUMOUR TARGETING

a. Polymeric Nanoparticles

Generally, polymers that are used for preparation of nanoparticles fall into two major categories: natural polymers and synthetic polymers. A number of natural polymers such as heparin, dextran, albumin, gelatine, alginate, collagen, and chitosan have been intensively investigated. Synthetic polymers including polyethylene glycol (PEG), polyglutamic acid (PGA), polylactic acid (PLA), polycaprolactone (PCL) and N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA) have been exploited as well. General requirements for those polymers are biocompatibility, biodegradability, and their capacity to be functionalized [7]. The polymeric nanoparticle consists of two parts, a hydrophobic core which serves as the container for anticancer agents and a hydrophilic shell which stabilizes the nanoparticle in aqueous environments. The drug can be loaded into polymeric nanoparticles through two methods: by physical entrapment or by chemical conjugation. A hydrophobic interaction between the core of the polymeric nanoparticle and the drug molecule allow the drug to be entrapped in the nanoparticle core [8, 9].

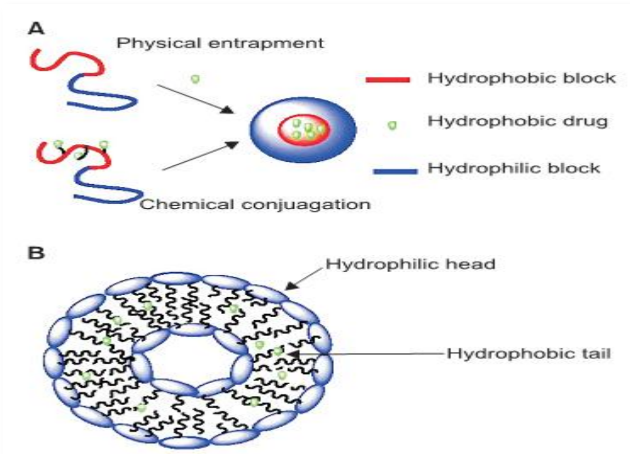

Figure 2: Polymeric Nanoparticles

b. Liposomes

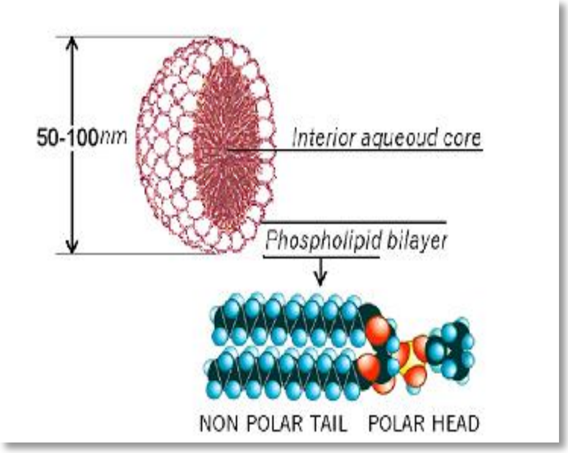

Figure 3: Liposomes

Liposomes are the simplest forms of nanovectors which are made up of lipids enclosing water core. They have found applications in various cancer indications [10]. With the aid of over expression of fenestrations in cancer neovasculature, they increase the drug concentration at the tumor sites (passive targeting). In passive targeting, the drug is targeted to the target site passively owing to the physiological conditions of the body. Various Doxorubin encapsulated liposomal formulations have been clinically utilized for the treatment of Kaposi's sarcoma, breast cancer and refractory ovarian cancer [11]. They were developed to improve therapeutic index of the conventional Doxorubin chemotherapy while maintaining its antitumor activity. Similarly, S. Kommareddy et al have shown effective utilization of gelatin based nanovectors in tumors. Here, PEG modified gelatin based nanovectors were used as safe and effective vehicle for the delivery of systemically administered genes for tumors. Ruthenium and complexes of several other heavy metals have shown potential applications in cancer therapeutics. Lipid based nanovectors containing such complexes have also been put forth as a potential route in cancer [12].

c. Dendrimers

Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous and monodisperse structure consisting of tree-like arms or branches. With the size ranging from 1 to 10 nm, dendrimers with different chemical structures and functional groups can be synthesized. Through a series of repeating chemical synthesis on the core, the size and shape of dendrimers are determined by the generation. The key useful character of dendrimers is the branches which can provide vast amounts of surface area for drugs and targeting molecules. Meanwhile, the surface functionalities, interior branching, and chemical composition of the core play a significant role in reactivating the macromolecule Dendrimer is one of the most elegant nanotechnology platform s for targeted drug delivery. Conjugated with biotin as the targeting moiety, the in vitro targeting ability of partially acetylated generation 5 polyamidoamine (PAMAM) dendrimer (Ac-G5) in HeLa cells was assessed. The multi-functional conjugate Ac-G5-biotin-FITC (fluorescein isothiocyanate) showed much higher cellular uptake than the conjugate without biotin. The energy dependent uptake process can be blocked effectively by biotin polymer conjugates, exhibiting an expected dose response curve [13, 14].

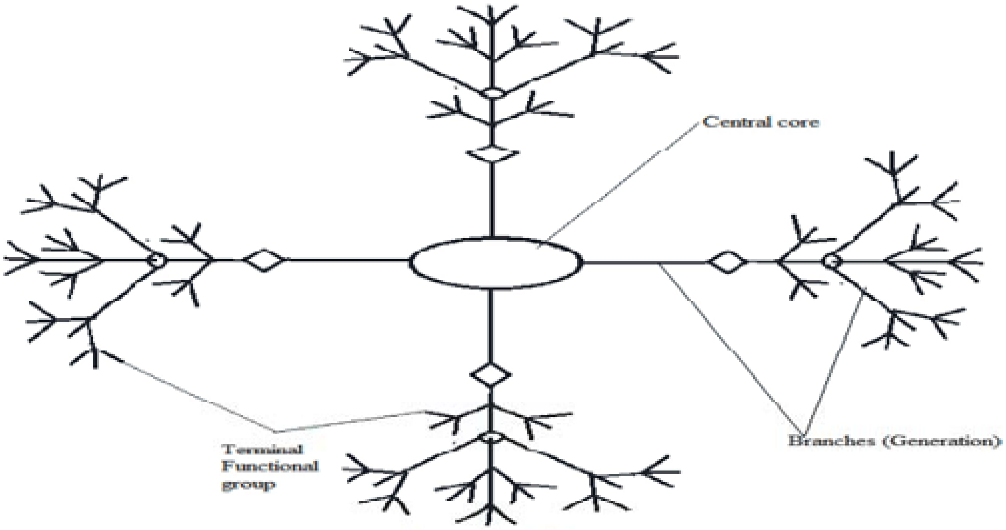

Figure 4: Structure of Dendrimers

d. Nanoshells

These are another recent invention. NS are miniscule beads coated with gold. By manipulating the thickness of the layers making up the NS, the beads can be designed that absorb specific wavelength of light. The most useful nanoshells are those that absorb near infrared light that can easily penetrate several centimeters in human tissues. Absorption of light by nanoshells creates an intense heat that is lethal to cells. Nanoshells can be linked to antibodies that recognize cancer cells. In laboratory cultures, the heat generated by the light-absorbing nanoshells has successfully killed tumor cells while leaving neighbouring cells intact [15].

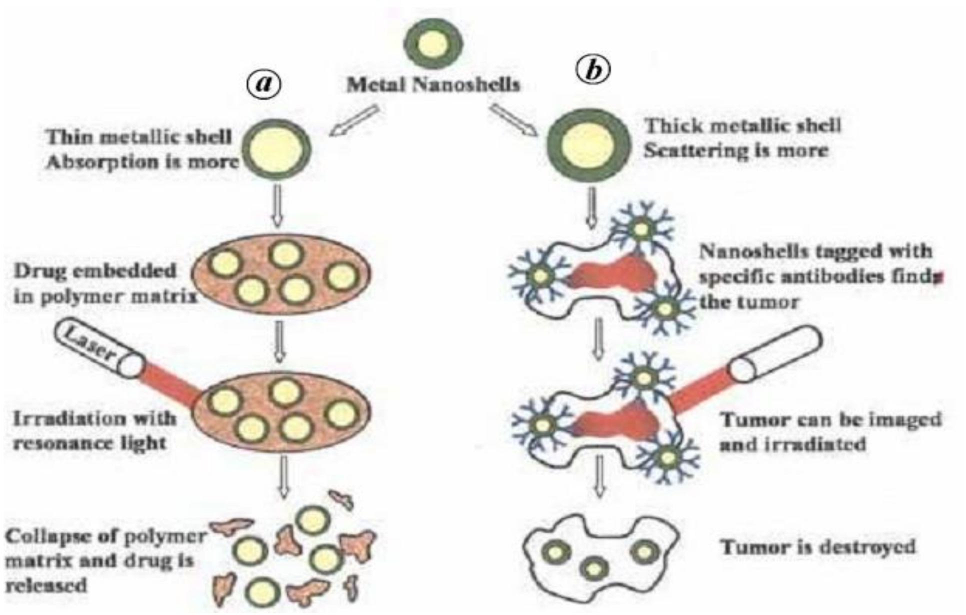

Figure 5: Drug delivery system based on Nanoshells

e. Carbon Nanotubes

Carbon nanotubes are cylinders of one several coaxial graphite layers with a diameter in the order of nanometers, and they serve as instructive examples of the Janus-like properties of nanomaterials [16]. They can be classified into two general categories based on their structure: single-walled carbon nanotubes (SWCNTs) with a single cylindrical carbon wall and multiwalled carbon nanotubes (MWCNTs) with multiple walls-cylinders nested within other cylinders [17]. Due to their unique electronic, thermal, and structural characteristics, they can offer a promising approach for gene and drug delivery for cancer therapy [18]. Heating of organs and tissues by placing multifunctional nanomaterials at tumor sites is emerging as an art of tumor treatment by "Nano thermal Therapy". Carbon nanotubes have become candidates to kill cancer cells via local hyperthermia, due to their thermal conductivity and optical properties [19].

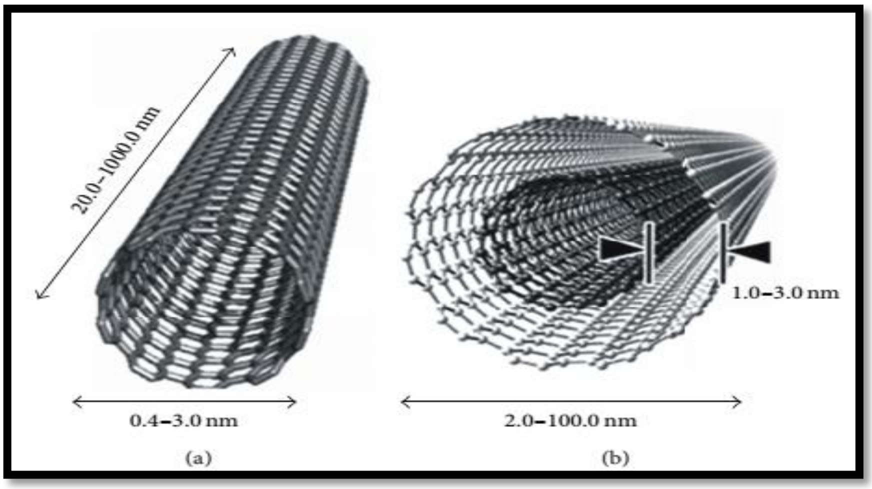

Figure 6: Carbon Nanotubes (a) single walled carbon nanotube and (b) multiwalled carbon nanotube

f. Quantum Dots

Over the past few decades quantum dots (QDs) have been an area of intense research due to their unique physical properties that can be exploited for cancerous tumor detection. QDs usually consist of an inorganic transition metal core/shell system, and the majority of QDs are made up of cadmium selenide (CdSe), cadmium telluride (CdTe), Indium phosphide (InP), and indium arsenide (InAs) as core elements inside a shell, usually zinc sulfide (ZnS). The major reasons that these inorganic-organic composite nanoparticles are extremely efficient agents for cancer detection in vivo are their small size, which gives them unhindered access to the systemic circulation, and at the same time their ability to conjugate targeting molecules that direct specific accumulation in neoplastic sites [20, 21]. Additionally, similar to other nanoparticles, QDs have sufficient surface area to attach therapeutic agents and tumor specific moieties for simultaneous drug delivery and in-vivo imaging and tissue engineering [22].Depending on size and the core/shell system, QDs have the ability to emit light across the visible and infrared wavelength spectrum, and thus one can choose a suitable color of light emission. The main advantage of the QDs is that with a single light source, the variously-sized QDs can be excited while preserving the narrow emission of each individual particle/wavelength[23]. Additionally, QDs have the ability to incorporate different markers simultaneously (multiplexing), enabling numerous targets to be imaged in a single experiment [24].

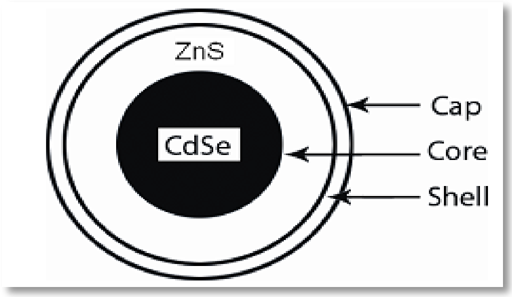

Figure 7: Schematic representation of Quantum Dots

g. Nanowires

A nanowire is a nanostructure, with the diameter of the order of a nanometer (10^{-9}meters). Alternatively, nanowires can be defined as structures that have a thickness or diameter constrained to tens of nanometers or less and an unconstrained length. At these scales, quantum mechanical effects are important which coined the term "quantum wires". Many different types of nanowires exist, including metallic (e.g., Ni, Pt, Au), semiconducting (e.g., Si, InP, GaN, etc.), and insulating (e.g., SiO2, TiO2). Molecular nanowires are composed of repeating molecular units either organic (e.g. DNA) or inorganic. The nanowires could be used, in the near future, to link tiny components into extremely small circuits. Using nanotechnology, such components could be created out of chemical compounds [25].

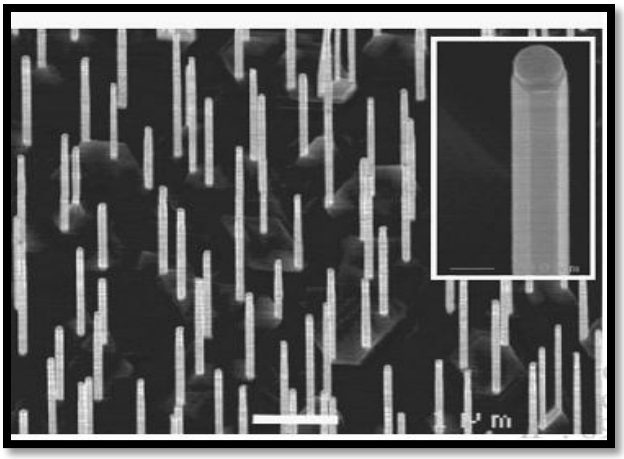

Figure 8: SEM of Nanowires

h. Nano-Cantilevers

Tiny bars anchored at one end can be engineered to bind to molecules associated with cancer. These molecules may bind to altered DNA proteins that are present in certain types of cancer. This will change the surface tension and cause the cantilevers to bend. By monitoring the bending of cantilevers, it would be possible to tell whether the cancer molecules are present and hence detect early molecular events in the development of cancer [15].

i. Superparamagnetic nanoparticles

Superparamagnetic nanoparticles refer to iron oxide particles or magnetite (Fe_3O_4) particles that are less than10 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 nanoparticles to targeted sites, a system known as magnetic drug targeting. Iron oxide nanoparticles can be water-solubilized with hydrophilic polymer coatings, such as dextran or PEG. In fact, attaching PEG to nanoparticles in general, not just to iron oxide particles, is a well documented means of sterically preventing opsonization of nanoparticles in the serum and reducing their uptake by the reticuloendothelial system. This effectively enhances biocompatibility and increases the circulation time of nanoparticles [26]. Iron oxide nanoparticles can also be made hydrophobic by coating with aliphatic surfactants or liposomes (resulting in magnetoliposomes) [27]. Magnetic nanoparticles can be remotely activated using electromagnetic fields, and they can also be used to thermally treat cancers [28]. Most recently, superparamagnetic nanoparticles have been used in clinical thermotherapy of locally recurrent prostate cancer. Thermotherapy is defined as the abilityto attain at least hyperthermic temperatures of up to 428 ºC, which can render cancer cells more susceptible to the effects of radiation and cause some apoptosis[29].

ACKNOWLEDGMENTS

The authors thankful to library department of Rayat Bahra Institute of Pharmacy, for providing literature facilities for preparation of this Review article.

CONFLICT OF INTERESTS

The authors declare that they do not have any financial and personal relationships with other people or any other organizations that could inappropriately influence this work.

CONCLUSION

The introduction of nanotechnology in pharmaceutical sciences has revolutionized the delivery of drugs, allowing the emergence of new treatments with an improved specificity. Nanotechnology is now widely implanted in the move of revisiting drug delivery methods. These new nanosystems can be tailor-made according to the desired functions and duty thanks to parallel progresses in the synthesis of colloidal systems with perfectly controlled characteristics. Nanotechnology is definitely a medical boon for diagnosis, treatment and prevention of cancer disease. It will radically change the way we diagnose, treat and prevent cancer to help meet the goal of eliminating suffering and death from cancer. The use of nanotechnology has introduced greater flexibility in the paradigm of cancer therapeutics and diagnostics by not only improving the efficacy, safety and tumour-targeting but by also aiding in the reduction of the adverse effects, invasiveness and risks associated with conventional drug therapy. The integration of nanotechnology into cancer diagnostics and therapeutics is a rapidly advancing field, and there is a need for wide understanding of these emerging concepts. The present paper reviews the use of nanotechnology as strategies to deliver existing chemotherapies and novel therapeutic molecules in a controlled manner to malignancies. Developments in such areas as polymeric nanoparticles, nanoshells, carbon nanotubes, dendrimers, quantum dots, superparamagnetic nanoparticles, and liposomes are making early detection, prevention and treatment with a high degree of accuracy and ease possible. Also other recent discoveries and inventions in nanotechnology are suggesting that a safe and effective cure for cancer is just around the corner.

REFERENCES

1. Kelly Y, Kim MA, Nanotechnology platforms and physiological challenges for cancer therapeutics, Nanomedicine, 2007, 3(2), 103-110.
2. Dan P, Jeffrey MP, Seungpyo H, Omid CF, Rimona M, Robert L., Nanocarriers as an emerging platform for cancer therapy. Nature Nanotechnology, 2007, 2, 751-760.
3. Mody HR, Cancer Nanotechnology: Recent Trends and Developments, Internet Journal of Medical Update, 2011, 6(1), 3-7.
4. Manikandan M, Kannan K, Manavalan R, Sundresh NJ, Design of nanoparticles for colon target drug delivery- A Review, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2011, 2(4), 128-139.
5. Tang MF, Lei L, Guo SR, Huang WL, Recent progress in nanotechnology for cancer therapy, Chinese Journal of Cancer, 2010, 29(9), 775-780.
6. Raval AG, Bharadia PD, Modi D, Pandya V, Nanotechnology: A targeted drug delivery system for cancer therapy, IJPI's Journal of Pharmaceutics and Cosmetology, 2011, 1(5), 67-75.
7. Tong R, Cheng J, Anticancer polymeric nanomedicines, Polymer Reviews, 2007, 47, 345-381.
8. Cho K, Wang X, Nie S, Chen ZG, Shin DM, Therapeutic nanoparticles for drug delivery in cancer, Clinical Cancer Research, 2008, 14(5), 1310-1316.
9. Zhang G, Niu A, Peng S, Jiang M, Tu Y, Li M, Wu C, Formation of novel polymeric nanoparticles, Accounts of Chemical Research, 2001, 34, 249-256.
10. Park JW, Liposome-based drug delivery in breast cancer treatment, Breast Cancer Research, 2002, 4(3), 95-99.
11. Paolo DA, Liposomal anticancer therapy: pharmacokinetic and clinical aspects, Journal of Chemotherapy, 2004, 16(4), 90-93.
12. Vaccaro M, Litto RD, Mangiapia G, Carnerup AM, D'Errico G, Ruffo F, Paduano L, Lipid based nanovectors containing ruthenium complexes: a potential route in cancer therapy, Chemical Communications, 2009, 11, 1404-1406.
13. Sampathkumar SG, Yarema KJ, Dendrimers in cancer treatment and diagnosis, Nanotechnologies for the Life Sciences, 2007, 7, 1-43.
14. Mousa SA, Bharali DJ, Nanotechnology-Based Detection and Targeted Therapy in Cancer: Nano-Bio Paradigms and Applications, Cancers, 2011, 3(3), 2888-2903.
15. Singh OP, Nehru RM, Nanotechnology and Cancer Treatment, Asian Journal of Experimental Sciences, 2008, 22(2), 45-50.
16. Shvedova A, Kisin ER, Porter D, Schulte P, Kagan VE, Fadeel B, Castranova V, Mechanisms of pulmonary toxicity and medical applications of carbon nanotubes: Two faces of Janus? Pharmacology and Therapeutics, 2009, 121(2), 192-204.
17. Lacerda L, Bianco A, Prato M, Kostarelos K, Carbon nanotubes as nanomedicines: from toxicology to pharmacology, Advanced Drug Delivery Reviews, 2006, 58(4), 1460-1470.
18. Tanaka T, Shiramoto S, Miyashita M, Fujishima Y, Kaneo Y, Tumor targeting based on the effect of enhanced permeability and retention (EPR) and the mechanism of receptor-mediated endocytosis (RME), International Journal of Pharmaceutics, 2004, 277(1-2), 39-61.
19. Sharma R, Chen CJ, Newer nanoparticles in hyperthermia treatment and thermometry, Journal of Nanoparticle Research, 2009, 11(3), 671–689.
20. Bharali DJ, Lucey DW, Jayakumar H, Pudavar HE, Prasad PN, Folate-receptor-mediated delivery of InP quantum dots for bioimaging using confocal and two-photon microscopy, Journal of the American Chemical Society, 2005, 127(32), 11364-11371.
21. Michalet X, Pinaud FF, Bentolila LA, Tsay JM, Doose S, Li JJ, Sundaresan G, Wu AM, Gambhir SS, Weiss S, Quantum dots for live cells, in vivo imaging, and diagnostics, Science, 2005, 307(5709), 538-544.
22. Howarth M, Takao K, Hayashi Y, Ting AY, Targeting quantum dots to surface proteins in living cells with biotin ligase, Proceedings of the National Academy of Sciences, 2005, 102(21), 7583-7588.
23. Smith AM, Dave S, Nie S, True L, Gao X, Multicolor quantum dots for molecular diagnostics of cancer, Expert Review of Molecular Diagnostics, 2006, 6(2), 231-244.
24. Stroh M, Zimmer JP, Duda DG, Levchenko TS, Cohen KS, Brown EB, Scadden DT, Torchilin VP, Bawendi MG, Fukumura D, Jain RK, Quantum dots spectrally distinguish multiple species within the tumor milieu in vivo. Nature Medicine, 2005, 11(6), 678-682.
25. Sivasankar M, Kuma BP, Role of nanoparticles in drug delivery system, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2010, 1(2), 41-66.
26. Harris JM, Martin NE, Modi M, Pegylation: a novel process for modifying pharmacokinetics, Clinical Pharmcokinetics, 2001, 40(7), 539-551.
27. Kubo T, Sugita T, Shimose S, Nitta Y, Ikuta Y, Murakami T, Targeted delivery of anticancer drugs with intravenously administered magnetic liposomes in osteosarcoma-bearing hamsters, International Journal of Oncology, 2000, 17(2): 309 - 315.
28. Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, Schlag PM, Hyperthermia in combined treatment of cancer. Lancet Oncology, 2002, 3(8), 487-497.
29. Johannsen M, Gneveckow U, Thiesen B, Taymoorian K, Cho CH, Waldofner N, Scholz R, Jordan A, Loening SA, Wust P, Thermotherapy of prostate cancer using magnetic nanoparticles: feasibility, imaging, and three-dimensional temperature distribution, European Urology, 2007, 52(6), 1653-1661.