

Review Paper:

Development of nano drugs: A promising avenue for cancer treatment

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Abstract

Cancer is one of the leading causes of death in the United States and cancer prevalence is increasing in developing countries. Chemotherapy, radiation and surgery represent the most common cancer treatment. Conventional chemotherapy has some severe side effects including damage to the immune system, other frequently proliferating cell organs due to non-specific targeting, lack of solubility, failure to reach the center of the tumors and poor survival treatment. Nanoparticulate technology is useful in developing a new generation of cancer therapies that are more effective in overcoming many biological obstacles due to their specific physicochemical properties such as ultra-small size, wide area to mass ratio and high reactivity. Nanotechnology is the control of matter within the 1–100 nm range. Most of the nanoparticles are carbon, metal, polymeric, ceramic and lipid-based nanoparticles.

Therapeutic nanoparticles have been found as a revolutionary and successful alternative to traditional small molecule chemotherapy, which shows increased therapeutic potency and diminishing side effect. It can be designed to identify cancer cells and provide selective and sustainable delivery of drugs to prevent contact with healthy cells. This review focuses on specific drug delivery potential of various nanoparticles and the side effects of conventional therapies with tailored cancer treatment.

Keywords: Cancer therapy, Nano carrier, Target drug delivery.

Introduction

Cancer is one of today's world most serious fatal diseases, killing millions of people each year. It is one of the 21st century's major health concerns, which has no boundaries and can affect any human organ from anywhere. It is a very complex disease to understand because it has many cellular physiological systems such as cell signalling and apoptosis^{5,25}. The most common cancer treatments are chemotherapy, hormone therapy, radiation and surgery. Chemotherapy, the most popular treatment provides patients with systemic anti-cancer drugs to manage uncontrolled cancer cell proliferation²⁷.

In recent times a variety of chemotherapy approaches are being practiced to treat cancer which has some significant limitations and side effect⁷⁰ such as nonspecific standardized distribution, insufficient drug concentrations reaching the tumour and ineffective recovering responses, Poor drug delivery and residency at the target site result in significant complications such as multi-drug resistance¹⁵.

The main challenge of cancer treatment is to distinguish between cancer cells and normal body cells. That is why the ultimate goal becomes to engineer the drug in such a way that it can identify the cancer cells to reduce their growth and proliferation. Many medical researchers have turned their attention to nanotechnology to find a more effective approach to drug delivery in cancer.

Nanotechnology has the potential to provide solutions to these present obstacles because of its unique size (1-100 nm) and large surface size ratios³⁶. The nanoparticles used in the delivery system for anticancer drugs can be prepared for a variety of materials including polymers, dendrimers, liposomes, viruses, carbon nanotubes and metals such as gold, silver and iron oxide¹⁸ (Table 1) which represent new directions for cancer diagnosis and treatment as successful as possible⁵.

Interestingly, nanocarrier systems are designed to communicate with target cells and tissues, or to respond well-controlled to desired physiological stimulus responses. Nanomaterials have the potential to deliver drugs directly to cancerous tissues, eliminating systemic toxicity and to open up entirely new modalities of cancer therapies such as photodynamic and hyperthermia treatments.

The nanocarriers have been increasingly focused on their ability to incorporate multiple therapeutic agents and synchronize their delivery to diseased cells. The drug-loaded nanocarriers have extended lifetime of systemic circulation, continuous drug release kinetics and improved tumor accumulations through both passive and active mechanisms⁶⁰.

In addition, they have the potential to increase the therapeutic index of drugs generally available by increasing drug effectiveness, reducing drug toxicity and achieving long-term stable therapeutic levels of drugs. Nanocarriers will also boost drug solubility and drug stability, enabling the production of potentially effective new chemical agents that were installed due to problematic pharmacokinetic or

biochemical properties during the preclinical or clinical growth.

Finally, nanocarriers will help to develop multifunctional systems for targeted drug delivery, integrated therapies or spontaneous applications for therapy and diagnosis. Recently marketed nanotechnology formulations include Daxil (Liposomal Doxorubicin) and Abraxane (Albumin bound paclitaxel). In this review we will focus on the development of smart drug delivery vehicle for cancer therapeutic applications that distinguish them from previous cancer therapy.

Drawbacks of conventional chemotherapy:

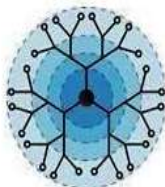
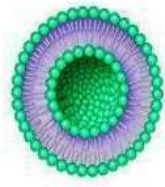
Chemotherapy is a therapy that uses hydrophobic chemical agents, whether plant or synthetic and includes solvents to formulate the dosage type that leads to extreme toxicity¹². It effectively damages fast-growing cells and prevents mitosis by blocking the cellular machinery involved in DNA synthesis and cell cycle arrest, which induces apoptosis in a programmed cell death. However, conventional chemotherapy meets some limitations. The main drawback

of conventional chemotherapy is that it does not provide selective action to cancer cells alone (Figure 1 shown the action of chemotherapy). It also destroys healthy normal cells including bone marrow, macrophages, digestive tract and hair follicles⁷⁰.

Properties of nanotechnology: Nanoparticles have unique physical properties (size, charge, bioaccumulation, solubility) that can be manipulated to increase the half-life of the circulation, resulting in increased particles and their associated drug inventory at the tumor site¹⁹. Nanotechnology for cancer imaging, molecular diagnosis and targeted therapy is under intense development⁶².

Under current development, pharmaceutical formulations based on nanotechnology aim to increase the therapeutic index for proven chemotherapeutic drugs by selectively delivering them to the cancer tissue¹⁸. Some beneficial advantages of nanoparticles were providing location-specific delivery of drugs, increase drug localization and cellular uptake, cancer diagnosis, reducing the volume of drugs that can decrease accumulation in healthy tissues.

Table 1
Types of Nanocarriers

Dendrimers	
Polymeric	
Liposome	
Gold	

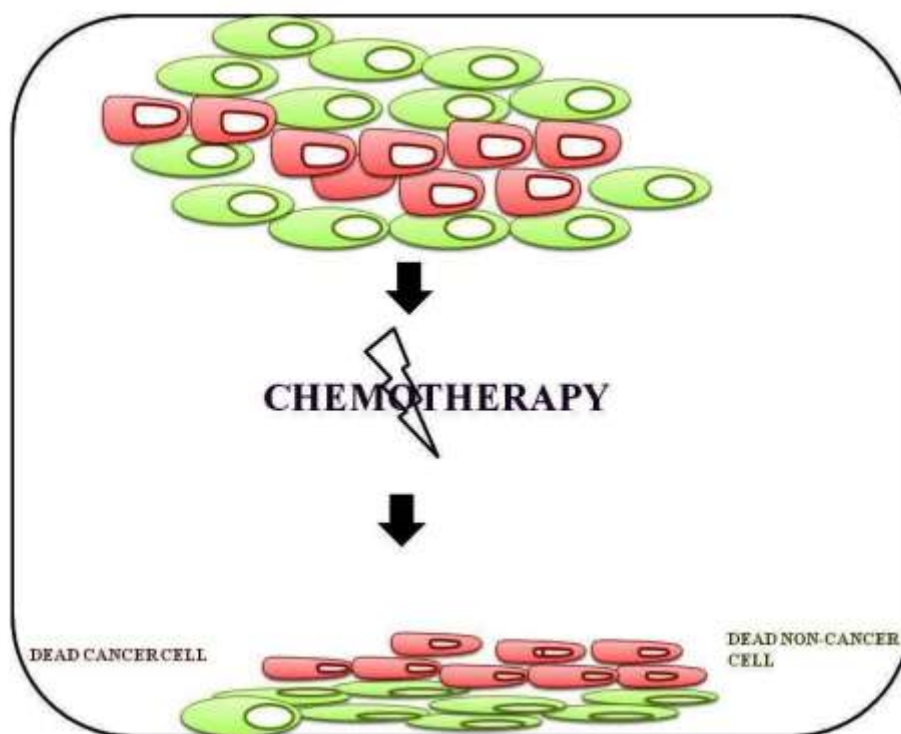


Figure 1: Action of conventional chemotherapy

Drug solubility: Since most drugs tend to be hydrophobic, they are poorly dispersed in aqueous based biological solutions. As a result, some of the drugs are not absorbed to the vascular system, which means that some of the drugs hadn't arrived at the target cells/tissue. Nanotherapies are highly minimized as the surface of the nanoparticle can be modified in a manner that enhances solubility by adding hydrophilic groups. This helps improve treatment.

Specificity: Nanotherapy enhances specificity of drug delivery by increasing the concentration of the drug compound at the target site while reducing damage to healthy cells/tissues.

Enhanced permeability and retention effect: Nanoparticles of a suitable size can escape tumor blood vessels with undeveloped, leaky endothelium due to the enhanced permeability and retention effect (EPR) and can be maintained in tumor tissue for days and weeks due to lack of lymphatic drainages. Furthermore, vasodilators have been reported to act as nitric oxide (NO), prostaglandins and bradykinin, enhancing the impact of EPR on the tumor by raising its vascular permeability.

Nanomedicine in cancer: Nanomedicine is an important part of nanotechnology, a highly specific molecular-scale clinical intervention for the detection, prevention and treatment of diseases and the use of materials ranging from 1 to 100 nm. Current problems in cancer treatment include poor specificity, rapid clearance of drugs and biodegradability and restricted targeting⁴⁵. The nanomedicine is a new form of cancer treatment as nanotherapeutics are increasingly evolving fields that are

used to overcome many shortcomings of the traditional drug delivery system, such as non-specific biodistribution, lack of targeting, lack of water solubility, weak oral bioavailability and low therapeutic indices^{56,63}.

Over the past three decades, extensive research has focused on developing cancer nanomedicines, which can overcome biological barriers and effectively transport chemotherapeutic agents to target sites, while reducing harmful effects on healthy tissues. The potential of nanomedicines can be expanded further into joint therapies that can detect tumors early, treat tumors earlier and more effectively.

Currently, a wide variety of sites are being explored as nanocarriers for cancer therapy including lipid-based, polymer-based, inorganic, viral and drug-integrated nanoparticles⁶³. The exponential development of new nanotechnology systems for use in the life science is that practical use of nanotechnology in medicine extends beyond these early applications substantially. National Cancer Institute(<http://nano.cancer.gov>) has identified the path of opportunities through six fields including: (1) Identification of the molecular modifications responsible for pathogenesis of diseases; (2) disease diagnosis and imaging; (3) drug delivery and therapy; (4) multifunctional systems for combined therapeutic and diagnostic applications; (5) vehicles to report the *in vivo* efficacy of a therapeutic agent; and (6) nanoscale enabling technologies, which will accelerate scientific discovery and basic research.

There are some important aspects to having a good nanomedicine not only for medicine but also for technology

transfer purposes; 1) Knowing the key elements and understanding their interactions; 2) Identify key characteristics and their relevance to performance; 3) Breeding under industrial production; 4) Effectiveness of sterile production; 5) Ability to target and / or accumulate cancer tissue within a reasonable time after overcoming appropriate pharmacology and biological barriers; 6) Stability, storage and acceptable properties of administration^{23,35}.

Polymers for developing drug carriers based on nanoparticles are commonly investigated materials¹³. Recently, the Food and Drug Administration (FDA) approved the albumin-paclitaxel (ToxoLDM) nanoparticle drug AbraxanetM for the treatment of breast cancer¹⁴.

Targeted drug delivery: Nanotechnology has made a big breakthrough in targeted cancer treatment. NPs can be designed to target neoplastic cells through various modifications, such as changing their size, shape, chemical and physical properties. Generally, anticancer drugs can be successful in treating cancer, so that they can reach the target tumor.

Second, the drug should have a selective effect on tumor cells after entering the tumor tissue without harming normal cells with a controlled release mechanism of the active form. Such two basic approaches are related to changes in patient safety and quality of life by increasing the doses of intravenous drugs and reducing toxicity that restricts the

dosage. In theory, passive or active target nanoparticles reach the delivery of anticancer drugs to the tumor tissue.

Under current development, most nanotechnology-based pharmaceutical formulations aim to increase the therapeutic index for chemotherapeutic drugs established through selective delivery to cancer tissue⁷ (Figure 2 shows action of nano particles). The advantage of nanocarriers is delivery in the aquatic phase, which avoids the use of solvent agents. One major milestone in the engineering of drug delivery systems was the development of technologies that can mask the immune system's nano delivery carriers.

Another new approach to specifically targeting tumor cells without collateral damage is the polymer-driven enzyme prodrug therapy, which uses a combination of a polymeric prodrug and polymer-enzyme conjugate to rapidly and selectively produce a cytotoxic drug within the tumors²⁰. Nanoparticles can be used to provide traditional chemotherapy without toxic agents for cancer cells and can be treated with anticancer treatment for conditions that occur over time¹⁷.

Active targeting: Active targeting was carried out to achieve a high degree of selectivity for different tissues and to increase the absorption of nanoparticles in target areas such as cancer cells and angiogenic microcapillaries developing around malignant cells. Nanoparticles are modified to target inherent features of cancer cells such as rapid proliferation and particular presentation of antigens. There are several ways to accomplish the active targeting.

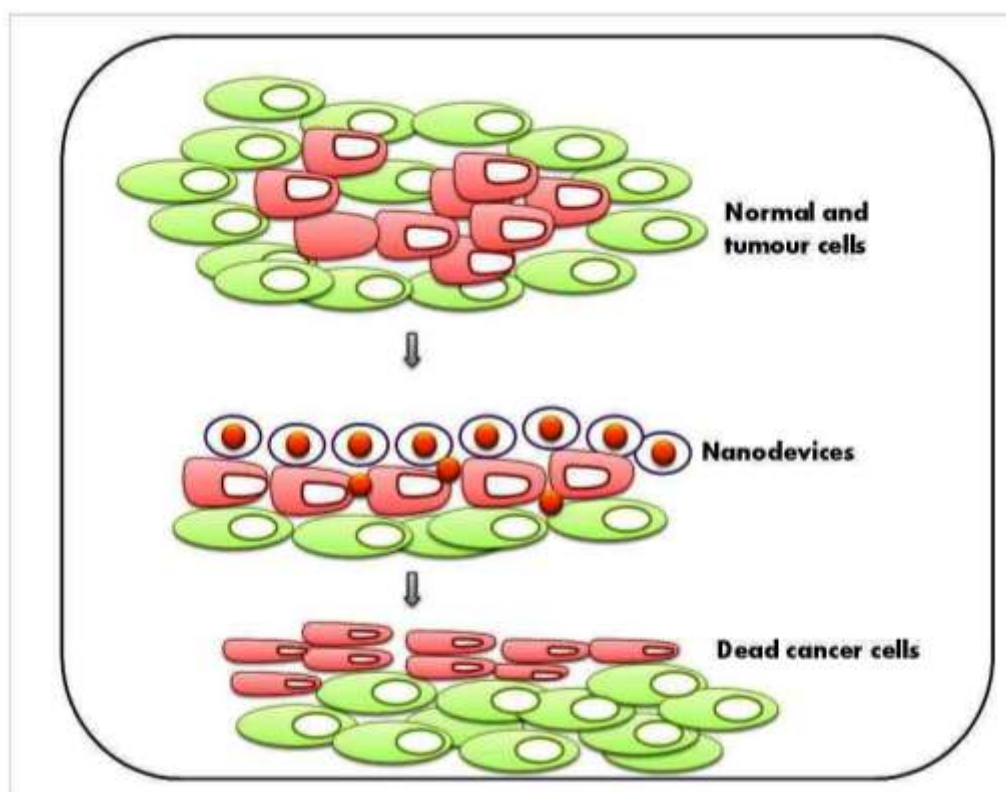


Figure 2: Action of targeted drug delivery

One means of actively targeting the body's exclusively diseased tissue is to know the nature of a receptor on the cell for which the drug is intended. Researchers can use cell-specific binding sites to directly bind the nanoparticle to the cell that has the complementary receptor. This method of active targeting was found to be effective when using transferrin as the cell-specific ligand. The transferrin was combined with the nanoparticles to target tumor cells with the transferrin-receptor controlling endocytosis pathways on their membrane. Compared to non-conjugated nanoparticles, this targeted means was found to increase the absorption²².

Passive targeting: Nanoparticulate delivery systems may exploit a characteristic of solid tumors such as accelerated permeability and retention (EPR) effect in which tumor tissues exhibit many distinctive features along with hypervascularity, defective vascular architecture and inadequate lymphatic drainage that contributes to preferential accumulation of macromolecules and particulates and to longer survival in tumors. There are now many nanocarrier-based medications available that rely on passive delivery through a process called "enhanced permeability and retention" due to their broad and surface effects⁶⁶. Tumors often appear to have leaky blood vessels and poor lymphatic drainage, resulting in nanoparticles building up in them, concentrating the attached cytotoxic drug where it is required, protecting healthy tissue and significantly reducing adverse side effects³¹.

Another passive targeting strategy consists of using myeloid cells such as macrophages, which absorb NPs and focus them on the site to be treated. These two challenges also can increase the efficiency of a chemotherapeutic drug resulting in greater reduction of tumors with lower doses of drugs⁴⁸.

Nanoparticles: Nanoparticles (NPs) have attracted the attention of growing researchers from many fields over the past 10 years and the basic building blocks of nanotechnology. The term nanoparticle was coined in the early 1990s with the concept of "nanoparticles" or "nanomaterialized" particles⁷. Synthesizing the particles in the range of nanoscale is ruining the new researches.

The size reduced particles gain their importance because of their better bioavailability and low toxicity compared with conventional. NPs based materials offer great opportunities for chemical and biological sensitivity because of their unique optical and mechanical properties⁶¹. Compared to larger biological molecules such as enzymes, receptors and antibodies, they are usually smaller than several hundred nanometers and a hundred to ten thousand times smaller than human cells¹¹.

It is primarily divided into two classes which are organic nanoparticles and inorganic nanoparticles (Figure 3). Organic nanoparticles are carbon nanoparticle and inorganic nanoparticles are magnetic nanoparticle, semiconductor nanoparticle⁴⁹. NPs are currently being tested for molecular

imaging in order to achieve a more accurate diagnosis with higher quality. The molecule can be prepared to improve the solubility, stability and absorption of many drugs, avoid the reticuloendothelial system and protect it from premature inactivation during its transport³⁷. These particles are versatile and adaptable to many aspects of health.

Over the past two decades, many nanoparticles based therapeutic and diagnostic agents have been developed for the treatment of cancer⁸. NPs can improve the intracellular concentration of drugs in cancer by using both inactive and active targeting strategies⁶⁸. The synthesis of nanoparticles using biological entities is of great interest due to their unusual optical, chemical, photovoltaic and electronic properties. A variety of physical, chemical and biological processes contribute to the synthesis of nanoparticles, some of which are novel and others more common³⁰.

Types of target agents

Dendrimers NPs: Dendrimers are highly branched, star-shaped macromolecules with nanometer-sized dimensions, synthetic polymers with an initiating core and multiple layers with active terminal groups. These layers consist of repetitive units and each layer is called a generation. They consist of three centers, the outer surface with a central core, an internal dendritic structure (branches) and functional surface groups⁶⁸. The first dendrimers, the Newcomb Tendirmer, were incorporated in 1985. The structure of the dendrimer molecule begins with a central atom or group of centrally named atoms.

From this central structure, the branches of other atoms, known as tetrazones, develop through a variety of chemical reactions. These exaggerated molecules were first discovered by Fritz Vogt in 1978¹⁰. The scale varies from 10 Å to 130 Å. It is a new class of drug delivery platform for nanoparticles due to its well-defined architecture and unique features⁶⁹. These dendritic polymers are similar to protein, enzymes and viruses and are easily functional⁴⁶.

In a different way used in early times, the set starts from the center of the dendrimers, the arms are attached by adding building blocks in an extensive and step-wise manner. This process enables dendrimers with increasing generation numbers.

Nevertheless, only one type of reaction can be activated at each step, giving only one exhibit of a functional group on the outer surface. In addition, defects may occur in subsequent generations due to partial reactions or severe disruptions²⁹. Individual dendritic compounds can be grouped together to form larger structures known as supramolecular dendrimers, a process known as supermolecular self-assembly. Drug molecules can be incorporated into the dendrimers and many surface groups or surface functional groups due to the well-defined 3D structure of the dendrimer.

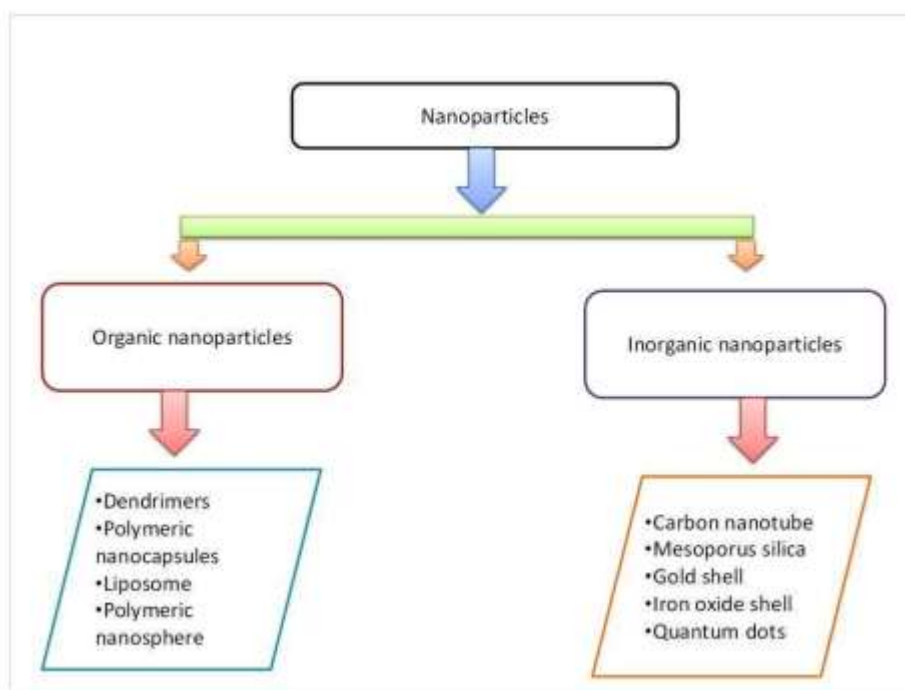


Figure 3: Types of nanoparticles

It can be used as drug carriers by combining drugs with functional groups through electrostatic or covalent bonds and modified with sulfonated naphthyl groups found to be useful as antiviral drugs against herpes simplex virus, can potentially prevent / reduce HIV transmission and other sexually transmitted diseases (STDs).

Interestingly dendrimer-based nanoparticles inhibit early-stage virus / cell absorption and subsequent stage virus transcription by coordinating reverse transcriptase and / or enzyme activities⁵⁸. It can act as carriers known as vectors in gene therapy and vectors transfer genes into the nucleus via the cell membrane³⁸. Pharmacological applications include photosynthesis, diagnosis, solubility enhancement, biomedical, gene delivery, drug delivery and synthetic enzymes.

In addition to that dendrimers have evolved into a nanoparticle carrier system that has greatly attracted the scientific community. These drug delivery systems have the potential to revolutionize the localization of cancer-specific drugs and therapies¹⁷. The growing role of dendritic macromolecules for anticancer therapies and diagnostic imaging highlights the benefits of these well-defined materials as new types of macromolecular nano-scale delivery devices.

General principles for designing dendrimer structures as delivery vehicles are established: 1) Negative charged and neutral dendrimers are typically biocompatible, although positively charged organisms have varying toxicity levels; 2) Dendrimer architecture can affect the pharmacokinetics dramatically; 3) PEGylation increases water solubility and dendrimer size and can lead to improved features of

retention and biodistribution; 4) Therapeutic agents can be rationalized in the empty space between the periphery and the core or connected covalently to functional surface groups; 5) Targeting dendrimer bound molecules can be used to treat cancer cells particularly with certain over-expressed receptor targets. When dendrimer structures have become more advanced, greater efficacy is achieved in *in vitro* and *in vivo* models¹⁴.

Frieboes et al²⁰ reported that nanoconstructs ranging from 1 to 10 nm would spread directly into tumor cells. The tree-like globular morphology begins from the middle and branches out symmetrically. The other functional groups may be coupled by electrostatic interactions with charged polar molecules, the hydrophobic pockets spanning the inside of dendrimers favor the encapsulation of uncharged, non-polar molecules.

Although dendrimers are as a drug delivery platform at a relatively early stage, their unique structural attribute has attracted interest in the simultaneous delivery of hydrophobic and hydrophilic therapeutic agents⁵³.

Polymeric NPs: Polymeric nanoparticles (PNPs) are large colloidal particles with a size of 50-500 nm and consist of biodegradable polymers or copolymers⁶⁴. Such nanoparticles have nanospheres and nanocapsules in them. A polymer matrix forms nanospheres where the molecules are adsorbed on the surface or encapsulated within the matrix. Nanocapsules form a vesicular structure, containing an inner reservoir where the molecules are trapped. The center is a liquid form (oil or water) surrounded by a solid material shell⁵⁰. Polymeric nanoparticles are colloidal solid

particles prepared from biodegradable polymers such as chitosan and collagen or non-biodegradable polymers such as poly (lactic acid) (PLA) and poly (lactic co-glycolic acid) (PLGA).

The main function of PNPs is to deliver the pharmaceutical agent to a specific site of action, to achieve a higher drug concentration and to improve the stability of volatile drugs and the potency and effectiveness of the product⁵². The use of polymer therapies has recently increased and has been identified as a new class of cancer treatment therapy²⁸. Such nanocarriers have been proposed as a means of improving delivery performance, reducing off-target effects, improving drug kinetics and providing a variety of therapeutic agents that is chemically diverse⁴⁷.

The deliveries of drugs are highly biodegradable and are biocompatible. Another area of medicinal use of polymeric NPs is neurodegenerative disorders (NDs), such as Alzheimer's disease (AD) and Parkinson's disease (PD)²⁴. The area of nanocarriers for drug delivery is cardiovascular disease management such as atherosclerosis and restenosis⁶⁵.

The drug-loading capability of polymeric micelles depends critically on the compatibility of the drug with the micelle core³². Such particles are made from different polymers (biocompatible and biodegradable), both synthetic and natural, with a unique architecture that serves as a putative delivery vehicle for the treatment of a particular disease⁴⁰.

In recent years, researchers have tried to address certain limitations by anchoring biocompatible polymers physically or chemically on the diagnostic nanomedicine surfaces³⁹. Isabella and Mirunalini²⁶ reported that polymeric chitosan nano particles are used for improved drug delivery system.

The polymeric delivery systems slowly release the encapsulated agent into tissues during incubation in water or after implantation, providing clinicians the opportunity to introduce large amounts of an anticancer agent directly at a tumor site for an extended period of time. Polymer delivery systems can be used to deliver better or safer chemotherapy by either increasing the length of systemic therapy or focussing drug therapy in a particular tissue area²¹. Polymer drug delivery systems provide a chance to deliver high, localized doses of chemotherapy after tumor resection for an extended period of time. Other polymer based delivery systems are also potentially useful for the delivery of chemotherapy to brain tumors⁹.

Chemoembolization is a desirable strategy for the production of chemotherapy, which aims to manipulate many aspects of polymer-based delivery systems. As such it is sometimes used for the prevention of pancreatic cancer and breast cancer. Advanced materials like thermo responsive polymers could further improve this technology¹.

Liposome NPs: Liposomes are closed spherical vesicles composed of a lipid bilayer formed in the shape of a hollow sphere that contains an aqueous phase. These are regarded as attractive drug delivery systems due to their size and hydrophilic and hydrophobic characteristics, in addition to biocompatibility⁶. The size range of the particles is 30 nm to several micrometres. They consist of one or more lipid bilayers surrounding aqueous units, in which the polar head groups are oriented in the inner and outer aqueous phases. In addition, they are commonly used as transporters for various molecules in the pharmaceutical and cosmetic industries.

In addition, the food and farming industries have studied extensively the uses of liposome encapsulation to build delivery systems that can imprison unstable compounds such as antioxidants, antimicrobials, flavors and bioactive elements and also shield their functionality⁶. They are the most easily synthesized class of nanoparticles capable of incorporating existing targeting ligands into already approved liposome drug carriers to create new potential combinations to enhance therapeutic delivery⁴¹.

Based on the successful use of liposome nanoparticles in the biomedical and pharmaceutical industries (cancer, drug delivery, etc.), scientists have now begun to use liposomes to control the delivery of functional components such as protein, polysaccharide, enzyme, vitamin and flavor in a variety of food practices³⁴.

Liposome nanoparticles have been used as a biological sensor for microbial pathogens, food contaminants and pesticides according to a recent literature study. Although a few nanobiosensors were designed for specific detection strategies, several other nanomaterials are also widely used as an alternative to liposome nanoparticles to detect foodborne pathogens and toxins⁵⁷. They also provide fast, sensitive and user-friendly detection assays that are portable and appropriate for in-field applications.

Nevertheless, many issues such as interference during real-sample analysis, reproducibility and toxicity remain to be resolved and therefore there is need for more effective nanosensors based on liposomes for the food and medical sciences.

Liposomes are small spherical artificial vesicles with a membrane consisting of bilayer phospholipids. They can be made from natural non-toxic phospholipids and cholesterol in the form of one or more condensed bilayers that can include hydrophilic and hydrophobic drugs⁴².

Because of their scale, biocompatibility, biodegradability, hydrophobic and hydrophilic character, low toxicity and immunogenicity, liposomes have shown one of the most developed nanoplatforms with several FDA-approved formulations for cancer treatment and have had the greatest impact on oncology to date⁵⁵.

In addition, liposomes also prolong drug exposure duration, acting as a slow release reservoir for various drug molecules that are encapsulated in them. Despite these multidimensional applications of liposomes, it is quite clear that they deliver an extremely flexible drug carrier modality with many promising prospects for antineoplastic drugs². Phosphatidylcholine, phosphatidylinositol and cholesterol are the most widely used lipids in liposome preparation which have minimal intrinsic toxicity and are present abundantly as the components of cell membranes.

Therefore, they do not evoke any kind of antigenic or pyrogenic effect when administered externally in the form of liposomes. Continuous work has contributed various liposomal formulations in both industry and clinical trials. Doxilw from Alza is a well-known drug containing liposomal doxorubicin for prostate cancer and breast cancer. Liposomes (phospholipid bilayer vesicles) are the most advanced form of drug carrier particulate matter. Due to their ability to enhance the pharmacokinetics and pharmacodynamics of their related medicines, several liposomal formulations of anticancer drugs have been clinically accepted⁵¹.

Metallic nanoparticles: Various materials such as gold (Au), copper (Cu) and silver (Ag) and inorganic carriers, such as silica or alumina, have been used for preparation of nanoparticles, among which gold nanoparticles is most promptly used due to their excellent optical and photoelectric properties.

Furthermore, gold exhibits certain advantages such as inertness and nanotoxicity, high stability, ease of preparation and the possibility of biomarkers and biomaterialization with thiol, disulfide and amine functional groups. The incorporation of thiolated PEG will improve the stability of its dispersion. Gold nanoparticles are highly effective contrast agents in the detection of cancer and in the treatment of phototherapy.

Gold NPs: Gold nanoparticles are distinct from gold particles; the larger size is a yellow inert solid while GNPs are an antioxidant agent in wine red. They have different sizes ranging from 1 nm to 8 μ m and at the same time have distinct forms such as suboctahedral, spherical, octahedral, multiple icosahedral twined, decahedral, multiple twined, tetrahedral, irregular shape, nanotriangles, hexagonal platelets, nanorods and nanoprisms⁴³. It is one of the most studied nanoparticles and very stable metal on the nanoscale as well as a good electron conductor and has a strong optical response on the nanoscale by creating resonant plasmon polaritons in a wavelength range dependent on the size when excited by an optical field.

Ultraviolet-visible Spectroscopy determined the size and shape of the synthesized gold nanoparticle³³. Gold nanoparticles with organic molecules⁴⁴ can be easily functionalised. It is a versatile material with a wide range of

applications including successful delivery of drugs, antibiotics, fungal, anti-microbial agents, biomedicines, biosensors and catalysts⁵⁴.

Moreover, gold nanoparticles grow as effective cancer therapy agents. Nowadays, interest in noble metal nanoparticles is rising. Scientists focus their attention on gold nanoparticles (AuNPs) which constantly characterize versatile properties and possible applications in cancer clinical chemistry, bioimaging and therapy as well as targeted drug delivery³. Au nanoparticles targeting may minimize the side effects of chemotherapy drugs by delivering the drugs to the target location using an exciting external source such as X-ray radiation¹⁶. These nanoparticles have a photoelectric effect that neutralizes the photo bleaching concerns of conventional fluorescent colors.

The surface alteration of the nanomaterials has a strong effect on the interaction between these nanomaterials and cells, as well as helping to turn toxic nanomaterials to less toxic. The unique property of nanoparticles to aggregate and interact with the tumor cells is enhanced permeability and retention (EPR). The second major advantage of gold nanoparticles is that they are non-cytotoxic and the third major advantage in terms of their surfaces, since they have a large surface area which makes their surfaces readily available for modification with molecules targeted³⁸. Drugs are loaded with the aid of pro-drug onto gold nanocarriers, which are processed by the cell. Thanks to their monolayers, gold nanoparticles have functional versatility, so they provide an efficient system⁶⁷.

Conclusion

Cancer nanotechnology is intended to develop safer yet more effective diagnostic and therapeutic modalities for cancer control. The most studied targeted approach in cancer chemotherapy is the nanoparticulate drug delivery mechanism such as folate mediated targeting, transfer targeting. The application of nanotechnology to drug delivery has already had a considerable impact on many medicine areas. Some formulations based on nanotechnology have been introduced in the marketplace and many are undergoing research and clinical trials.

Continuous efforts on advancing combinatorial nanoparticles can result in the perfect combination therapy.

Nonetheless, we believe a growing number of nanotechnology-based cancer therapeutics and diagnostics are likely to reach the clinic over the next few years.

References

1. Aigner K.R., Regional chemotherapy for non resectable, locally metastasized pancreatic cancer-four studies including 164 cases, *Reg Cancer Treat.*, **1(1)**, 1-2 (1993)
2. Allen T.M. and Cullis P.R., Drug delivery systems: entering the mainstream, *Science*, **303(5665)**, 1818-1822 (2004)

3. Arvizo R.R., Bhattacharyya S., Kudgus R.A., Giri K., Bhattacharya R. and Mukherjee P., Intrinsic therapeutic applications of noble metal nanoparticles: past, present and future, *Chemical Society Reviews*, **41**(7), 2943-2947 (2012)
4. Barbara K. and Maria B., Review Dendrimers: properties and applications, *Acta biochimica Polonica*, **48**(1), 199-208 (2001)
5. Bharali D.J. and Mousa S.A., Emerging nanomedicines for early cancer detection and improved treatment: current perspective and future promise, *Pharmacology and Therapeutics*, **128**(2), 324-335 (2010)
6. Bobo D., Robinson K.J., Islam J., Thurecht K.J. and Corrie S.R., Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date, *Pharmaceutical Research*, **33**(10), 2373-87 (2016)
7. Boskovic L. and Agranovski I.E., Removal of fine particles on fibrous filters: a review, *In Environanotechnology*, **1**(1), 245-257 (2010)
8. Brannon-Peppas L. and Blanchette J.O., Nanoparticle and targeted systems for cancer therapy, *Advanced Drug Delivery Reviews*, **56**(11), 1649-1659 (2004)
9. Brem H. and Langer R., Polymer-based drug delivery to the brain, *Science and Medicine*, **3**(1), 52-61 (1996)
10. Bryszewska B.K., Dendrimers: properties and applications, *Acta Biochim. Pol.*, **48**(1), 199-208 (2001)
11. Cai W., Gao T., Hong H. and Sun J., Applications of gold nanoparticles in cancer nanotechnology, *Nanotechnology, Science and Applications*, **1**(1), 17 (2008)
12. Chidambaram M., Manavalan R. and Kathiresan K., Nanotherapeutics to overcome conventional cancer chemotherapy limitations, *Journal of Pharmacy and Pharmaceutical Sciences*, **14**(1), 67-77 (2011)
13. Couvreur P., Kante B., Roland M. and Speiser P., Adsorption of antineoplastic drugs to polyalkylcyanoacrylate nanoparticles and their release in calf serum, *Journal of Pharmaceutical Sciences*, **68**(12), 1521-1524 (1979)
14. Cucinotto I., Fiorillo L., Gualtieri S., Arbitrio M., Ciliberto D., Staropoli N., Grimaldi A., Luce A., Tassone P., Caraglia M. and Tagliaferri P., Nanoparticle albumin bound Paclitaxel in the treatment of human cancer: nanodelivery reaches prime-time?, *Journal of Drug Delivery*, **1**(1), 1-7 (2013)
15. Ehdaie B., Application of nanotechnology in cancer research: review of progress in the National Cancer Institute's Alliance for Nanotechnology, *International Journal of Biological Sciences*, **3**(2), 108 (2007)
16. El-Sayed I.H., Huang X. and El-Sayed M.A., Surface plasmon resonance scattering and absorption of anti-EGFR antibody conjugated gold nanoparticles in cancer diagnostics: applications in oral cancer, *Nano Letters*, **5**(5), 829-834 (2005)
17. Faisant N., Siepmann J. and Benoit J.P., PLGA-based microparticles: elucidation of mechanisms and a new, simple mathematical model quantifying drug release, *European Journal of Pharmaceutical Sciences*, **15**(4), 355-366 (2002)
18. Farrell D., Ptak K., Panaro N.J. and Grodzinski P., Nanotechnology-based cancer therapeutics promise and challenge lessons learned through the NCI alliance for nanotechnology in cancer, *Pharmaceutical Research*, **28**(2), 273-278 (2011)
19. Ferrari M., Cancer nanotechnology: opportunities and challenges, *Nature Reviews Cancer*, **5**(3), 161 (2005)
20. Frieboes H.B., Sinek J.P., Nalcioğlu O., Fruehauf J.P. and Cristini V., Nanotechnology in cancer drug therapy: a biocomputational approach, *In Bio MEMS and Biomedical Nanotechnology*, **1**(1), 435-460 (2006)
21. Fung L.K. and Saltzman W.M., Polymeric implants for cancer chemotherapy, *Advanced Drug Delivery Reviews*, **26**(2-3), 209-30 (1997)
22. Galvin P., Thompson D., Ryan K.B., McCarthy A., Moore A.C., Burke C.S., Dyson M., MacCraith B.D., Gunko Y.K., Byrne M.T. and Volkov Y., Nanoparticle-based drug delivery: case studies for cancer and cardiovascular applications, *Cellular and Molecular Life Sciences*, **69**(3), 389-404 (2012)
23. Gerlowski L.E. and Jain R.K., Microvascular permeability of normal and neoplastic tissues, *Microvascular Research*, **31**(3), 288-305 (1986)
24. Goldsmith M., Abramovitz L. and Peer D., Precision nanomedicine in neurodegenerative diseases, *ACS Nano*, **8**(3), 1958-1965 (2014)
25. Hanahan D. and Weinberg R.A., The hallmarks of cancer, *Cell*, **100**(1), 57-70 (2000)
26. Isabella S. and Mirunalini S., Protective effect of 3, 3'-Diindolylmethane encapsulated chitosan nanoparticles prop up with lipid metabolism and biotransformation enzymes against possible mammary cancer, *Journal of Applied Pharmaceutical Science*, **7**(03), 194-201 (2017)
27. Jabir N.R., Tabrez S., Ashraf G.M., Shakil S., Damanhour G.A. and Kamal M.A., Nanotechnology-based approaches in anticancer research, *International Journal of Nanomedicine*, **7**(1), 4391 (2012)
28. Jaeger E. and Giacomelli F.C., Soft matter assemblies as nanomedicine platforms for cancer chemotherapy: a journey from market products towards novel approaches, *Current Topics in Medicinal Chemistry*, **15**(4), 328-44 (2015)
29. Kesrevani R.K. and Sharma A.K., Nanoarchitected biomaterials: present status and future prospects in drug delivery, Nanoarchitectonics for Smart Delivery and Drug Targeting; Elsevier BV: Amsterdam, The Netherlands (2016)
30. Krolikowska A., Kudelski A., Michota A. and Bukowska J., SERS studies on the structure of thioglycolic acid monolayers on silver and gold, *Surface Science*, **532**(1), 227-232 (2003)
31. Lai X., Tan L., Deng X., Liu J., Li A., Liu J. and Hu J., Coordinatively self-assembled luminescent gold nanoparticles:

fluorescence turn-on system for high-efficiency passive tumor imaging, *ACS Applied Materials and Interfaces*, **9(6)**, 5118-5127 (2017)

32. Latere Dwanisa J.P., Rouxhet L., Preat V., Brewster M.E. and Arien A., Prediction of drug solubility in amphiphilic di-block copolymer micelles: the role of polymer-drug compatibility, *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, **62(7)**, 499-504 (2007)

33. Leff D.V., Brandt L. and Heath J.R., Synthesis and characterization of hydrophobic, organically-soluble gold nanocrystals functionalized with primary amines, *Langmuir*, **12(20)**, 4723-4730 (1996)

34. Leonard P., Hearty S., Brennan J., Dunne L., Quinn J., Chakraborty T. and Okenedy R., Advances in biosensors for detection of pathogens in food and water, *Enzyme and Microbial Technology*, **32(1)**, 3-13 (2003)

35. Matsumura Y. and Maeda H., A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumorotropic accumulation of proteins and the antitumor agent smancs, *Cancer Research*, **46(12)**, 6387-6392 (1986)

36. McNeil S.E., Nanotechnology for the biologist, *Journal of Leukocyte Biology*, **78(3)**, 585-594 (2005)

37. Medina C., Santos-Martinez M.J., Radomski A., Corrigan O.I. and Radomski M.W., Nanoparticles: pharmacological and toxicological significance, *British Journal of Pharmacology*, **150(5)**, 552-558 (2007)

38. Mendoza K.C., McLane V.D., Kim S. and Griffin J.D., Invitro application of gold nanopores in live neurons for phenotypical classification, connectivity assessment and electrophysiological recording, *Brain Research*, **1325(1)**, 19-27 (2010)

39. Mikhaylova M., Kim D.K., Bobrysheva N., Osmolowsky M., Semenov V., Tsakalakos T. and Muhammed M., Superparamagnetism of magnetite nanoparticles: dependence on surface modification, *Langmuir*, **20(6)**, 2472-2477 (2004)

40. Moghimi S.M., Hunter A.C. and Murray J.C., Long-circulating and target-specific nanoparticles: theory to practice, *Pharmacological Reviews*, **53(2)**, 283-318 (2001)

41. Mohan A. et al, Encapsulation of food protein hydrolysates and peptides: a review, *RSC Advances*, **5(97)**, 79270-79278 (2015)

42. Muthu M.S. and Singh S., Targeted nanomedicines: effective treatment modalities for cancer, *AIDS and Brain Disorders*, **1(1)**, 105-118 (2009)

43. Nafisi S. and Maibach H.I., Nanotechnology in cosmetics, *In Cosmetic Science and Technology: Theoretical Principles and Applications*, **337 (1)**, 1-1 (2017)

44. Nguyen M., Felidj N. and Mangeney C., Looking for synergies in molecular plasmonics through hybrid thermoresponsive nanostructures, *Chemistry of Materials*, **28(11)**, 3564-3577 (2016)

45. Park K., Nanotechnology: What it can do for drug delivery, *Journal of Controlled Release: Official Journal of the Controlled Release Society*, **120(1)**, 1-2 (2007)

46. Patel H.N. and Patel P.M., Dendrimer applications—a review, *Int J Pharm Bio Sci.*, **4(2)**, 454-63 (2013)

47. Patel T., Zhou J., Piepmeyer J.M. and Saltzman W.M., Polymeric nanoparticles for drug delivery to the central nervous system, *Advanced Drug Delivery Reviews*, **64(7)**, 701-705 (2012)

48. Polo E., Collado M., Pelaz B. and Del Pino P., Advances toward more efficient targeted delivery of nanoparticles in vivo: understanding interactions between nanoparticles and cells, *ACS Nano*, **11(3)**, 2397-402 (2017)

49. Pradhan S., Comparative analysis of Silver Nanoparticles prepared from Different Plant extracts (Hibiscus rosa sinensis, Moringa oleifera, Acorus calamus, Cucurbita maxima, Azadirachta indica) through green synthesis method, (Doctoral dissertation) (2013)

50. Rao J.P. and Geckeler K.E., Polymer nanoparticles: preparation techniques and size-control parameters, *Progress in Polymer Science*, **36(7)**, 887-913 (2011)

51. Rosarin F.S. and Mirunalini S., Nobel metallic nanoparticles with novel biomedical properties, *J. Bioanal. Biomed.*, **3(4)**, 85-91 (2011)

52. Safari J. and Zarnegar Z., Advanced drug delivery systems: Nanotechnology of health design A review, *Journal of Saudi Chemical Society*, **18(2)**, 85-99 (2014)

53. Sengupta S. and Sasisekharan R., Exploiting nanotechnology to target cancer, *British Journal of Cancer*, **96 (9)**, 1315-1319 (2007).

54. Shan J. and Tenhu H., Recent advances in polymer protected gold nanoparticles: synthesis, properties and applications, *Chemical Communications*, **1(44)**, 4580-4598 (2007)

55. Sharma G., Anabousi S., Ehrhardt C. and Ravi Kumar M.N., Liposomes as targeted drug delivery systems in the treatment of breast cancer, *Journal of Drug Targeting*, **14(5)**, 301-310 (2006)

56. Sinha R., Kim G.J., Nie S. and Shin D.M., Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery, *Molecular Cancer Therapeutics*, **5(8)**, 1909-1917 (2006)

57. Torchilin V., Antibody-modified liposomes for cancer chemotherapy, *Expert opinion on Drug Delivery*, **5(9)**, 1003-1025 (2008)

58. Tripathy S. and Das M.K., Dendrimers and their applications as novel drug delivery carriers, *J Appl Pharm Sci.*, **3(9)**, 142-149 (2013)

59. Wagner A. and Vorauer-Uhl K., Liposome technology for industrial purposes, *Journal of Drug Delivery*, **1(1)**, 1-2 (2011)

60. Wang A.Z., Gu F., Zhang L., Chan J.M., Radovic-Moreno A., Shaikh M.R. and Farokhzad O.C., Biofunctionalized targeted nanoparticles for therapeutic applications, *Expert Opinion on Biological Therapy*, **8(8)**, 1063-1070 (2008)

61. Wang J., Polsky R. and Xu D., Silver-enhanced colloidal gold electrochemical stripping detection of DNA hybridization, *Langmuir*, **17(19)**, 5739-5741 (2001)

62. Wang M.D., Shin D.M., Simons J.W. and Nie S., Nanotechnology for targeted cancer therapy, *Expert Review of Anticancer Therapy*, **7(6)**, 833-837 (2007)
63. Wicki A., Witzigmann D., Balasubramanian V. and Huwyler J., Nanomedicine in cancer therapy: challenges, opportunities and clinical applications, *Journal of Controlled Release*, **200(1)**, 138-57 (2015)
64. Yadav H.K., Almokdad A.A., Sumia I.M. and Debe M.S., Polymer-based nanomaterials for drug-delivery carriers, *In Nanocarriers for Drug Delivery*, **1(1)**, 531-556 (2019)
65. Yin R.X., Yang D.Z. and Wu J.Z., Nanoparticle drug-and gene-eluting stents for the prevention and treatment of coronary restenosis, *Theranostics*, **4(2)**, 175 (2014)
66. Yu H.P., Aljuffali I. and Fang J.Y., Injectable drug-loaded nanocarriers for lung cancer treatments, *Current Pharmaceutical Design*, **23(3)**, 481-494 (2017)
67. Yu L., Qiu J.J., Cheng H. and Luo Z.H., Facile preparation of gold nanoparticles using the self-assembled ABC non-amphiphilic fluorosilicone triblock copolymer template, *Materials Chemistry and Physics*, **138(2)**, 780-6 (2013)
68. Zhang L., Gu F.X., Chan J.M., Wang A.Z., Langer R.S. and Farokhzad O.C., Nanoparticles in medicine: therapeutic applications and developments, *Clinical Pharmacology and Therapeutics*, **83(5)**, 761-769 (2008)
69. Zhang L., Radovic-Moreno A.F., Alexis F., Gu F.X., Basto P.A., Bagalkot V., Jon S., Langer R.S. and Farokhzad O.C., Co-delivery of hydrophobic and hydrophilic drugs from nanoparticle–aptamer bioconjugates, *Chem Med Chem: Chemistry Enabling Drug Discovery*, **2(9)**, 1268-1271 (2007)
70. Zhao G. and Rodriguez B.L., Molecular targeting of liposomal nanoparticles to tumor microenvironment, *International Journal of Nanomedicine*, **8 (1)**, 61 (2013).

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