

RECENT TRENDS IN SMART DELIVERY SYSTEMS FOR EXTENDED DRUG RELEASE IN CANCER THERAPY

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Abstract: The main aim of this present article is to study the nanostructured drug delivery systems which allow the development of novel platforms for the efficient transport and controlled release of drug molecules in the harsh microenvironment of diseased tissues of living systems. Nanocarriers and nanoparticles drug delivery system are controls the some of the limitations associated with traditional cancer therapy administration such poor oral bioavailability, reduced drug solubility, chemo resistance, toxicity, and narrow therapeutic index. A recent advancement techniques in the field of Nanoparticles includes smart or multiple levels of targeting and extended release drug delivery systems that provide additional methods of controlling these disadvantages. More recently development of this smart drug delivery system for extended release has emerged in aspiration of developing mostly efficient nanoparticles with enhanced delivery, bioavailability and safety profiles. Smart drug delivery systems are used to deliver drugs to the targeted tissue sites, reduced dosage frequency and in a spatially controlled manner to reduce the side effects experienced in Controlled drug delivery systems. A smart drug delivery system consists such as smart nanocarriers, targeting mechanisms and stimulus techniques. This review highlights the recent development of smart drug delivery systems for a number of smart nanocarriers including composed of organic (including polymeric micelles and vesicles, liposomes, dendrimers and hydrogels) and inorganic (including quantum dots, gold and mesoporous silica nanoparticles, super paramagnetic iron oxide, carbon nanotubes and Exosomes etc.) materials. The development of smart drug delivery system for cancer treatment and it exhibits enhanced pharmacokinetic and pharmacodynamic profiles over conventional formulations due to their Nanoscale size and unique physicochemical characteristics.

Keywords: Nanomedicine, smart drug delivery system, Nanocarries, stimulus techniques, targeting mechanisms.

Introduction: Cancer is the one of the cause of death worldwide. Chemotherapy is an important role in treating unnoticeable cancer micro focuses and free cancer cells. Chemotherapy uses chemicals to kill the growth of cancer cells. (1, 6) As cancer cells grow faster than healthy cells, fast-growing cells are the major targets of chemotherapeutics. However, because the main disadvantages are the drugs used in chemotherapy also attack those healthy cells and multi drug resistance (MDR) is another drawback to successful chemotherapy. (1) This unwanted attack results in the failure of conventional chemotherapy. This limitations of conventional chemotherapy have lead to the development of smart Nanocarrier based drug delivery systems, which are also known as Smart Drug Delivery System (SDDSs).(2) Smart drug nanostructured materials are used to deliver drugs to the targeted tissues with reduced dosage frequency and in a controlled manner to decrease the side effects experienced with traditional therapies. The Smart drug delivery systems is resolving the issues experienced with conventional pharmaceutical treatments such as the uncontrollable release of drugs, nonspecific distribution, rapid clearance and low bioavailability. Recent advancement techniques in nanoparticles design propose that there is a focus on multifunctional targeting, which includes multiple complementary targeting mechanisms such as passive, active, and stimuli-responsive targeting.(11) The extended drug-release properties could further increase multifunctional targeting, where by smart extended release Nanoparticles (SER NPs) can gives additional physiological and clinical benefits, especially in the treatment of cancer and also enhance their therapeutic effects and reduce side effects.(6)

Targeting mechanisms

They are utilizes by the three types of targetings such as passive targeting, active targeting and Stimuli-responsive targeting.

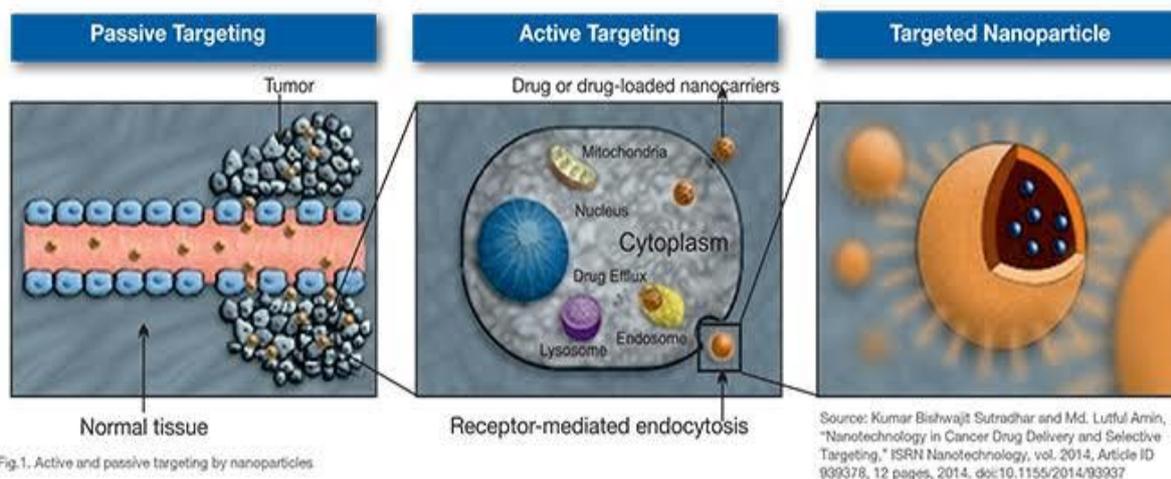


Fig.1. Active and passive targeting by nanoparticles

1) Passive targeting

A drug-loaded nanocarrier of accumulation rate into a tumor is much higher than in normal tissue due to the leaky endothelium of the tumor vasculature. This phenomenon is known as the enhanced permeability effect. The lymphatic system is one part of the immune system of the body. A deficiency of the lymphatic system leads to the retention of the nanoparticles in the tumor. (4) This retention is known as the enhanced retention effect. Both the phenomena are collectively known as the EPR effect. The high intestinal fluid pressure in cancer cells can be reduced successful uptake and uniformly distribution of drug.(6) Long-circulating liposomes, polymers, and micelles are examples of Nanoparticles that take advantage of the leaky vasculature of tumors that ultimately allows for the entrapment and accumulation of Nanoparticles.

2) Active targeting

Guiding the drug carrying Nanocarriers to the cancer cells such as guided missiles. Cancer cells and normal cells can be separated in terms of cell surface receptor and antigen expression.(4) The delivery of Nanoparticles can be increased by functionalizing Nanoparticles with a variety of targeting molecules that are commonly over expressed on malignant cells such as antibodies, ligands and carbohydrates.(7) Drug-loaded nanocarriers are conjugated with targeting ligands. These ligands identify their matching target over expressed on the cancer cell surface. Folate, antibodies, peptides, transferrin and aptamers are some proposed ligands. (8)

3) Stimuli-responsive targeting

1) Exogenous stimulus

A extra-corporal signal to release drugs from Nanocarriers, such as a magnetic field, ultrasound waves, electric field, a temperature change is known as exogenous stimulus.

a) Magnetic field responsive stimulus

An extra-corporal magnetic field is used to drug-loaded Nanocarriers are accumulate in tumor sites after the injection of Nanocarriers. (9) Core-shell shaped nanoparticles coated with silica, polymer or magneto liposome (maghemite Nanocrystals encapsulated in liposomes) are some ideal candidates for magnetic stimulus. Magnetic Nanocarriers produce heat in the surrounding medium when they are placed under an oscillating magnetic field. This heat brings changes in the structures of Nanocarriers. (3)

b) Thermo-responsive stimulus

Temperature is one of the most effective factors to control the drug release compared with other stimuli. Normally, pathophysiological conditions such as inflammation and tumors have higher temperatures than normal tissues. (4) The functionalized nanoparticles can be stimulated to increase their drug release in tumors. Some other temperature-responsive stimulus is that the tumor site could be heated by external triggers such as US, magnetic field, to enhance the drug release within the tumor vasculature microenvironment. (5)

c) Light-triggered stimulus

The recent technique of light-triggered drug delivery is a new avenue for on-demand drug delivery. The light may be in the ultraviolet, visible or near-infrared ranges.(4) The stimulus is achieved by making the nanocarriers sensitive to light carbon nanotubes and gold nanoparticles are good candidates for light-triggered stimulus, especially for the near-infrared (NIR) range. Metallic Nanocarriers absorb light and convert the absorbed light to heat in order to kill cancer cells. (7)

d) Ultrasound-responsive stimulus

Ultrasound is under intense expression to release drugs from nanocarriers because of its non-invasiveness characteristics, deep penetration into the body and non-ionizing irradiation. By using ultrasound, both thermal and mechanical effects can be induced in the Nanocarriers to release the loaded-drug. (8)

e) Electric field-responsive stimulus

This stimulus system uses an electric field to release payloads. The electric field responsive is easy to generate and control to release drugs into tumor cells. (8) Conducting polymers such as polypyrrole (PPy) are in consideration for electric-responsive stimulus. Conducting polymers are used to modify Nanocarriers and the success of conducting polymers depends on the choice of dopant (electronics) and the molecular weight of the drug. (7)

2) Endogenous stimulus

Endogenous stimulus is also called as intrinsic stimulus. In endogenous stimulus, the triggering signal comes from the internal pH level, enzyme activity and Redox activity of the body. (4)

a) The pH-responsive stimulus

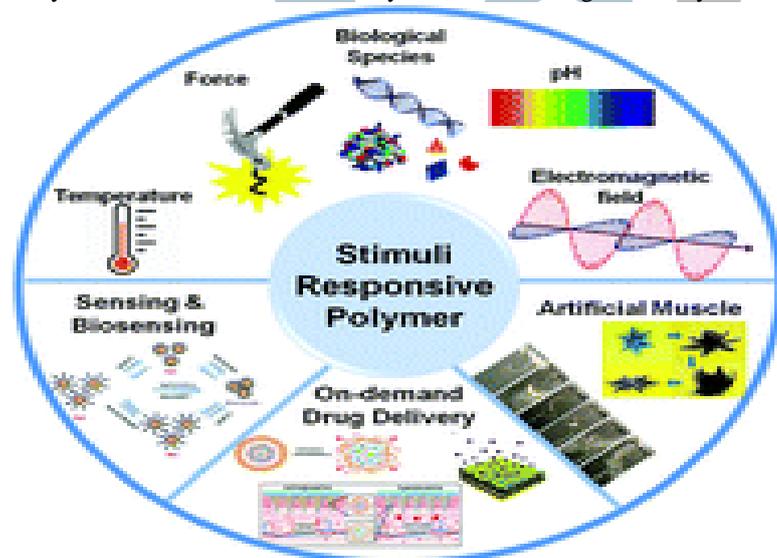
pH is one of the most regularly used stimuli for drug release. The conventional pH-responsive carriers are based on available variation of pH values in different organs such as stomach (pH \approx 2) and intestinal tract (pH \approx 7). (2) Example Eudragit S100 coated citrus pectin nanoparticles (E-CPNs) were formulated for the colon specific targeting of 5-Fluorouracil (5-FU). The pH-sensitive Nanocarriers usually store and stabilize anticancer drugs at physiological pH, but rapidly release the drug at a pH trigger point, which ensures that intracellular drug concentration reaches a peak. (4) The target can be reached by different approaches including the introduction of ionizable chemical groups, such as amines, phosphoric acid and carboxyl groups, among others. These groups undergo pH dependent physical and chemical changes which result in drug release. (1)

b) Redox sensitive stimulus

Redox responsive stimuli have contained great attention for disease therapy and widely used in intracellular Drug delivery systems. The design and invention of nanoparticles responsive to Glutathione (GSH) can be a promising approach for targeting drug delivery. Glutathione sulfhydryl (GSH) is a highly effective antioxidant. (4) It consists of three amino acids. GSH is found at higher concentrations in all mammalian tissue. GSH controls the reductive microenvironment. The concentration of GSH in a tumor site is at least 4 times higher than in normal cells. The intracellular concentration of GSH is 1000 times higher than in the blood stream, functional group with the structure R-S-S-, can reduce the disulfide bonds of nanocarriers leads to the release of an encapsulated drug. (5)

c) Enzyme stimulus

Nanocarriers whose surfaces are modified to make the nanocarriers responsive to the bio-catalytic action of enzymes are known as enzyme-stimulus nanocarriers. (6) Enzymes used as triggers in the design of smart drug delivery systems have been an emerging field in recent years owing to its unique superiorities such as substrate specificity and high selectivity under mild conditions. Since enzymes such as phospholipase or proteases, glycosidases and lipase are related to almost all the biological and metabolic process. They can be utilized to achieve enzyme mediated drug release by the biocatalytic action at the cancer.



Novel approaches to smart drug delivery systems

Lipid based Drug carriers

1) Liposome

Liposomes were initially produced by Alec D. Bangham in 1961. Liposomes are small lipoidal vesicles of spherical shape drug delivery system, which are under extensive exploration as drug carriers for improving the delivery of therapeutic agents, composed of relatively biodegradable and biocompatible material and they consist of an aqueous volume entrapped by one or more bilayers of natural and synthetic lipids. (4) Phospholipids are main ingredient of the cell membrane consist of a fatty acid based hydrophobic tail and phosphate based hydrophilic head. There are various methods to prepare liposomes. (2) They are thin film hydration method or Bangham method, reverse phase evaporation, solvent injection technique, and detergent dialysis. Conventional methods have many disadvantages. To remove those limitations, some novel technologies have been devised, such as supercritical fluid technology, the supercritical anti-solvent method, and supercritical reverse phase evaporation. Smart nanocarriers can differentiate between healthy and tumor cells. Monoclonal antibodies, carbohydrates, antibody fragments, proteins, peptides, vitamins and glycoproteins are grafted on the liposomes to target the tumor cells. (6) Smart liposomes are responsive to external and internal factors, such as pH change, oxidation-reduction reaction, light, ultrasound, enzyme transformation and microwaves. A liposome

functionalized with a radioligand is known as a radiolabeled liposome. Radiolabeled liposomes can be used to assess the liposome bio-distribution in the body and tumor diagnose along with carrying out therapy. (1, 4)

2) Exosomes

Exosomes are nanosized membrane vesicles produced by special cells related tissues or cells in responding to the endogenous or exogenous stimulation. (4, 6) The uses of exosomes are rapidly increased in recent years as one of the biomaterials for drug delivery. For example, exosomes can be targeted directly to specific tissues, while maintaining their biological functions. Exosomes appear to play a vital role in many diseases like cancers and inflammation. (2, 5) Many characteristics suggest that the exosomes are ideal drug delivery vehicles. Firstly, exosomes will load with particular drugs to serve as carriers for customized medicine. Since exosomes produced from different types of host cells, they show different biological effects and targeting specificities. Secondly, exosomes are well biocompatible with the lowest cytotoxicity. Exosomes reproducible upon sonication and extrusion with saponin formulated in more loading capacity, sustained release and catalase protection against proteases degradation. (3) Thus, it can serve as a versatile strategy to treat neurodegenerative and inflammatory disorders. Exosomes are used to deliver chemotherapeutics such as DOX to tumor tissues. Nie's group has utilized the mouse immature dendritic cells (imDCs) to produce exosome then the exosomal membrane protein (Lamp2b) fused to αv integrin-specific iRGD peptide (CRGDKGPDC) and DOX were loaded into purified exosomes from imDCs via electroporation. iRGD exosomes have demonstrated highly efficient targeting the growth of tumor was well controlled without overt toxicity. Exosomes may serve as a promising candidate for smart drug delivery nanocarrier due to non-cytotoxic effect, nature targeting feature, and a great drug loading capacity. (4)

3) Transfersomes

Gregor Ceve introduced transfersomes in 1991. Synthesized the cisplatin and imiquimod loaded transfersomes with a particle size of 429.5 nm and zeta potential 68.1 mV. The drug-excipient interactions were determined by thin-layer chromatography (TLC), Fourier-trans-form infrared spectroscopy (FTIR) and X-ray diffraction (XRD). The combinatorial drug delivery-based transforms can be ideal vesicles for the improvement of anti-tumor activity and efficient targeting against skin that is related to carcinomas. (4, 2)

4) Cubosomes

Cubosomes are lipid-based nanostructured carrier, having the particle range between 100 and 300 nm with large surface area and low viscosity. This technique was used for the co-delivery of cisplatin with metformin via the emulsification technique. The developed cubosomes were characterized and optimized for further exploration. The enzyme-linked immunosorbent assay (ELISA) technique was used for AMPK/mTOR metabolic and the Akt/MT OR pathways. Meanwhile, cubosomes had increased their cytotoxicity based on the addition of metformin. This novel cubosomes based formulation exaggerated different intracellular targets with efficient inhibition effect on tumor linked with different metabolic pathways leading to increase the apoptosis. (4, 2, 5)

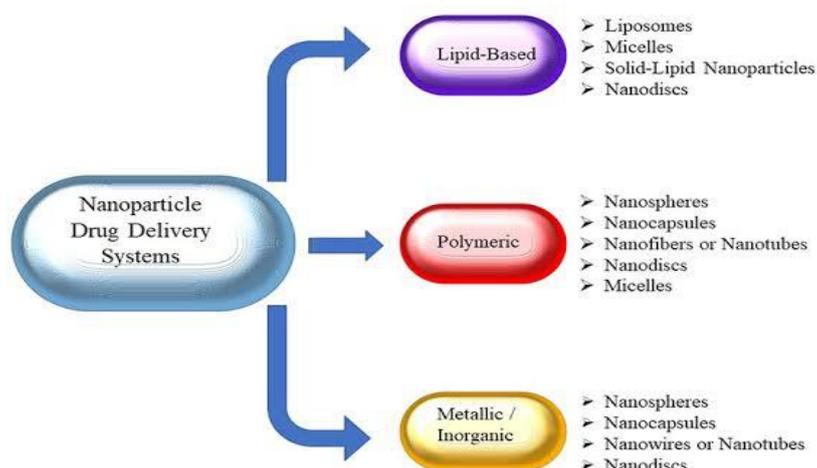
Organic nanoparticles

1) Hydrogels

Hydrogels are a network of hydrophilic polymer with variable structures. A novel injectable thermo-sensitive polypeptide-based CDDP with loaded hydrogel was formulated for improving the efficacy of the localized anti-tumors. Enhanced antitumor activity of cisplatin-loaded thermal sensitive injectable hydrogel had been noticed, in contrast to the free drug with improved localized delivery to target sites. (6,7) The mechanism behind to explain the enhanced anti-cancer efficacy of hydrogels based on depicting more sustained release of cisplatin from hydrogels. Dual drug CDDP/PTX-loaded injectable hydrogel is used for the treatment of ovarian cancer. The sustained release of dual drug was performed for about 2 1/2 months, with increased anti-cancer effect against the SKOV-3 ovarian cancer xenograft mouse models. (8) Super molecular alpha-cyclodextrin dual drug CDDP/PTX was formulated to control the acute toxicity. XRD and FTIR were performed to determine the drug-polymer interactions. This study reported that the injectable super molecular PEG-modified cisplatin-loaded hydrogel was developed to improve the anti-tumor effect. Thermo-sensitive poly-peptide hydrogel was used for the combination of cisplatin and interleukin-15(IL-15) for localized drug delivery system. Dual drug loaded hydrogel can decrease the systemic toxicity and enhance the synergistic effect against the B16F0-RFPmelanoma cells. (11)

2) Micelles

Amphiphilic molecules, having both hydrophilic and hydrophobic portions, show unique features of self-assembly when exposed to a solvent. (9) If the solvent is hydrophilic and its concentration exceeds the critical micelle concentration (CMC), the polar parts of the co-polymer are attracted toward the solvent, while hydrophobic parts away from the solvent. In this way, the hydrophilic is form a corona and hydrophobic is form a core such known as direct or regular polymeric micelle and on the other hand, amphiphilic molecules exposed to a hydrophobic solvent formed a reverse structure known as a reverse micelle, i.e. the hydrophilic portions form a core and the hydrophobic portions form a corona in a reverse micelle. The formulation of micelles depends on the solubility of the co-polymers. For a relatively water-soluble co-polymer, two methods are used such as the direct dissolution method and the film casting method. There are two types of cross-linking strategy: core cross-linked polymer micelles and the shell cross-linked polymer micelles. (12) To actively target cancer cells, various types of ligands are used to decorate the micelle surface such as peptides, carbohydrates, antibodies, folic acid and aptamers, etc. To produce the anticancer drug at the right concentration, the core or the corona of the micelle can be functionalized. The stimulation utilized in micelle based Smart drug delivery systems are temperature changes, ultrasound, pH gradients, enzymes and oxidation. Using a multifunctional micelle, the co-delivery technique is very important for the synergetic effects in cancer treatment. (15) PG-PCL, PEEP-PCL, PEG-PCL and PEG-DSPE are examples of some micelles.



3) Dendrimers

Dendrimers drug delivery system are protected from drug degradation and ensure that drug reaches proper permeability properties and further allows a combined protection and transportation system against the natural barriers, as done by the dendrimers.(13) Dendrimer has three distinguishable parts: a core, branching dendrons and surface-active groups. The active groups on the dendrimer surface are used to determine the physiochemical properties of the dendrimer. (4, 6, 10) Depend upon the surface groups, it may be either hydrophobic or hydrophilic. Due to its nanoscale size, water solubility, biocompatibility, monodisperse nature and highly branched structure, it is of high interest. Because of the nanoscale size, it can be utilized as a drug carrier. (12) The branched structure produces the dendrimer versatile, which results in a higher drug encapsulation rate. Various types of dendrimer, such as PAMAM, POPAM, POMAM, poly (propylene mine) (PPI or POPAM), carbon/oxygen-based dendrimer, ionic dendrimer, silicon-based dendrimer, porphyrin based dendrimer, polylysine dendrimer, dendritic hydrocarbon, phosphorus based dendrimer, and Newkome dendrimer have been reported. The commonly reported methods to produce dendrimers include the divergent method and the convergent method. (14)

Inorganic nanoparticles

1) Mesoporous silica nanoparticles (MSNs)

Mesoporous silica nanoparticles (MSNs) are novel drug carrier due to their special mesoporous silica structure that provides a level of biocompatibility, surface functionality and chemical stability. Mesoporous silica nanoparticles was discovered by the Mobile Oil Corporation in 1992 have collected extended attention because of their superior textual properties such as high surface area, narrow pore size distribution, large pore volume and tunable pore diameter.(8) The large surface areas of the internal surface (pores) and external surface are acceptable for grafting different functional groups on MSNs.(11) Apart from bio-compatibility, adhesion of this carrier to cancer cells by the EPR effect. There are mainly two types of Mesoporous silica nanoparticles, such as 1) ordered mesoporous silica nanoparticles (MCM-41, MCM-48, and SBA-15), and 2) hollow or rattle-type mesoporous silica nanoparticles. The ways to manufacture of Mesoporous silica nanoparticles are the soft template method and hard template method. PEGylation helps offset those causes. The pore openings of smart MSNs can be controlled by grafting co-polymers on their surfaces. (6, 12) Grafted copolymers work as gatekeepers. Polymer-grafted Mesoporous silica nanoparticles provide zero premature produce of loaded drugs. For active targeting, the surface of mesoporous silica nanoparticles (MSNs) can be modified using folate, mannose, transferrin and peptides. Mesoporous silica nanoparticles can release the drugs in response to diverse stimuli, including pH change, Redox reaction, enzyme transformation, temperature change, light, magnetic field, etc. (13)

2) Gold nanocarriers

Gold nanoparticles are beneficial in diagnosis of cancer due to their photophysical property and optical property. The golden nanoparticle approach uses no toxic chemical and no radiation, reducing the risk of unpleasant side effects. This therapy will work on any soft tissue tumors such as the breast, prostate, brain, skin, head, neck and cervix. The nanoparticles are designed to change light into heat-blasting away the surrounding cancer tissue. (8) Gold nanoparticles are metallic nanocarriers available in custom shapes and sizes. Gold nanoparticles have great prospects as metallic candidates for delivering payloads. Payloads could be drug molecules or large biomolecules such as proteins, DNA and RNA. (6,2) GNPs are also interesting due to the surface Plasmon resonance (SPR) phenomenon, which enable them to converts light to heat and scatter the produced heat to kill the cancer cells. GNPs are mainly synthesized via a number of routes, including (1) chemical, (2) physical and (3) biological methods. Smart nanocarriers should be chemically stable in biological media, biocompatible, efficient in targeting and responsive to external or internal stimuli. GNPs without modification are unstable in blood and face higher uptake by the RES. (4) to overcome these factor gold nanocarriers require being PEGylated. Under physiological conditions, PEGylated gold nanoparticles show enhanced solubility and stability. The gold nanoparticles surface could also be modified by folic acid, as folic acid receptors are also overexpressed on various cancer cells. (10)

3) Super paramagnetic iron oxide nanoparticles (SPIONs)

When magnetic particles are reduced to 10–20 nm, they show a unique phenomenon called super paramagnetism. On the application of a magnetic field, the magnetic nanoparticles are magnetized up to their saturation, but show no residual magnetism upon removal of the magnetic field. (12) The fabrication of super paramagnetic iron oxide nanoparticles includes 3 methods such as a physical method, wet chemical method and microbial method. There are various methods to synthesis SPIONs, such as, co-precipitation, thermal decomposition, hydrothermal, micro emulsion, sonochemical, and microwave-assisted synthesis methods. The smartness of post-fabricated SPIONs depends on the functionalization.(4,2) Functionalization reduces the aggregation of SPIONs, protects their surfaces from oxidation, provides a surface to conjugate drugs and targeting ligands, increases the blood circulation by avoiding the RES, and reduces nonspecific targets. Stimuli responsive polymer-coated SPIONs are under intensive investigation for targeted drug delivery. Responsive polymers undergo physical and chemical transitions such as phase, solubility and hydrophobicity conformation. (1)

4) Carbon nanotubes (CNTs)

Carbon Nanotubes long, and thin cylinders of carbon, were discovered by Sumio Iijima in 1991. These are large macromolecules that are special for their particles shape, size, and remarkable physical properties. Carbon nanotubes can be thought of as a sheet of graphite rolled into a cylinder.(5,4) Nanotubes have a broad range of structural, electronic and thermal properties that change based on the various kinds of nanotube (defined by its diameter, length, and chirality, or twist). To manufactured objectives more interesting, a side from a single cylindrical wall (SWNTs), Nanotubes can have multiple walls (MWNTs)--cylinders inside the other cylinders.(2) To address the controls of the controlled flame environment, electric arc discharges, the chemical vapor deposition method and the laser ablation method have been reported. Due to the better defined walls of SWCNTs and relatively more structural faults of MWCNTs, SWCNTs are more efficient than MWCNTs in drug delivery.(9) PEGylation is a very vital step to enhance solubility, avoid the RES and to decrease the toxicity. Poly (N-isopropyl acrylamide) (PNIPAM) is a temperature-sensitive polymer. Due to their low critical stimulus temperature (LCST), PNIPAM could be used to modify CNTs for temperature stimulus. The disulfide cross-linker, based on methacrylate cysteine, is used for enzyme responsive drug release. For pH responsiveness, an ionizable polymer with a pKa value between 3 and 10 is an ideal candidate. Carbon nanotubes have shown in carrying the plasmid DNA, small-interfering ribonucleic acid (siRNA), antisense oligonucleotides, and aptamers. It can be used for the thermal ablation of a cancer site Functionalized CNTs can be used as diagnostic tools for the early identification of cancer. (15)

5) Quantum dots (QDs)

Quantum dots fluorescent semi-conducting nanocarriers are often made of hundreds to thousands of atoms of group II and group VI molecule and have special photo-physical properties. (11) This nanocarrier could be used to visualize the tumor while the drug is being released at the targeted site. Most commercially available Quantum dots consist of three parts: a core, a shell, and a capping material. The core consists of a semiconductor material, e.g., CdSe. Another semiconductor, such as ZnS is used to build up shell surround the semiconductor core. A cap encapsulates the double layer Quantum dots with various materials. Quantum dots based Smart drug delivery systems have attracted significant interest for several reasons. (8) First, QDs possess an extremely small core size of 2–10 nm in diameter. This characteristic makes it useful as a tracer in other drug delivery systems. Second, versatile surface chemistry allows different approaches for the surface changes of QDs. Third, their photo-physical properties provide QDs extra mileage for real-time monitoring of drug-carrying and drug release.(14) To synthesize QDs, either a top-down approach or a bottom-up method can be employed. PEGylation is an excellent solution for QDs as well Properly PEGylated QDs are able to accumulate in tumor sites by an enhanced permeability and retention (EPR) effect without a targeting ligand. To actively target a tumor site, various ligands such as peptides, folate, and large proteins (monoclonal antibodies) can be grafted on the QD surface. They covalently linked Quantum dots to the tumor targeting module biotin to find the biotin receptor overexpressed on tumor cells. This system can successfully release a drug under pH stimulus. (13, 14, 15)

Recently approved marketed drugs for cancer therapy

Drug product	Active ingredients	Drug delivery	Indications	Approval year
Abraxane	Nab paclitaxel in combination with gemcitabine	Nano spheres	Metastatic pancreatic cancer	2013
Myocet	Doxorubicin	Liposomes	Breast cancer	2000
Marqibo	Vincristine	Liposomes	Philadelphia chromosome negative lymphoblastic leukemia	2012
Doxil/Caelyx	Doxorubicin	Liposomes	Ovarian, breast cancers	1995-2008
Onivyde	Irinotecan	Liposomal	Pancreatic cancer	2015
Depocyt	Cytarabine	Liposomal injection	Lymphomatous	1999

Doxorubicin hydrochloride	Doxorubicin hydrochloride	Liposomal	Bone cancer	2013
Cosmegen	Dactinomycin	i.v injection	Bone cancer	2019
Erbitux	Cetuximad	i.v injection	Colorectal Cancer	2004
Eloxatin	Oxaliplatin	i.v injection	Colorectal Cancer	2004
Keytruda	Pembrolizumab	i.v injection	Metastatic small cell lung cancer	2015
BiNU	Carmustine	i.v injection	Brain cancer	2018
Abraxane	Paclitaxel albumin-stabilized nanoparticle formulation	i.v injection	Non small cell lung cancer	2006

Conclusions and Future Perspectives

The present review discusses the recent trends in NP design have led to the development of drug-delivery systems that can overcome several physiological and clinical barriers associated with the traditional administration of chemotherapeutic agents. The main aim of efficient nanostructured delivery systems is to reduce the drug dose needed to achieve a specific therapeutic effect, thus lowering the costs and reducing the side effects associated with their use. The two main categories of organic and inorganic nanostructured materials widely used in drug delivery processes present a variety of complementary and synergistic properties that can be profitably exploited. Future, Nano medicine based drug delivery system still looks promising, where it can provide a better outcome in cancer therapy. Besides, more new attempts must be designed for targeting moiety to reduce the toxicities, which are the major problem for cancer drugs.

References

- [1] Sarwar Hossen, M. Khalid Hossain, M.K. Basher, M.N.H. Mia, M.T. Rahman, M. Jalal Uddin, Smart Nano carrier-based drug delivery systems for cancer therapy and toxicity studies; 23 June 2018.
- [2] Sudipta Senapati, Arun Kumar Mahanta, Sunil Kumar and Pralay Maiti, Controlled drug delivery vehicles for cancer treatment and their performance; (2018) 3:7 <https://doi.org/10.1038/s41392-017-0004-3>.
- [3] Jayanta Kumar Patra, Gitishree Das, Leonardo Fernandes Fraceto, Estefania Vangelie Ramos Campos, Maria del Pilar Rodriguez-Torres, Laura Susana Acosta-Torres, Luis Armando Diaz-Torres, Renato Grillo, Mallappa Kumara Swamy, Shivesh Sharma, Solomon Habtemariam and Han-Seung Shin Nano based drug delivery systems: recent developments and future prospects; (2018) 16:71 <https://doi.org/10.1186/s12951-018-0392-8>
- [4] Dong Liu, Fang Yang, Fei Xiong, and Ning Gu The Smart Drug Delivery System and Its Clinical Potential; 2016; 6(9): 1306-1323. doi: 10.7150/thno.14858
- [5] Domenico Lombardo, Mikhail A. Kiselev, and Maria Teresa Caccamo, Smart Nanoparticles for Drug Delivery Application: Development of Versatile Nanocarrier Platforms in Biotechnology and Nanomedicine; Volume 2019, Article ID 3702518, 26 pages <https://doi.org/10.1155/2019/3702518>
- [6] Regina-veronicka Kalaydina, Komal Bajwa, Bessi Qorri, Alexandria Decarlo Myron R Szewczuk, Recent advances in “smart” delivery systems for extended drug release in cancer therapy; 2018:13 4727–4745
- [7] Muhammad Asim Farooq, Md Aquib, Anum Farooq, Daulat Haleem Khan, Mily Bazezy Joelle Maviah, Mensura Sied Filli, Samuel Kesse, Kofi Oti Boakye-Yiadom, Rukhshona Mavlyanova, Amna Parveen & Bo Wang, Recent progress in nanotechnology-based novel drug delivery systems in designing of cisplatin for cancer therapy; 08 May 2019.
- [8] Sugapriya Dhanasekaran and Sumitra Chopra, Getting a Handle on Smart Drug Delivery Systems –A Comprehensive View of Therapeutic Targeting Strategies; <http://dx.doi.org/10.5772/61388>
- [9] Paola Sánchez-Moreno, Juan Luis Ortega-Vinuesa, José Manuel Peula-García, Juan Antonio Marchal, e and Houria Boulaiz, e,* Smart Drug-Delivery Systems for Cancer Nanotherapy.
- [10] Dimendra J Patel*1, Pratik A Mistri1, Jatin J Prajapati1 1Department of pharmaceuticals, Baroda College of Pharmacy, Limda, Vadodara – 391760, Treatment of cancer by using Nanoparticles as a Drug Delivery.

- [11] BENJAMIN N. HO, CLAIRE M. PFEFFER and AMARESHWAR T.K. SINGH, Update on Nanotechnology-based Drug Delivery Systems in Cancer Treatment.
- [12] Janice Leung, Recent Advances in Nanoparticle-Based Cancer Drug Delivery.
- [13] Stephanie Tran^{1,†}, Peter-Joseph DeGiovanni^{1,2,†}, Brandon Piel^{2,†} and Prakash Rai^{2*}, Cancer Nano medicine: a review of recent success in drug delivery.
- [14] Catarina Oliveira Silva ^{1,†} , Jacinta Oliveira Pinho ^{1,†}, Joana Margarida Lopes ² , António J. Almeida ¹ , Maria Manuela Gaspar ^{1,*} and Catarina Reis ^{1,3}, Current Trends in Cancer Nanotheranostics: Metallic, Polymeric, and Lipid-Based Systems.
- [15] Ankita Dadwala,^b Ashish Baldib and Raj Kumar Naranga, Nanoparticles as carriers for drug delivery in cancer.

