ISSN No:-2456-2165

Impact of Novel Techniques of Smart Drugs Delivery System for Cancer Treatment and its Challenges

Tarun Kumar
Department of pharmaceutical sciences, HNB Garhwal University (A Central University), Srinagar, Uttarakhand 246001 (India)

Kuldeep saini
Department of pharmaceutical sciences, Kumaun University, (A Central University), Nainital, Uttarakhand 243136 (India)

Peeush Singhal*
Department of Pharmaceutical Sciences (FAMS), Gurukul Kangri University, Haridwar-249404 (India)

Abstract:- "A smart drug delivery system consists of intelligent nanocarriers, process selection, and relaxation techniques. This study highlights the recent novel development of Smart Drug Delivery Systems for a variety of technical nanocarriers, including liposomes, micelles, dendrimers, mesoporous silica nanoparticles, gold nanoparticles, super paramagnetic iron oxide nanoparticles, carbon nanotubes, and quantum dots and their impact on cancer treatments. This study is expected to be of widespread interest to those who are looking for new future research in this field and to those who are about to start their research into smart nano-carrier-based drug delivery. Smart Drug Delivery Systems could distribute drugs to low-dose sites and regulate means to remove the side effects that are otherwise induced by traditional drug delivery systems. Chemotherapy is widely used for treating cancer, which would be the world's second-largest cause of death." Choosing the best strategies for cancer cell detection follows the selection of an acceptable kind of nanocarrier. SDDs identify cancer sites by using the physiochemical variations between cancer cells and healthy cells. The location of the cancer cells is described precisely by two main methods: passive targeting and active targeting. Passive targeting allows for the cancer site to be recognized implicitly by using the Enhanced Permeability (EPR) effect. Active targeting uses cancer cell surface receptors which are over expressed specifically for targeting cancer cells. The next move is to discharge drugs at a particular concentration at the stated site. Drugs can be released by external or internal stimulation from nanocarriers, depending on the shape and smartness of nano-carriers.

Keywords:- *Novel techniques, smart drugs delivery system (SDDS), cancer, treatment, challenges.*

I. INTRODUCTION

Cancer is the world's second-largest cause of death. "It is responsible for reported deaths of 9.6 million in 2018. About 1 in 6 deaths worldwide are due to cancer. Around 70 percent of cancer deaths occur in low- and middle-income countries such as India [1, 2]. Chemotherapy [3, 4] plays a vital role in the treatment of the micro-focuses on undetectable cancer and free cancer cells. Chemotherapy chemicals destroy or block cancer cell growth [5]. As cancer cells evolve faster than healthy organisms, the key targets of chemotherapeutic agents are fast-growing cells; and as there are healthier cells that still grow rapidly, chemotherapy drugs often destroy such fast-growing healthy cells. This needless attack causes a malfunction in traditional chemotherapy [6]. Moreover, multidrug resistance (MDR)[7–9] provides another big impediment to effective chemotherapy. By developing cytotoxic drug tolerance during or shortly after therapy, MDR helps cancer cells avoid the chemotherapeutic impact. Conventional chemotherapy drawbacks have led to the development of advanced Nano carrier-based drug delivery schemes, also known as the Advanced Drug Delivery System (SDDS). SDDSs consent to prescribe medications to particular targeted sites [10]. While Paul Ehrlich's magic bullet concept [11]is the cornerstone of the connection between drug delivery and nanoparticles, Speiser et al. [12] first reported well-controlled active delivery using a bead polymerization technique.

The SDDS are the basis for Nano carriers. Unfortunately, not all kinds of Nano carriers are effective as drug carriers in SDDSs. In order to qualify as an ideal Nano carrier in SDDSs, a Nano carrier should meet certain basic criteria, addressed in detail in the related sections. This analysis highlights the most known Nano carriers: Liposomes, micelles, dendrimers, mesoporous silica nanoparticles (MSNs), gold nanoparticles (GNPs), super-paramagnetic iron oxide nanoparticles (SPIONs), carbon nanotubes (CNTs), and quantum dots (QDs) in their structure, classification, synthesis, and smartness. Choosing the best cancer cell detection strategies follows the selection of a suitable kind of Nano carrier. SDDS uses the physiochemical differences between cancer cells and healthy cells in order to recognize cancer sites. The cancer cell site is precisely defined by two main methods: passive targeting and active targeting. Passive targeting enables an implied detection of the cancer site by the use of the Enhanced Permeability (EPR) effect [13]. The direct response uses surface receptors of cancer cells that are expressed on

ISSN No:-2456-2165

the surface to specifically target cancer cells like a guided missile [14]. The next step is to release drugs at the specified location at a specific concentration. Medicines may have been released from either the Nano carriers by external or internal stimulation, depending on the form of Nano carriers and their intelligence [15].

This study concentrates on three different forms of DDS nanoparticles reflecting different sources of nanoparticles materials: nanoparticles (MSNs), gold nanoparticles (GNPs), super-paramagnetic iron oxide nanoparticles (SPIONs), carbon nanotubes (CNTs). They integrate the methods and applications in providing smart drugs for effects on cancer care. The study also outlines the current barriers that nanoparticles could face for clinical use, and the future development of DDS nanoparticles.

II. SCOPE AND CHALLENGES

SDDS reflects no exception. The obstacles to efficient SDDSs are the toxicity of the Nano carriers of the human body, cost-effectiveness of the system, diversity and heterogeneity in cancer, and lack of clear regulatory guidance. Nano carriers carry and activate the anticancer drugs at the targeted sites to destroy the cancer cell. The concern is with the ultimate fate of drug-carrying Nano carriers. Traditional Nano carriers accumulate in different vital organs such as the lungs, spleen, kidneys, liver, and heart, depending on the chemical composition, size, form, specific surface area, surface charge, and the presence and absence of a shell around the Nano carrier. In animal cases, several in vitro and in vivo toxicity tests have been carried out; toxicity studies in the human body are, unfortunately, very limited. There is a large area available for toxicity research. In the transformation of CNTs into the best bioactive management modules, there are great challenges, including purification and dispersibility. Taking into account their positive characteristics such as biocompatibility, non-immunogenicity, stability, and easy modification, they appear to be very promising as drug delivery systems. However, limitations, such as the surface / mass ratio, non-biodegradability, and purification, pose challenges. In conclusion, before fully exploiting the potential of the CNT, it is imperative to generate data on their safety, effectiveness, and profitability.

III. IMPACT OF NOVEL TECHNIQUES OF SMART DRUGS DELIVERY SYSTEM

The drug delivery system (DDS) was clinically and preclinically used to distribute medicinal substances for the treatment of diseases. Conventional DDS is either given orally or by injection. Notwithstanding many benefits of traditional DDS, such as ease of administration and widespread acceptance by patients. A smart drug delivery system utilizing liposomes as Nano carriers consist of smart Nano carriers carrying anti-cancer drugs to the cancer site, cancer site location mechanisms, and pre-located cancer site stimulation techniques. The following sections analyze eight Nano carriers in detail, their targeting mechanisms, and stimulus techniques.

Smart Nano carrier particles in the order of 1–100 nm are popularly known as nanoparticles, with at least one dimension. Currently, nanoparticles are graded as Variable Surface Volume (VSSA). Nanoparticles are generally defined as particles with a volume of VSSA equal to or greater than 60 m2 / cm3 of the material [16]. If nanoparticles are used as transport tubes for other compounds, they'll be called Nano carriers. Conventional Nano carriers do not have the ability to retain and release drugs at the right concentration on the target site, under external or internal strain. Therefore archetypal Nano carriers aren't smart. They have to be changed or functionalized to make them smart. Smart Nano carriers should have the following characteristics. Second, smart Nano carriers can prevent surgery from cleaning up the body's immune system. Second, they can accumulate only at the target site. Thirdly, smart Nano carrier will release the cargo at the targeted site at the correct concentration under external or internal stimulation. Finally, chemotherapeutics and other items should be co-delivered, such as genetic materials, imaging agents, etc.[17–19].

There are several steps to turn traditional Nano carriers into intelligent ones, depending on the Nano carriers types and applications (Table .1). Second, Nano carriers face many biological barriers including the reticuloendothelial system (RES) cleaning up on the way to the intended location. The RES briefly takes the Nano carrier out of circulation and accumulates in the liver, spleen, or bone marrow some Nano carriers carrying anti-cancer drugs. PEGylation is a special way of finishing the washing process. PEGylation lets Nano carriers escape RES. First described on PEGylation, by Davies and Abuchowsky[20]. Unfortunately, PEGylation greatly decreases cell intake of medicinal products [21, 22]. This twist is known as the PEGylation dilemma [23, 24]. Second, Nano carriers can be functionalized to distinguish the cancer cells precisely out of healthy ones. The physiochemical variations between cancer cells and healthy ones are the distinguishing marks that distinguish the two types of cells. The surface of the cancer cells overexpresses a few proteins. The main destinations of the smart Nano carrier are the over-expressed proteins. The Nano carriers are modified with ligands to balance the overexpressed proteins. The smart Nano carrier’s ligands identify the receptor proteins into cells. Thirdly, delivering the drug to the destination site is not the end of the process. The next big challenge is to free up the drug under pressure from the smart bag. To make Nano carriers sensitive to the stimulus system, different chemical groups may be grafted on the surface of the Nano carriers. Fourth, it also modifies the codelivery of anti-cancer drugs along with other substances, including genetic materials [25], imaging agents, or even additional anti-cancer drugs. Liposomes, micelles, dendrimers, GNPs, quantum dots, and MSNs show co-delivery promise [26–30]. Eight promising Nano carriers are discussed in detail below concerning their structure, classification, synthesis, and smartness (Table.1).

ISSN No:-2456-2165

Subject	Novel Techniques/Research Gap	Future Recommendation
Smart nanocarriers	PEGylation[20]. This having some research gap either than liposome.	PEGylation greatly decreases cell intake of medicinal products[21,22]Various studies indicate the possibility of stopping the cancer-causing by PEGylation
Liposome and its smartness	largeuni-lamellar (LUV) vesicles and small uni-lamellar (SUV) vesicles[33,34]. This having some research gap either than Micelles	Liposome to target the cancer site specifically. Several studies indicate the possibility of stopping the cancer-causing byliposome
Micelles and its smartness	PG-PCL, PEEP-PCL[64], PEG-PCL[65] and PEG-DSPE[66]. This having some research gap either than Dendrimers	The co-delivery technique, using a multifunctional micelle, is very important for the synergetic effects in cancer treatment. Several studies indicate the possibility of stopping the cancer-causing byMicelles
Dendrimers and its smartness	nucleus, dendron-branching, and surface-active groups[75], poly (PPI or POPAM), PAMAM, POPAM, POMAM[78], polylysinedendrimer, dendritic hydrocarbon, dendrimer based on carbon / oxygen, dendrimer based on porphyrin, ionic dendrimer, silicon based dendrimer, dendrimer based on phosphorus[79], and Newkomedendrimer[80]. This having some research gap either than mesoporous silica	The cationic nature of PAMAM, among other dendrimers, makes this extremely useful for the transmission of genetic materials. Many studies indicate the possibility of stopping the cancer-causing byDendrimers
Nanoparticles from mesoporous silica and its smartness	porous silica (SiO2), mixtures of zeolite-silica gel with a well-defined and uniform porosity[96] Usually there are two types of MSNs, namely (1) ordered hollow or rattle-like meso-porous silica NPs (MCM-41, MCM-48, and SBA-15), and (2) meso-porous silica NPs[102]. This having some research gap either than Gold nanocarriers	Its controlled drug delivery capacity. So many studies indicate the possibility of stopping the cancer-causing by various kind of nanoparticles from mesoporous silica.
Gold nanocarriers and its smartness	GNPs [113] are metal nanocarriers that come in special shapes and sizes. GNPs have excellent prospects as metallic candidates to carry payloads. This having some research gap either than SPIONs	Various ligands can change the surface of GNPs for targeted delivery of drugs. Various studies indicate the possibility of silencing the cancer-causing gene by transfection of GNP
Super paramagnetic iron oxide nanoparticles (SPIONs) and its smartness	The SPIONs group also includes mixed iron oxides, such as copper, cobalt, and nickel. As magnetic particles are reduced to 10–20 nm they show a strange phenomenon called super para-magnetism [130,131]. This having some research gap either than CNTs	SPION synthesis methods are distinct, including co-precipitation processes, thermal decomposition, hydrothermal, micro-emulsion, sono-chemical, microwave-assisted synthesis. Some studies indicate the possibility of stopping the cancer-causing bySPIONs
Carbon nanotubes (CNTs) and its smartness	There are two types of CNTs: single walled (SWCNT) and multi-walled (MWCNT) [141,142]. This having some research gap either than QDs	Functionalized CNTs can be used as early cancer diagnostic instruments [153]. Many studies indicate the possibility of stopping the cancer-causing byCNTs
Quantum dots (QDs) and their smartness	QD-based SDDSs had drawn significant attention for a variety of reasons. QD's have a tiny core diameter of 2–10 nm. This having some research gap either than current new possibilities.	QDs are especially common for cancer imaging, due to their inherent florescence. Some studies indicate the possibility of stopping the cancer-causing byQuantum dots

Table 1: Novel techniques of smart drugs delivery system have played more important role for the cancer treatment

A. LIPOSOME AND ITS SMARTNESS

Liposomes [31], based on phospholipids are naturally occurring amphipathic nanocarriers. Phospholipids, an essential part of the cell membrane, consist of a hydrophobic fatty acid tail and a phosphate-dependent hydrophilic head. Gregory Gregordians demonstrated in 1973 that when phospholipids are introduced into an aqueous medium, they self-assemble into a two-layer vesicle with the non-polar ends forming a bilayer, and the polar ends facing the water. The center of the bilayer will pull water or water-soluble medicines [32] in. Depending on the number of bilayers and the size of the liposome, there are two forms: multi-lamellar vesicles and uni-lamellar vesicles It is possible to divide uni-lamellar vesicles further into two groups: large uni-lamellar (LUV) vesicles and small uni-lamellar (SUV) vesicles [33, 34]. Many methods for preparing liposomes [35, 36] are available,

ISSN No:-2456-2165

including the thin film hydration process or the Banghammethod [37], reverse phase evaporation [38], solvent injection technique [39], and detergent dialysis [40]. Many failures are linked to conventional methods. To overcome these constraints, some revolutionary technologies such as supercritical fluid technology, a supercritical anti-solvent method [41], and supercritical reverse-phase evaporation [42] have been built.

Conventional liposomes have many problems, including instability, insufficient preparation of drugs, the quicker release of drugs, and shorter circulation times in the blood, so they are not wise. Conventional liposomal functionality [44], makes them intelligent. Like other nanocarriers, liposomes need to resolve the RES issue, too. PEGylation allows the liposomes to escape RES. PEGylated liposomes, therefore, have a longer circulating time in the blood [45]. Smart nanocarriers can compute the difference between healthy cells and cancerous ones. Monoclonal antibodies, antibody fragments, proteins, peptides, vitamins, carbohydrates, and glycoproteins are usually grafted onto the liposome to target the cancer site specifically [46–49]. Smart liposomes are responsive to various external and internal stimulants including changes in pH, transformation of enzymes, redox reactions, light, ultrasound, and microwaves [50–52]. A radio-ligand-functionalized liposome is recognized as a liposome marked with radiation. Radiolabeled liposomes [53] can be used to determine the biodistribution of liposomes in the body and to diagnose the tumor in accordance with treatment. Theranosticliposomes [55, 56] are classified as liposomes that can contain both therapeutic agents as well as imagery [54]. In addition to providing imaging agents along with chemotherapy, liposomes are promising in the co-delivery of two chemotherapeutic drugs, chemotherapeutic gene agents [57] and chemotherapeutic anticancer drugs [58].

B. MICELLES AND ITS SMARTNESS

Having both hydrophilic and hydrophobic elements, amphiphilic molecules show peculiar self-assembly characteristics when exposed to a solvent. If the solvent is hydrophilic and its concentration reaches the critical concentration of the micelle (CMC), the polar parts of the co-polymer are drawn toward the solvent, while the hydrophobic parts are oriented away from the solvent. The hydrophobic portions thus form a nucleus, whereas the hydrophilic portions form a crown. This type of arrangement is called a polymeric micellar direct or regular [59, 60]. Amphiphilic molecules exposed to a hydrophobic solvent on the other hand build a reverse structure known as a reverse micelle. That is, in a reverse micelle, the hydrophilic portions make the heart and the hydrophobic portions make the corona [61–63]. Examples of some micelles are PG-PCL, PEEP-PCL [64], PEG-PCL [65], and PEG-DSPE [66].

The processing of micelles is based on the copolymer solubility used [67]. Two processes are used for a relatively water-soluble co-polymer, namely the direct dissolution method and the casting process for films. By contrast, dialysis or oil is used in water treatment because the co-polymer is not readily water-soluble [68, 69]. By crossing the CMC, Micelles can experience the immature release of the drugs. In addition, animals blood contact and plasma protein absorption can disrupt the micelle-blood balance. The solution to that problem is a smart micellar. Usually, micelles are cross-linked to overcome the aforementioned problems; that is, they bind two polymer chains by forming disulfides [70]. There are two types of cross-linking schemes: core cross-linking polymer micelles, and cross-linking polymer micelles. Various types of ligands are used to actively target cancer cells to decorate the micellar surface, including folic acid, peptides, carbohydrates, antibodies, aptamers, and so on[66]. The micelle's heart or corona may be functionalized at the right concentration to activate the anti-cancer drug. In micellular SDDSs, the stimuli used are pH gradients, temperature changes, ultrasound [71], enzymes, and oxidation [66]. The co-delivery technique, using a multifunctional micelle, is very important for the synergetic effects in cancer treatment. Seo et al .have reported a method of co-delivery based on the temperature-responsive micelle, which can hold genes together with anti-cancer drugs [72]. In cancer detection and monitoring, single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and ultrasonography all play an important role. The surface of the micelle can be drawn with an imager[73]. Kennedy and colleagues reported combined doxorubicin delivery with ultrasound imaging of tumors [74].

C. DENDRIMERS AND THEIR SMARTNESS

Polymers with several branches are called dendrimers and can be represented as a suction cup graphically. There are three distinct sections of Dendrimer: nucleus, dendron-branching, and surface-active groups [75]. The dendrimer's physiochemical properties are calculated on the dendrimer surface by the active groupings. Depending on the surface groups this can be either hydrophobic or hydrophilic. Because of its nanoscale size, its monodispersenature [76], water-solubility, bio-compatibility, and highly branched structure, it is of great interest. Because of the size of the nanoscale, it growing to be used as a drug carrier [77]. The branched structure makes polyvalent the dendrimer. Moreover, all its active surface groups face outwards, resulting in a greater degree of encapsulation of the compound. Different forms of dendrimer have been reported, such as poly (PPI or POPAM), PAMAM, POPAM, POMAM[78], polylysinedendrimer, dendritic hydrocarbon, dendrimer based on carbon/oxygen, dendrimer based on porphyrin, ionic dendrimer, silicon-based dendrimer, dendrimer based on phosphorus[79], and Newkomedendrimer[80]. Dendrimer model approaches which are commonly known include the divergent method [81] and the convergent method [82], respectively. Fritz Vogtle et al. in 1978 first introduced to Dendrimers[83]. The poly (amidoamine) of Tomalia (PAMAM) [84, 85] and the 'arboreal system' of Newcome[86,87] are the dendritic structures that have been extensively investigated and gained widespread attention.

Conventional dendrimers face rapid clearance of the immune system and lower absorption of cells from cancer. Adjustment to dendrimer is the solution to those limitations. Chemical modification, linear polymer copolymerization,

ISSN No:-2456-2165

and hybridization with other nanocarriers, as mentioned to date [89], are options to overcome those limitations. Peptides, proteins, carbohydrates, aptamers, antibodies, etc. may modify the surface of dendritic structures to actively target the cancer site. For different stimulus-responsive systems such as light, heat, pH transfer, protein, and enzyme transformation, the dendrimer surface can also be changed [90, 91]. The cationic nature of PAMAM, among other dendrimers, makes this extremely useful for the transmission of genetic materials. Efficiency in distribution is a function of producing PAMAM. In 1993 Haensler and Szoka were the first to announce the availability of PAMAM based nucleic acid [75, 92]. A very promising tumor-imaging dendritic contrast agent [93].

D. NANOPARTICLES FROM MESOPOROUS SILICA AND ITS SMARTNESS

Mesoporous materials are materials containing pores in diameters between 2 and 50 nm, as described by IUPAC [94]. MSNs [95] have porous silica (SiO2) structures similar to that of a rabbit. 40 years ago, the term MSN was coined to describe mixtures of zeolite-silica gel with a well-defined and uniform porosity [96]. MSNs are widely studied because of their tunable particle size (50 nm to 300 nm), uniform and adjustable pore size (2–6 nm) [97], large area, high pore volume, and biocompatibility [98–100]. Tunable particle size is an important requirement for being a smart nanocarrier, and the size of the tunable pore allows the loading of drugs of different molecular types. The high surface areas of the inner (pores) and outer surface are suitable for grafting on MSNs of different functional classes. Besides bio-compatibility, the adhesion of this carrier to cancer cells by the action of the EPR makes it a great choice for them [101]. Usually, there are two types of MSNs, namely (1) ordered hollow or rattle-like mesoporous silica NPs (MCM-41, MCM-48, and SBA-15), and (2) mesoporous silica NPs[102,104,105]. Among those MSNs, MCM-41, synthesized by a Mobil Corporation scientist, is the most researched MSN for Biomedical Applications. In 2001, MCM-41 became known for its controlled drug delivery capacity [96]. Methods for generating MSNs are the soft template method and the hard template method [106-110].

E. GOLD NANOCARRIERS AND THEIR SMARTNESS

Due to their unique features such as customizable size, large surface-to-volume ratio, easy synthesis, noble optical properties, cancer cell thermal ablation, and quick surface functionalization, metallic nanocarriers are of considerable interest [111]. Studies show that the size and shape of the colloidal nanocarriers depend on the intercellular take-up of nanocarriers[112]. GNPs [113] are metal nanocarriers that come in special shapes and sizes. GNPs have excellent prospects as metallic candidates to carry payloads. Payloads may be drug molecules or large bimolecular like proteins, DNA, and RNA. GNPs are also interesting because of the surface plasmon resonance (SPR) phenomenon [114,115] which enables them to convert light to heat and disperse the heat produced to kill the cancer cells. GNPs are mainly synthesized by a variety of paths, including chemical [116], physical [117], and biological [118,119]. The blood-brain barrier (BBB) [120] could be greatly surmounted by greasing GNP surfaces with proper ligands. Smart nanocarriers should be chemically stable in biological media, biocompatible, efficient in targeting, and sensitive to external or internal stimuli. Unmodified GNPs are unstable in blood and face a higher absorption of RES. To surmount these limits, gold nanocarriers need to be PEGylated. Under physiological conditions, PEGylated GNPs exhibit greater solubility and stability [122]. Various ligands can change the surface of GNPs for the targeted delivery of drugs. For example, transferrin (TF) can be grafted to the surface of GNPs, because many tumors over-express the TF receptor on their surface [123]. Even folic acid may alter the surface of GNP since folic acid receptors are often overexpressed on different tumor cells [124,125]. The substance can be discharged from GNP by either (1) external stimuli (laser, ultrasound, and X-ray, light [126] or (2) internal stimuli (pH, redox, metalloproteinase matrix)[127]. Various studies indicate the possibility of silencing the cancer-causing gene by transfection of GNP [128]. GNPs combined with fluorescently labeled heparin can be used to diagnose cancer sites [129].

F. SUPERPARAMAGNETIC IRON OXIDE NANOPARTICLES (SPIONS) AND THEIR SMARTNESS

In 1960 Freeman et al. proposed the concept of using magnetic materials along with magnetic fields in medicine [109]. The magnetic materials have the commonly studied SPIONs. Two SPIONs are small, synthetic maghemite and magnetite particles (Fe3O4) with cores ranging in diameter from 10 to 100 nm. The SPIONs group also includes mixed iron oxides, such as copper, cobalt, and nickel. As magnetic particles are reduced to 10–20 nm they show a strange phenomenon called super para-magnetism. When applying a magnetic field, the magnetic nanoparticles are magnetized to their saturation but do not have any residual magnetism after removing the magnetic field [130,131]. Production of SPIONs includes three processes including a physical process, a wet chemistry process, and a microbial system [132]. SPION synthesis methods are distinct, including co-precipitation processes, thermal decomposition, hydrothermal, micro-emulsion, sonochemical, microwave-assisted synthesis [133]. Chemical synthesis is amongst others the most prevalent.

The functionality builds on the smartness of post-manufactured SPIONs. Functionalization prevents aggregation of SPIONs, protects their surfaces from oxidation, provides a barrier for drug conjugation and ligand targeting increases blood circulation by avoiding RES, and decreases non-specific targets [130]. Stimulus-responsive polymer-coated SPIONs undergo intensive research for selective drug delivery. Responsive polymers undergo physical and chemical transformations including process, hydrophobicity, solubility, and conformation. A recent study has shown that polymer-modified SPIONs are dually sensitive to pH gradients and temperature changes [135]. For regulating the carrier an external magnetic field can be used. Because of the existence of the phosphate group, nucleic acids are negatively charged; thus SPIONs can be modified to carry genetic materials with cationic lipids and polymers [136]. SPIONs are members of the theranostic-property family of nanocarriers. This is observed by an external magnetic field as a magnetic nanocarrier[137,138].

ISSN No:-2456-2165

G. CARBON NANOTUBES (CNTS) AND THEIR SMARTNESS

The CNTs are a type of fullerene, a class of hollow spheres, ellipsoid, tubes, and several other types of allotropic carbon [139,140]. The type is called the CNT when a sheet of graphene is rolled up into a smooth cylindrical tube. There are two types of CNTs: single-walled (SWCNT) and multi-walled (MWCNT) [141,142]. The strong optical absorption of the CNT in the near-infrared region makes this particle a good candidate for photothermal ablation; however, nanoparticles with sizes ranging from 50 to 100 nm are easy to absorb. MWCNTs may cross the boundary between various cellular compartments, and PEGylated SWCNTs may be located in a specific cellular compartment. The CNTs can be synthesized by heating carbon black and graphite in a controlled flame environment. But this method cannot control the shape, scale, mechanical strength, consistency, and purity of the synthesized CNTs. Electric arc discharges [142,143,144], the chemical vapor deposition method [145,146,147], and the laser ablation method have been reported to address the limitations of the controlled flame collection. SWCNTs are more efficient in drug delivery than MWCNTs because of the better-defined SWCNT walls and comparatively more structural MWCNT defects [5,144,148,149,150-153].

H. QUANTUM DOTS (QDS) AND THEIR SMARTNESS

Quantum dots[154], semiconducting fluorescent nanocarriers, often consisting of hundreds to thousands of group II and group VI atoms and possessing unique photophysical properties[155]. This nanocarrier may be used when releasing the drug at the desired position to image the tumor. The majority of commercially available QDs are made up of three components: a nucleus, a shell, and a cap. The center consists of a semiconductor material, e.g. CdSe. See. Another semiconductor, such as ZnS, is used to create shells that surround the semi-conductor center. A cap encapsulates the double layer QD's with various materials [156]. QD-based SDDSs had drawn significant attention for a variety of reasons. QD's have a tiny core diameter of 2–10 nm. This role renders it useful as a tracer in other drug delivery systems. Second, versatile surface chemistry enables different approaches to modification of the surface of QD. Third, their photophysical properties provide extra QD mileage for real-time monitoring of drug-carrying and drug release [157]. To synthesize QD's, either a top-down approach or a bottom-up process can be used. Molecular beam epitaxy (MBE) [158], ion implantation, e-beam lithography, and x-ray lithography [159] are part of top-down processing; on the other hand, colloidal QDs are prepared by self-assembly in chemical reduction solution, which is a bottom-up approach[160]. As with other smart nanocarriers, the functionalization of archetypal QDs also plays an important role. As recorded for other nanocarriers, QDs also experience non-specific RES uptake. PEGylation is also a fantastic remedy for QDs. Properly PEGylated QDs can accumulate in tumor sites without a targeting ligand through an increased permeability and retention (EPR) effect. In order to effectively target a tumor site, various ligands such as peptides, folate, and large proteins (monoclonal antibodies) can be grafted onto the QD surface [162]. Iannazzo and others. The promising prospects of controlled drug delivery based on graphene QD have recently been demonstrated. They covalently attached QDs to the tumor-targeting module, biotin, to find the biotin receptor overexpressed on tumor cells. This process will successfully release a drug under pH stimulation [163]. QDs are especially common for cancer imaging, due to their inherent fluorescence. A complex of folic acids has been used to diagnose ovarian cancer [164]. Chemotherapeutic and siRNA co-delivery was developed to combat MDR [165]. Gao et al .researched and optimized bioconjugated and polymer-encapsulated QD samples for cancer imaging [166,167].

IV. MECHANISM OF CANCER TREATMENT AND IMPACT OF STIMULUS

When the anti-cancer drug-carrying intelligent nanocarrier passes the cleaning phase of our body's immune system, then the smart nanocarrier can find the cancerous area of the body. A smart drug delivery system uses two ways of focusing: passive targeting and active targeting [168,169]. Passive targeting makes use of the EPR effect [170] for the cancer site role. Successful targeting uses the ligand-receptor technique to locate the ultimate objective-the individual cancer cell.

A. Passive targeting

The penetration rate of drug-laden nanocarriers 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 corporeal drainage system is the lymphatic channel. A defect in the lymphatic system contributes to nanoparticles deposited in the tumor. This retention is known as the enhanced retention effect. Both phenomena are collectively known as the EPR [171] effect. Compared to healthy body tissue, the concentration of anti-cancer drugs in the tumor could be multiply increased by using this EPR effect. Another barrier to efficient accumulation of drug-laden nanocarriers in a solid tumor is interstitial fluid pressure (IFP)[172,173]however; successful nanocarrier modifications can overcome many biological barriers, including IFP and RES[174].

B. Active targeting

Active targeting means directing the nanocarriers that deliver the drug into cancer cells, such as guided missiles [175]. Cancer cells and regular cells can be distinguished in terms of cell surface receptor expression and antigen production. Cell surface receptors are proteins found in the cell membrane that are responsible for trans-membrane communication. Cancer cells have various cell surface receptors usually recognized as cell markers such as folic acid and cell surface antigen suppression or overexpression. Drug-packed nanocarriers are equipped with targeting ligands. These ligands recognize their corresponding target on the surface of over-expressed cancer cells. Some ligands examined include folate, transferrin, anticorps, peptides, and aptamers.

ISSN No:-2456-2165

C. The stimulus for drug release

Both kinds of stimuli are exogenous and are endogenous. An extra-corporeal signal is known as a temperature shift for the extraction of drugs from nanocarriers, such as a magnetic field, electromagnetic waves, an electric field, an exogenous stimulus. An endogenous stimulus is called a signal that is produced from within the body to release anti-cancer drugs. Examples of endogenous triggers include pH transition, the transformation of the enzymes, temperature, and redox reactions [176].

D. Endogenous stimulus and its Impact

In the case of endogenous stimulation, the triggering signal comes from the internal pH level, the action of enzymes, and the action of body redox. Different forms of endogenous stimuli are discussed in more detail below [177].

E. The pH-responsive stimulus

According to the Warburg effect, the tumor cells produce energy primarily via enhanced glycolysis, followed by lactic acid fermentation in the cytosol[178]. This production of extra acids helps decrease the pH in cancer cells. The pH-responsive drug delivery mechanism is important because the pH level varies from organ to organ, and from tissue to tissue. In tumors, the extracellular pH has an acidic state compared to an intracellular pH much more stable [179]. Thus pH has been described as an important physiological property for the delivery of smart drugs to tumor sites across several studies. This acidic extracellular pH is the result of poor blood flow, hypoxia, and lactic acid [180] in tumors. The extracellular pH range approximately is 6–7[181]. Apart from this pH gradient between cells, there is a pH change between cell compartments. The lysosomal pH is approximately 5 while the cytosol has a pH of 7.2[182]. Usually, pH-sensitive nanocarriers store and stabilize anti-cancer drugs at physiological pH, then release the drug rapidly at a pH trigger stage; ensuring intracellular drug concentration reaches a peak. The goal can be accomplished by various methods 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 that result in the release of drugs.

F. Redox sensitive stimulus

Glutathione sulfhydryl (GSH) has the greatest efficacy as an antioxidant. It contains 3 amino acids. GSH is present in higher concentrations in any mammalian tissue [183]. GSH governs the reductive microenvironment. GSH concentration is at least four times higher in a tumor site than in normal cells. The intracellular concentration of GSH is 1000 times that of the bloodstream [70,184]. GSH, a functional group with an R-S-S structure, will reduce the disulfide bonds of the nanocarriers. Disulfide bond reductions lead to the release of an encapsulated drug[185]for instance, the GHS cell-site can reduce the disulfide bond of cross-linked micelles. Reducing disulfide bonds results in efficient unloading of nano-vehicle cargo [186].

G. Enzyme stimulus

The nanocarriers of the enzyme-stimulus are called nanocarriers whose surfaces are modified to make the nanocarriers responsive to enzyme bio-catalytic action. Enzymes are catalysts for biochemical reactions which are produced by living organisms. Enzymes play a key role in regulating the functioning of cells; thus, they are very important targets for drug delivery. Enzymetriggered approaches use the enzyme that is overexpressed from the extracellular environment of tumor sites. This technique does not apply to the release of intracellular drugs, because intracellular enzyme concentrations in cancer cells and healthy cells are approximately the same [187]. Proteases, an enzyme that breaks down proteins and peptides, are an ideal candidate for the extraction of liposomal drugs [188,189].

H. Exogenous stimulus

In extrinsic stimulation systems, contrast agents have been used to imaging the accumulation of nanocarriers in cancer sites. An external factor such as a magnetic field, ultrasonic waves, light and electric fields [190] stimulates the accumulated nanocarriers to release drugs at the correct concentration.

I. Magnetic field responsive stimulus

An extracorporeal magnetic field is used in magnetically induced systems after the injection of nanocarriers to store drug-charged nanocarriers in tumor sites. Some suitable candidates for magnetic stimulation are core-shell-shaped nanoparticles filled with silica, polymer, or magnetoliposome (liposome-encapsulated maghemitenanocrystals) [191,192]. Magnete-guided nanocarriers may also carry genetic materials. The magnetic nanocarriers emit heat in the surrounding medium when positioned under an oscillating magnetic field. This heat brings with it structural changes in nanocarriers[193–195].

J. Thermo-responsive stimulus

The drug-charged nanocarriers release their payloads in response to temperature changes in this process. At a predetermined temperature, the nanocarriers change their conformation, solubility, or hydrophilic and hydrophobic balance. A few nanocarriers release their cargo if they undergo a temperature change. The thermo-sensitive nanocarriers show a lower critical solution temperature (LCST) phenomenon [196,197]. The aqueous polymer solutions show one phase below LCST and above-temperature phase separation. There is a systematic thermo-responsive analysis of micelles [198, 1999]. Thermo-sensitive hydrogels and poly (N-isopropyl acrylamide) (PNIPAAm) display sol-gel reactive temperature transitions [200].

K. Light-triggered stimulus

The latest development of light-triggered drug delivery is a new path for the on-demand distribution of drugs. The light can be visible or near-infrared in the ranges of ultraviolet. The stimulation is accomplished by sensitizing the nanocarriers[201–203] to the sun. CNTs and GNPs are good candidates for light stimulation, especially for the Near Infrared Range (NIR). Nanocarriers of metal absorb light and heat the absorbed light to kill cancer cells [204].

ISSN No:-2456-2165

L. Ultrasound-responsive stimulus

Ultrasound is under comprehensive investigation for the extraction of drugs from nanocarriers due to its non-invasive properties, deep body penetration, and non-ionizing irradiation [205]. Using ultrasound can cause both mechanical and thermal effects to release the charged drug into the nanocarriers. Dromi et al.[206] used high-intensity ultrasound-based waves to investigate the release of drugs from temperature-sensitive liposomes in 2007 [207 208].

M. Electric field-responsive stimulus

This stimulation approach uses an electrical field to switch on payloads. The aforementioned thermo-responsive, light-triggered, and ultrasonic stimulating systems also require large or specialized drug release equipment. On the contrary, electric fields can be easily manufactured and regulated [209]. The conduction of polymers such as polypyrrole (PPy) is responsible for the electrical response stimulus. The nanocarriers are modified by conducting polymers, and the efficacy of conducting polymers depends on the choice of dopant and molecular weight of the medicine. Biotin is a dopant that has been tested experimentally [210]. MWCNTs can be used as a conductive additive to boost electrical conductivity [211]; however, hydrogels from polyelectrolytes are also considered [212,213].

V. CONCLUSION

In summary, Cancer varies in severity and heterogeneity; that is, cancers still have undetermined types. Furthermore, the physical nature of cancer may vary from one person to another. Personalizing anti-cancer treatment is also a significant challenge. DNA /RNA-focused anti-cancer therapies have a promising future for making medicines safer and more personalized. The Drug Delivery System (DDS) based on nanoparticles is considered promising in treating cancer. Compared to conventional DDS, the DDS based on nanoparticles shows enhanced efficacy by increasing the half-life of vulnerable drugs and proteins; enhancing the solubility of hydrophobic drugs and allowing controlled and targeted release of drugs to diseased sites[214]. Therefore the development of nanocarriers as carriers of DNA / RNA to destroy cancer cells can be a promising research field. The way traditional nanocarriers locate cancer cells, such as RES, rapid blood clearance (ABC), etc., faces several biological obstacles. Traditional nanocarriers are modified using different methods to resolve these barriers, including PEGylation, grafting ligands on the surface of nanocarriers; however, the nanocarriers need to be functionalized to release the drugs under stimulation at target sites. These modifications result in increased production steps which in turn lead to a higher final cost of the product. The cost-benefit balance should be beneficial for any product launched to be competitive on the market." Hence it would be said that these novel techniques of smart drugs delivery systems have played a more important role in cancer treatment and it obvious they have more challenges day by day.

ACKNOWLEDGEMENT

We thankful to Department of Pharmaceutical Sciences, H.N.B. Garhwal Central University, Srinagar, Uttarakhand, India, for providing Technical facilities.

- **Conflict Of Interset:** There is no conflict of interest.

REFERENCES

[1.] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: a cancer journal for clinicians. 2017; 65(1):5-29.

[2.] Cokkinides V, Albano J, Samuels A, Ward M, Thum J. American cancer society: Cancer facts and figures. Atlanta: American Cancer Society. 2005.

[3.] Chabner BA, Roberts TG. Chemotherapy and the war on cancer.Nature Reviews Cancer. 2005 Jan;5(1):65-72.

[4.] DeVita VT, Chu E. A history of cancer chemotherapy.Cancer research. 2008 Nov 1; 68(21):8643-53.

[5.] Zhang W, Zhang Z, Zhang Y. The application of carbon nanotubes in target drug delivery systems for cancer therapies.Nanoscale research letters. 2011 Dec; 6(1):1-22.

[6.] Ahmad SS, Reinius MA, Hatcher HM, Ajithkumar TV. Anticancer chemotherapy in teenagers and young adults: managing long term side effects. Bmj. 2016 Sep 7; 354.

[7.] Gillet J, Gottesman MM. Multi-Drug Resistance in Cancer. vol. 596.

[8.] Alfarouk KO, Stock CM, Taylor S, Walsh M, Muddathir AK, Verduzco D, Bashir AH, Mohammed OY, Elhassan GO, Harguindey S, Reshkin SJ. Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp. Cancer cell international. 2015 Dec; 15(1):1-3.

[9.] Nooter K, Stoter G. Molecular mechanisms of multidrug resistance in cancer chemotherapy. Pathology-Research and Practice. 1996 Jan 1; 192(7):768-80.

[10.] Gupta PK. Drug targeting in cancer chemotherapy: a clinical perspective. Journal of pharmaceutical sciences. 1990 Nov; 79(11):949-62.

[11.] Kreuter J. Nanoparticles—a historical perspective. International journal of pharmaceutics. 2007 Feb 22; 331(1):1-0.

[12.] Brossard C, Des Ylouses DL, Duchene D, Puisieux F, Carstensen JT. Dissolution of a soluble drug substance from vinyl polymer matrices. Journal of pharmaceutical sciences. 1983 Feb 1; 72(2):162-9.

[13.] Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer research. 1986 Dec 1;46(12 Part 1):6387-92.

[14.] Bae YH, Park K. Targeted drug delivery to tumors: myths, reality and possibility. Journal of controlled release. 2011 Aug 10; 153(3):198.

[15.] Ding C, Tong L, Feng J, Fu J. Recent advances in stimuli-responsive release function drug delivery systems for tumor treatment. Molecules. 2016 Dec; 21(12):1715.
[16.] Kreyling WG, Semmler-Behnke M, Chaudhry Q. A complementary definition of nanomaterial.Nano today. 2010 Jun 1; 5(3):165-8.
[17.] Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nature nanotechnology. 2007 Dec; 2(12):751-60.
[18.] Lee BK, Yun YH, Park K. Smart nanoparticles for drug delivery: Boundaries and opportunities. Chemical Engineering Science. 2015 Mar 24; 125:158-64.
[19.] Liu D, Yang F, Xiong F, Gu N. The smart drug delivery system and its clinical potential.Theranostics. 2016; 6(9):1306.
[20.] Abuchowski A, McCoy JR, Palczuk NC, van Es T, Davis FF. Effect of covalent attachment of polyethylene glycol on immunogenicity and circulating life of bovine liver catalase. Journal of Biological Chemistry. 1977 Jun 10; 252 (11):3582-6.
[21.] Moghimi SM, Szebeni J. Stealth liposomes and long circulating nanoparticles: critical issues in pharmacokinetics, opsonization and protein-binding properties. Progress in lipid research. 2003 Nov 1; 42(6):463-78.
[22.] Moghimi SM, Hunter AC, Murray JC. Long-circulating and target-specific nanoparticles: theory to practice. Pharmacological reviews. 2001 Jun 1; 53(2):283-318.
[23.] Knop K, Hoogenboom R, Fischer D, Schubert US. Poly (ethylene glycol) in drug delivery: pros and cons as well as potential alternatives. Angewandtechemie international edition. 2010 Aug 23; 49(36):6288-308.
[24.] Verhoef JJ, Anchordoquy TJ. Questioning the use of PEGylation for drug delivery.Drug delivery and translational research. 2013 Dec 1; 3(6):499-503.
[25.] Xu H, Li Z, Si J. Nanocarriers in gene therapy: a review. Journal of biomedical nanotechnology. 2014 Dec 1; 10(12):3483-507.
[26.] Qi SS, Sun JH, Yu HH, Yu SQ. Co-delivery nanoparticles of anti-cancer drugs for improving chemotherapy efficacy. Drug delivery. 2017 Jan 1;24(1):1909-26.
[27.] Kang L, Gao Z, Huang W, Jin M, Wang Q. Nanocarrier-mediated co-delivery of chemotherapeutic drugs and gene agents for cancer treatment. ActaPharmaceuticaSinica B. 2015 May 1;5(3):169-75.
[28.] Janib SM, Moses AS, MacKay JA. Imaging and drug delivery using theranostic nanoparticles. Advanced drug delivery reviews. 2010 Aug 30;62(11):1052-63.
[29.] Srinivasan M, Rajabi M, Mousa SA. Multifunctional nanomaterials and their applications in drug delivery and cancer therapy.Nanomaterials. 2015 Dec;5(4):1690-703.
[30.] Parvanian S, Mostafavi SM, Aghashiri M. Multifunctional nanoparticle developments in cancer diagnosis and treatment. Sensing and Bio-Sensing Research. 2017 Apr 1;13:81-7.
[31.] Bangham AD, Standish MM, Weissmann G. The action of steroids and streptolysin S on the permeability of phospholipid structures to cations. Journal of molecular biology. 1965 Aug 1;13(1):253-IN28.
[32.] Gregoriadis G. Drug entrapment in liposomes. FEBS letters. 1973 Nov 1;36(3):292-6.
[33.] Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, Samiei M, Kouhi M, Nejati-Koshki K. Liposome: classification, preparation, and applications. Nanoscale research letters. 2013 Dec;8(1):1-9.
[34.] Sharma A, Sharma US. Liposomes in drug delivery: progress and limitations. International journal of pharmaceutics. 1997 Aug 26;154(2):123-40.
[35.] Huang Z, Li X, Zhang T, Song Y, She Z, Li J, Deng Y. Progress involving new techniques for liposome preparation. asian journal of pharmaceutical sciences. 2014 Aug 1;9(4):176-82.
[36.] Carugo D, Bottaro E, Owen J, Stride E, Nastruzzi C. Liposome production by microfluidics: potential and limiting factors. Scientific reports. 2016 May 19;6(1):1-5.
[37.] Bangham AD. Properties and uses of lipid vesicles: an overview. Annals of the New York Academy of Sciences. 1978 Jun;308(1):2-7.
[38.] Szoka F, Papahadjopoulos D. Procedure for preparation of liposomes with large internal aqueous space and high capture by reverse-phase evaporation. Proceedings of the national academy of sciences. 1978 Sep 1;75(9):4194-8.
[39.] Deamer DW. Preparation and properties of ether-injection liposomes.Annals of the New York Academy of Sciences. 1978 Jun;308(1):250-8.
[40.] Zumbuehl O, Weder HG. Liposomes of controllable size in the range of 40 to 180 nm by defined dialysis of lipid/detergent mixed micelles. BiochimicaetBiophysicaActa (BBA)-Biomembranes. 1981 Jan 8;640(1):252-62.
[41.] Lesoin L, Crampon C, Boutin O, Badens E. Preparation of liposomes using the supercritical anti-solvent (SAS) process and comparison with a conventional method. The journal of supercritical fluids. 2011 Jun 1;57(2):162-74.
[42.] Otake K, Shimomura T, Goto T, Imura T, Furuya T, Yoda S, Takebayashi Y, Sakai H, Abe M. Preparation of liposomes using an improved supercritical reverse phase evaporation method. Langmuir. 2006 Mar 14;22(6):2543-50.
[43.] Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK, Hua S. Advances and challenges of liposome assisted drug delivery. Frontiers in pharmacology. 2015 Dec 1;6:286.
[44.] Bozzuto G, Molinari A. Liposomes as nanomedical devices. International journal of nanomedicine. 2015;10:975.
[45.] Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications.

Advanced drug delivery reviews. 2013 Jan 1;65(1):36-48..
[46.] Noble GT, Stefanick JF, Ashley JD, Kiziltepe T, Bilgicer B. Ligand-targeted liposome design: challenges and fundamental considerations. Trends in biotechnology. 2014 Jan 1;32(1):32-45.
[47.] Sapra P, Allen TM. Ligand-targeted liposomal anticancer drugs.Progress in lipid research. 2003 Sep 1;42(5):439-62.
[48.] Sawant RR, Torchilin VP. Challenges in development of targeted liposomal therapeutics.The AAPS journal. 2012 Jun; 14(2):303-15..
[49.] Ruoslahti E. Peptides as targeting elements and tissue penetration devices for nanoparticles. Advanced materials. 2012 Jul 24;24(28):3747-56.
[50.] Lee Y, Thompson DH. Stimuli-responsive liposomes for drug delivery. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2017 Sep;9(5):e1450.
[51.] Huang SL, MacDonald RC. Acoustically active liposomes for drug encapsulation and ultrasound-triggered release.BiochimicaetBiophysicaActa (BBA)-Biomembranes. 2004 Oct 11;1665(1-2):134-41.
[52.] Jin Y, Liang X, An Y, Dai Z. Microwave-triggered smart drug release from liposomes co-encapsulating doxorubicin and salt for local combined hyperthermia and chemotherapy of cancer. Bioconjugate chemistry. 2016 Dec 21;27(12):2931-42.
[53.] Ogihara-Umeda I, Sasaki T, Kojima S, Nishigori H. Optimal radiolabeled liposomes for tumor imaging. Journal of Nuclear Medicine. 1996 Feb 1;37(2):326-32.
[54.] Petersen AL, Hansen AE, Gabizon A, Andresen TL. Liposome imaging agents in personalized medicine. Advanced drug delivery reviews. 2012 Oct 1;64(13):1417-35.
[55.] Li S, Goins B, Zhang L, Bao A. Novel multifunctional theranostic liposome drug delivery system: construction, characterization, and multimodality MR, near-infrared fluorescent, and nuclear imaging. Bioconjugate chemistry. 2012 Jun 20;23(6):1322-32.
[56.] Muthu MS, Feng SS. Theranostic liposomes for cancer diagnosis and treatment: current development and pre-clinical success. Expert opinion on drug delivery. 2013 Feb 1;10(2):151-5.
[57.] Samson AA, Park S, Kim SY, Min DH, Jeon NL, Song JM. Liposomal co-delivery-based quantitative evaluation of chemosensitivity enhancement in breast cancer stem cells by knockdown of GRP78/CLU.Journal of liposome research. 2019 Jan 2;29(1):44-52.
[58.] Vahed SZ, Salehi R, Davaran S, Sharifi S. Liposome-based drug co-delivery systems in cancer cells. Materials Science and Engineering: C. 2017 Feb 1;71:1327-41.
[59.] Shin DH, Tam YT, Kwon GS. Polymeric micelle nanocarriers in cancer research.Frontiers of Chemical Science and Engineering. 2016 Sep;10(3):348-59.
[60.] Cagel M, Tesan FC, Bernabeu E, Salgueiro MJ, Zubillaga MB, Moretton MA, Chiappetta DA. Polymeric mixed micelles as nanomedicines: Achievements and perspectives. European Journal of Pharmaceutics and Biopharmaceutics. 2017 Apr 1;113:211-28.
[61.] Trivedi R, Kompella UB. Nanomicellar formulations for sustained drug delivery: strategies and underlying principles. Nanomedicine. 2010 Apr;5(3):485-505.
[62.] Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: design, characterization and biological significance. Advanced drug delivery reviews. 2001 Mar 23;47(1):113-31.
[63.] Chen Y, Liu Y, Yao Y, Zhang S, Gu Z. Reverse micelle-based water-soluble nanoparticles for simultaneous bioimaging and drug delivery. Organic &biomolecular chemistry. 2017;15(15):3232-8.
[64.] Tang LY, Wang YC, Li Y, Du JZ, Wang J. Shell-detachable micelles based on disulfide-linked block copolymer as potential carrier for intracellular drug delivery. Bioconjugate chemistry. 2009 Jun 17; 20(6):1095-9.
[65.] Deng H, Liu J, Zhao X, Zhang Y, Liu J, Xu S, Deng L, Dong A, Zhang J. PEG-b-PCL copolymer micelles with the ability of pH-controlled negative-to-positive charge reversal for intracellular delivery of doxorubicin. Biomacromolecules. 2014 Nov 10; 15(11):4281-92.
[66.] Sutton D, Nasongkla N, Blanco E, Gao J. Functionalized micellar systems for cancer targeted drug delivery. Pharmaceutical research. 2007 Jun; 24(6):1029-46.
[67.] Letchford K, Burt H. A review of the formation and classification of amphiphilic block copolymer nanoparticulate structures: micelles, nanospheres, nanocapsules and polymersomes. European journal of pharmaceutics and biopharmaceutics. 2007 Mar 1; 65(3):259-69.
[68.] Liu J, Xiao Y, Allen C. Polymer–drug compatibility: a guide to the development of delivery systems for the anticancer agent, ellipticine. Journal of pharmaceutical sciences. 2004 Jan 1; 93(1):132-43.
[69.] Kohori F, Yokoyama M, Sakai K, Okano T. Process design for efficient and controlled drug incorporation into polymeric micelle carrier systems. Journal of controlled release. 2002 Jan 17; 78(1-3):155-63.
[70.] Cajot S, Schol D, Danhier F, Préat V, Gillet De Pauw MC, Jérôme C. In Vitro Investigations of Smart Drug Delivery Systems Based on Redox-S ensitive Cross-L inked Micelles. Macromolecular bioscience. 2013 Dec; 13(12):1661-70.
[71.] Husseini GA, Runyan CM, Pitt WG. Investigating the mechanism of acoustically activated uptake of drugs from Pluronic micelles.Bmc Cancer. 2002 Dec;2(1):1-6.
[72.] Seo SJ, Lee SY, Choi SJ, Kim HW. Tumor-Targeting Co-Delivery of Drug and Gene from Temperature-Triggered Micelles.Macromolecular bioscience. 2015 Sep;15(9):1198-204.
[73.] Blanco E, Kessinger CW, Sumer BD, Gao J. Multifunctional micellarnanomedicine for cancer

therapy. Experimental biology and medicine. 2009 Feb; 234(2):123-31.
[74.] Rapoport N, Gao Z, Kennedy A. Multifunctional nanoparticles for combining ultrasonic tumor imaging and targeted chemotherapy. Journal of the National Cancer Institute. 2007 Jul 18;99(14):1095-106.
[75.] Palmerston Mendes L, Pan J, Torchilin VP. Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy.Molecules. 2017 Sep;22(9):1401.
[76.] Jackson CL, Chanzy HD, Booy FP, Drake BJ, Tomalia DA, Bauer BJ, Amis EJ. Visualization of dendrimer molecules by transmission electron microscopy (TEM): Staining methods and cryo-TEM of vitrified solutions. Macromolecules. 1998 Sep 8;31(18):6259-65.
[77.] Nanjwade BK, Bechra HM, Derkar GK, Manvi FV, Nanjwade VK. Dendrimers: emerging polymers for drug-delivery systems. European Journal of Pharmaceutical Sciences. 2009 Oct 8; 38(3):185-96.
[78.] Majoros IJ, Williams CR, Tomalia DA, Baker Jr JR. New dendrimers: synthesis and characterization of POPAM− PAMAM hybrid dendrimers. Macromolecules. 2008 Nov 25;41(22):8372-9.
[79.] Caminade AM. Phosphorus dendrimers for nanomedicine.Chemical Communications. 2017;53(71):9830-8.
[80.] Vögtle F, Richardt G, Werner N. Types of Dendrimers and their Syntheses. Dendrimer Chemistry: Concepts, Syntheses, Properties, Applications. 2009:81-167.
[81.] Tomalia DA, Baker H, Dewald J, Hall M, Kallos G, Martin S, Roeck J, Ryder J, Smith P. A new class of polymers: starburst-dendritic macromolecules. Polymer journal. 1985 Jan;17(1):117-32.
[82.] Hawker CJ, Frechet JM. Preparation of polymers with controlled molecular architecture. A new convergent approach to dendritic macromolecules.Journal of the American Chemical Society. 1990 Oct;112(21):7638-47.
[83.] Buhleier E, Wehner W, Vögtle F. ‘‘Cascade’- and ‘‘nonskid-chain-like’syntheses of molecular cavity topologies. Synthesis (Stuttg), 1978;1978: 155–8.
[84.] Bosman DA, Janssen HM, Meijer EW. About dendrimers: structure, physical properties, and applications. Chemical reviews. 1999 Jul 14; 99(7):1665-88.
[85.] Esfand R, Tomalia DA. Poly (amidoamine) (PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications. Drug discovery today. 2001 Apr 15;6(8):427-36.
[86.] Newkome GR, Yao Z, Baker GR, Gupta VK. Micelles.Part 1. Cascade molecules: a new approach to micelles. A [27]-arborol.The Journal of Organic Chemistry. 1985 May;50(11):2003-4.
[87.] Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, Hanifehpour Y, Nejati-Koshki K, Pashaei-Asl R. Dendrimers: synthesis, applications, and properties. Nanoscale research letters. 2014 Dec;9(1):1-0.
[88.] Jain K, Kesharwani P, Gupta U, Jain NK. Dendrimer toxicity: Let's meet the challenge. International journal of pharmaceutics. 2010 Jul 15;394(1-2):122-42.
[89.] Bugno J, Hsu HJ, Hong S. Tweaking dendrimers and dendritic nanoparticles for controlled nano-bio interactions: potential nanocarriers for improved cancer targeting. Journal of drug targeting. 2015 Sep 14;23(7-8):642-50.
[90.] Wang H, Huang Q, Chang H, Xiao J, Cheng Y. Stimuli-responsive dendrimers in drug delivery. Biomaterials science. 2016;4(3):375-90.
[91.] Mignani S, El Kazzouli S, Bousmina M, Majoral JP. Dendrimer space concept for innovative nanomedicine: A futuristic vision for medicinal chemistry. Progress in polymer science. 2013 Jul 1;38(7):993-1008.
[92.] Madaan K, Kumar S, Poonia N, Lather V, Pandita D. Dendrimers in drug delivery and targeting: Drug-dendrimer interactions and toxicity issues. Journal of pharmacy &bioallied sciences. 2014 Jul;6(3):139.
[93.] Ye M, Qian Y, Tang J, Hu H, Sui M, Shen Y. Targeted biodegradable dendritic MRI contrast agent for enhanced tumor imaging. Journal of Controlled Release. 2013 Aug 10;169(3):239-45.
[94.] Pasqua L, Leggio A, Sisci D, Andò S, Morelli C. Mesoporous silica nanoparticles in cancer therapy: Relevance of the targeting function. Mini reviews in medicinal chemistry. 2016 Jun 1;16(9):743-53.
[95.] Watermann A, Brieger J. Mesoporous silica nanoparticles as drug delivery vehicles in cancer. Nanomaterials. 2017 Jul; 7(7):189.
[96.] Roggers R, Kanvinde S, Boonsith S, Oupický D. The practicality of mesoporous silica nanoparticles as drug delivery devices and progress toward this goal.AapsPharmscitech. 2014 Oct; 15(5):1163-71.
[97.] Nandiyanto AB, Kim SG, Iskandar F, Okuyama K. Synthesis of spherical mesoporous silica nanoparticles with nanometer-size controllable pores and outer diameters. Microporous and Mesoporous Materials. 2009 Apr 15; 120(3):447-53.
[98.] Slowing II, Vivero-Escoto JL, Wu CW, Lin VS. Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. Advanced drug delivery reviews. 2008 Aug 17; 60(11):1278-88.
[99.] Li N, Wang Z, Zhang Y, Zhang K, Xie J, Liu Y, Li W, Feng N. Curcumin-loaded redox-responsive mesoporous silica nanoparticles for targeted breast cancer therapy. Artificial cells, nanomedicine, and biotechnology. 2018 Nov 5; 46(sup2):921-35.
[100.] Lin YS, Haynes CL. Synthesis and characterization of biocompatible and size-tunable multifunctional porous silica nanoparticles. Chemistry of Materials. 2009 Sep 8; 21(17):3979-86.
[101.] Popat A, Liu J, Lu GQ, Qiao SZ. A pH-responsive drug delivery system based on chitosan coated mesoporous silica nanoparticles. Journal of Materials Chemistry. 2012; 22(22):11173-8.
[102.] Tang F, Li L, Chen D. Mesoporous silica nanoparticles: synthesis, biocompatibility and drug

ISSN No:-2456-2165

delivery. Advanced materials. 2012 Mar 22; 24(12):1504-34.
[103.] Yamamoto E, Kitahara M, Tsumura T, Kuroda K. Preparation of size-controlled monodisperse colloidal mesoporous silica nanoparticles and fabrication of colloidal crystals. Chemistry of Materials. 2014 May 13; 26(9):2927-33.
[104.] He Q, Zhang J, Shi J, Zhu Z, Zhang L, Bu W, Guo L, Chen Y. The effect of PEGylation of mesoporous silica nanoparticles on nonspecific binding of serum proteins and cellular responses.Biomaterials. 2010 Feb 1; 31(6):1085-92.
[105.] Paris JL, Cabañas MV, Manzano M, Vallet-Regí M. Polymer-grafted mesoporous silica nanoparticles as ultrasound-responsive drug carriers. ACS nano. 2015 Nov 24; 9(11):11023-33.
[106.] Yanes RE, Tamanoi F. Development of mesoporous silica nanomaterials as a vehicle for anticancer drug delivery. Therapeutic delivery. 2012 Mar; 3(3):389-404.
[107.] Nadrah P, Planinšek O, Gaberšček M. Stimulus-responsive mesoporous silica particles. Journal of Materials Science. 2014 Jan; 49(2):481-95.
[108.] Song Y, Li Y, Xu Q, Liu Z. Mesoporous silica nanoparticles for stimuli-responsive controlled drug delivery: advances, challenges, and outlook. International journal of nanomedicine. 2017;12:87.
[109.] Chetwynd AJ, Guggenheim EJ, Briffa SM, Thorn JA, Lynch I, Valsami-Jones E. Current application of capillary electrophoresis in nanomaterial characterisation and its potential to characterise the protein and small molecule corona. Nanomaterials. 2018 Feb;8(2):99.
[110.] Zhang Z, Gao W, Zhou L, Chen Y, Qin S, Zhang L, Liu J, He Y, Lei Y, Chen HN, Han J. Repurposing brigatinib for the treatment of colorectal cancer based on inhibition of ER-phagy. Theranostics. 2019;9(17):4878.
[111.] Doria G, Conde J, Veigas B, Giestas L, Almeida C, Assunção M, Rosa J, Baptista PV. Noble metal nanoparticles for biosensing applications.Sensors. 2012 Feb;12(2):1657-87.
[112.] Chithrani BD, Ghazani AA, Chan WC. Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells.Nano letters. 2006 Apr 12;6(4):662-8.
[113.] Kong FY, Zhang JW, Li RF, Wang ZX, Wang WJ, Wang W. Unique roles of gold nanoparticles in drug delivery, targeting and imaging applications. Molecules. 2017 Sep;22(9):1445.
[114.] Noguez C. Surface plasmons on metal nanoparticles: the influence of shape and physical environment. The Journal of Physical Chemistry C. 2007 Mar 15; 111(10):3806-19.
[115.] El-Sayed IH, Huang X, El-Sayed MA. Surface plasmon resonance scattering and absorption of anti-EGFR antibody conjugated gold nanoparticles in cancer diagnostics: applications in oral cancer. Nano letters. 2005 May 11;5(5):829-34.
[116.] Kimling J, Maier M, Okenve B, Kotaidis V, Ballot H, Plech A. Turkevich method for gold nanoparticle synthesis revisited. The Journal of Physical Chemistry B. 2006 Aug 17; 110(32):15700-7.
[117.] Mafuné F, Kohno JY, Takeda Y, Kondow T. Full physical preparation of size-selected gold nanoparticles in solution: laser ablation and laser-induced size control. The Journal of Physical Chemistry B. 2002 Aug 8;106(31):7575-7.
[118.] Song JY, Jang HK, Kim BS. Biological synthesis of gold nanoparticles using Magnolia kobus and Diopyros kaki leaf extracts. Process Biochemistry. 2009 Oct 1;44(10):1133-8.
[119.] Khan AK, Rashid R, Murtaza G, Zahra AJ. Gold nanoparticles: synthesis and applications in drug delivery. Tropical journal of pharmaceutical research. 2014;13(7):1169-77.
[120.] Clark AJ, Davis ME. Increased brain uptake of targeted nanoparticles by adding an acid-cleavable linkage between transferrin and the nanoparticle core.Proceedings of the National Academy of Sciences. 2015 Oct 6;112(40):12486-91.
[121.] Dreaden EC, Austin LA, Mackey MA, El-Sayed MA. Size matters: gold nanoparticles in targeted cancer drug delivery. Therapeutic delivery. 2012 Apr;3(4):457-78.
[122.] Qian W, Murakami M, Ichikawa Y, Che Y. Highly efficient and controllable PEGylation of gold nanoparticles prepared by femtosecond laser ablation in water. The Journal of Physical Chemistry C. 2011 Dec 1;115(47):23293-8.
[123.] Yang PH, Sun X, Chiu JF, Sun H, He QY. Transferrin-mediated gold nanoparticle cellular uptake.Bioconjugate chemistry. 2005 May 18;16(3):494-6.
[124.] Han G, Ghosh P, Rotello VM. Functionalized gold nanoparticles for drug delivery.
[125.] Dixit V, Van den Bossche J, Sherman DM, Thompson DH, Andres RP. Synthesis and grafting of thioctic acid− PEG− folate conjugates onto Au nanoparticles for selective targeting of folate receptor-positive tumor cells. Bioconjugate chemistry. 2006 May 17; 17(3):603-9.
[126.] Dykman LA, Khlebtsov NG. Gold nanoparticles in chemo-, immuno-, and combined therapy: review. Biomedical optics express. 2019 Jul 1;10(7):3152-82.
[127.] Salve R, Kumar P, Ngamcherdtrakul W, Gajbhiye V, Yantasee W. Stimuli-responsive mesoporous silica nanoparticles: A custom-tailored next generation approach in cargo delivery. Materials Science and Engineering: C. 2021 Mar 31:112084.
[128.] Mendes R, Fernandes AR, Baptista PV. Gold nanoparticle approach to the selective delivery of gene silencing in cancer—the case for combined delivery?. Genes. 2017 Mar;8(3):94.
[129.] Tiwari PM, Vig K, Dennis VA, Singh SR. Functionalized gold nanoparticles and their biomedical applications. Nanomaterials. 2011 Dec;1(1):31-63.
[130.] Wahajuddin SA. Superparamagnetic iron oxide nanoparticles: magnetic nanoplatforms as drug carriers. International journal of nanomedicine.2012; 7: 3445.

[131.] Issa B, Obaidat IM, Albiss BA, Haik Y. Magnetic nanoparticles: surface effects and properties related to biomedicine applications. International journal of molecular sciences. 2013 Nov; 14(11):21266-305.
[132.] Yang SJ, Tseng SY, Wang CH, Young TH, Chen KC, Shieh MJ. Magnetic nanomedicine for CD133-expressing cancer therapy using locoregional hyperthermia combined with chemotherapy. Nanomedicine. 2020 Sep; 15(26):2543-61.
[133.] Kandasamy G, Maity D. Recent advances in superparamagnetic iron oxide nanoparticles (SPIONs) for in vitro and in vivo cancer nanotheranostics. International journal of pharmaceutics. 2015 Dec 30; 496(2):191-218.
[134.] Cole AJ, Yang VC, David AE. Cancer theranostics: the rise of targeted magnetic nanoparticles. Trends in biotechnology. 2011 Jul 1; 29(7):323-32.
[135.] Patra S, Roy E, Karfa P, Kumar S, Madhuri R, Sharma PK. Dual-responsive polymer coated superparamagnetic nanoparticle for targeted drug delivery and hyperthermia treatment. ACS applied materials & interfaces. 2015 Apr 20; 7(17):9235-46.
[136.] Mok H, Zhang M. Superparamagnetic iron oxide nanoparticle-based delivery systems for biotherapeutics. Expert opinion on drug delivery. 2013 Jan 1; 10(1):73-87.
[137.] Laurent S, Saei AA, Behzadi S, Panahifar A, Mahmoudi M. Superparamagnetic iron oxide nanoparticles for delivery of therapeutic agents: opportunities and challenges. Expert opinion on drug delivery. 2014 Sep 1;11(9):1449-70.
[138.] Santhosh PB, Ulrih NP. Multifunctional superparamagnetic iron oxide nanoparticles: promising tools in cancer theranostics. Cancer letters. 2013 Aug 9; 336(1):8-17.
[139.] Jeffreys AJ, Wilson V, Thein SL. Individual-specific 'fingerprints' of human DNA. Nature. 1985 Jul; 316(6023):76-9.
[140.] Krätschmer W, Lamb LD, Fostiropoulos KH, Huffman DR. Solid C 60: a new form of carbon. Nature. 1990 Sep; 347(6291):354-8.
[141.] Liu Z, Robinson JT, Tabakman SM, Yang K, Dai H. Carbon materials for drug delivery & cancer therapy. Materials today. 2011 Jul 1; 14(7-8):316-23.
[142.] Iijima S. Helical microtubules of graphitic carbon. nature. 1991 Nov; 354(6348):56-8.
[143.] Cantoro M, Hofmann S, Pisana S, Scardaci V, Parvez A, Ducati C, Ferrari AC, Blackburn AM, Wang KY, Robertson J. Catalytic chemical vapor deposition of single-wall carbon nanotubes at low temperatures. Nano Letters. 2006 Jun 14; 6(6):1107-12.
[144.] Eatemadi A, Daraee H, Karimkhanloo H, Kouhi M, Zarghami N, Akbarzadeh A, Abasi M, Hanifehpour Y, Joo SW. Carbon nanotubes: properties, synthesis, purification, and medical applications. Nanoscale research letters. 2014 Dec; 9(1):1-3.
[145.] Bianco A, Kostarelos K, Prato M. Applications of carbon nanotubes in drug delivery. Current opinion in chemical biology. 2005 Dec 1; 9(6):674-9.
[146.] Li Z, de Barros AL, Soares DC, Moss SN, Alisaraie L. Functionalized single-walled carbon nanotubes: cellular uptake, biodistribution and applications in drug delivery. International journal of pharmaceutics. 2017 May 30; 524(1-2):41-54.
[147.] .Lay CL, Liu J, Liu Y. Functionalized carbon nanotubes for anticancer drug delivery. Expert review of medical devices. 2011 Sep 1; 8(5):561-6.
[148.] Schmaljohann D. Thermo-and pH-responsive polymers in drug delivery. Advanced drug delivery reviews. 2006 Dec 30; 58(15):1655-70.
[149.] Wang JT, Al-Jamal KT. Functionalized carbon nanotubes: revolution in brain delivery. Nanomedicine. 2015 Sep; 10(17):2639-42.
[150.] Kafa H, Wang JT, Rubio N, Venner K, Anderson G, Pach E, Ballesteros B, Preston JE, Abbott NJ, Al-Jamal KT. The interaction of carbon nano-tubes with an in vitro blood-brain barrier model and mouse brain in vivo.Biomaterials.2015 Jun 1; 53:437-52.
[151.] Son KH, Hong JH, Lee JW. Carbon nanotubes as cancer therapeutic carriers and mediators.International journal of nanomedicine.2016; 11: 5163.
[152.] Madani SY, Naderi N, Dissanayake O, Tan A, Seifalian AM. A new era of cancer treatment: carbon nanotubes as drug delivery tools. International journal of nanomedicine.2011; 6: 2963.
[153.] Chen Z, Zhang A, Wang X, Zhu J, Fan Y, Yu H, Yang Z. The advances of carbon nanotubes in cancer diagnostics and therapeutics.Journal of Nanomaterials.2017 Aug 9; 2017.
[154.] Matea CT, Mocan T, Tabaran F, Pop T, Mosteanu O, Puia C, Iancu C, Mocan L. Quantum dots in imaging, drug delivery and sensor applications. International journal of nanomedicine.2017; 12:5421.
[155.] Zrazhevskiy, P., Sena, M. and Gao, X., 2010. Designing multifunctional quantum dots for bioimaging, detection, and drug delivery.Chemical Society Reviews, 39(11), pp.4326-4354.
[156.] Ghasemi Y, Peymani P, Afifi S. Quantum dot: magic nanoparticle for imaging, detection and targeting. Acta Biomed. 2009 Aug 1; 80(2):156-65.
[157.] Probst CE, Zrazhevskiy P, Bagalkot V, Gao X. Quantum dots as a platform for nanoparticle drug delivery vehicle design. Advanced drug delivery reviews. 2013 May 1; 65(5):703-18.
[158.] Nakata Y, Mukai K, Sugawara M, Ohtsubo K, Ishikawa H, Yokoyama N. Molecular beam epitaxial growth of InAs self-assembled quantum dots with light-emission at 1.3 μm. Journal of Crystal Growth. 2000 Jan 1; 208(1-4):93-9.
[159.] Bertino MF, Gadipalli RR, Martin LA, Rich LE, Yamilov A, Heckman BR, Leventis N, Guha S, Katsoudas J, Divan R, Mancini DC. Quantum dots by ultraviolet and x-ray lithography.Nanotechnology. 2007 Jul 6;18(31):315603.
[160.] Valizadeh A, Mikaeili H, Samiei M, Farkhani SM, Zarghami N, Akbarzadeh A, Davaran S. Quantum dots: synthesis, bioapplications, and toxicity. Nanoscale research letters. 2012 Dec;7(1):1-4.
[161.] Gui R, Wan A, Zhang Y, Li H, Zhao T. Ratiometric and time-resolved fluorimetry from quantum dots featuring drug carriers for real-time monitoring of

drug release in situ. Analytical chemistry. 2014 Jun 3;86(11):5211-4.
[162.] Yang G, Liu J, Wu Y, Feng L, Liu Z. Near-infrared-light responsive nanoscale drug delivery systems for cancer treatment. Coordination Chemistry Reviews. 2016 Aug 1; 320:100-17.
[163.] Iannazzo D, Pistone A, Salamò M, Galvagno S, Romeo R, Giofré SV, Branca C, Visalli G, Di Pietro A. Graphene quantum dots for cancer targeted drug delivery. International journal of pharmaceutics. 2017 Feb 25; 518(1-2):185-92.
[164.] Zhao MX, Zhu BJ. The research and applications of quantum dots as nano-carriers for targeted drug delivery and cancer therapy.Nanoscale research letters. 2016 Dec; 11(1):1-9.
[165.] Rajitha B, Malla RR, Vadde R, Kasa P, Prasad GL, Farran B, Kumari S, Pavitra E, Kamal MA, Raju GS, Peela S. Horizons of nanotechnology applications in female specific cancers. InSeminars in cancer biology 2019 Jul 10.Academic Press.
[166.] Senapati S, Mahanta AK, Kumar S, Maiti P. Controlled drug delivery vehicles for cancer treatment and their performance. Signal transduction and targeted therapy. 2018 Mar 16; 3(1):1-9.
[167.] Gao X, Cui Y, Levenson RM, Chung LW, Nie S. In vivo cancer targeting and imaging with semiconductor quantum dots.Nature biotechnology. 2004 Aug; 22(8):969-76.
[168.] Danhier F, Feron O, Préat V. To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. Journal of controlled release. 2010 Dec 1; 148(2):135-46.
[169.] Mohanty C, Das M, R Kanwar J, K Sahoo S. Receptor mediated tumor targeting: an emerging approach for cancer therapy. Current drug delivery. 2011 Jan 1; 8(1):45-58.
[170.] Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer research. 1986 Dec 1; 46(12 Part 1):6387-92.
[171.] Nakamura Y, Mochida A, Choyke PL, Kobayashi H. Nanodrug delivery: is the enhanced permeability and retention effect sufficient for curing cancer?. Bioconjugate chemistry. 2016 Oct 19;27(10):2225-38.
[172.] Jain RK. Transport of molecules across tumor vasculature.Cancer and Metastasis Reviews. 1987 Dec;6(4):559-93.
[173.] Heldin CH, Rubin K, Pietras K, Östman A. High interstitial fluid pressure—an obstacle in cancer therapy. Nature Reviews Cancer. 2004 Oct;4(10):806-13..
[174.] Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nature biotechnology. 2015 Sep;33(9):941-51..
[175.] Villiers CL, Freitas H, Couderc R, Villiers MB, Marche PN. Analysis of the toxicity of gold nano particles on the immune system: effect on dendritic cell functions. Journal of Nanoparticle Research. 2010 Jan; 12(1):55-60.
[176.] Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nature materials. 2013 Nov;12(11):991-1003.
[177.] Liu M, Du H, Zhang W, Zhai G. Internal stimuli-responsive nanocarriers for drug delivery: Design strategies and applications. Materials Science and Engineering: C. 2017 Feb 1;71:1267-80.
[178.] VanderHeiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation.Science. 2009 May 22; 324(5930):1029-33.
[179.] Gerweck LE, Seetharaman K. Cellular pH gradient in tumor versus normal tissue: potential exploitation for the treatment of cancer. Cancer research. 1996 Mar 15; 56(6):1194-8..
[180.] Vaupel P, Kallinowski F, Okunieff P. Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumors: a review. Cancer research. 1989 Dec 1;49(23):6449-65.
[181.] Engin K, Leeper DB, Cater JR, Thistlethwaite AJ, Tupchong L, McFarlane JD. Extracellular pH distribution in human tumours.International Journal of Hyperthermia. 1995 Jan 1;11(2):211-6.
[182.] Nilsson C, Kågedal K, Johansson U, Öllinger K. Analysis of cytosolic and lysosomal pH in apoptotic cells by flow cytometry. Methods in cell science. 2004 Jan;25(3):185-94.
[183.] Gamcsik MP, Kasibhatla MS, Teeter SD, Colvin OM. Glutathione levels in human tumors. Biomarkers. 2012 Dec 1;17(8):671-91.
[184.] Meng F, Hennink WE, Zhong Z. Reduction-sensitive polymers and bioconjugates for biomedical applications. Biomaterials. 2009 Apr 1; 30(12):2180-98.
[185.] Wen H, Li Y. Redox sensitive nanoparticles with disulfide bond linked sheddable shell for intracellular drug delivery. Med. Chem. 2014; 4(11):748-55.
[186.] Cheng R, Feng F, Meng F, Deng C, Feijen J, Zhong Z. Glutathione-responsive nano-vehicles as a promising platform for targeted intracellular drug and gene delivery. Journal of controlled release. 2011 May 30; 152(1):2-12.
[187.] Andresen TL, Thompson DH, Kaasgaard T. Enzyme-triggered nanomedicine: Drug release strategies in cancer therapy (Invited Review). Molecular membrane biology. 2010 Oct 1; 27(7):353-63.
[188.] Andresen TL, Jensen SS, Jørgensen K. Advanced strategies in liposomal cancer therapy: problems and prospects of active and tumor specific drug release. Progress in lipid research. 2005 Jan 1; 44(1):68-97.
[189.] Meers P. Enzyme-activated targeting of liposomes. Advanced drug delivery reviews. 2001 Dec 31; 53(3):265-72.
[190.] Yao J, Feng J, Chen J. External-stimuli responsive systems for cancer theranostic. Asian journal of pharmaceutical sciences. 2016 Oct 1; 11(5):585-95.
[191.] Hua MY, Liu HL, Yang HW, Chen PY, Tsai RY, Huang CY, Tseng IC, Lyu LA, Ma CC, Tang HJ,

Yen TC. The effectiveness of a magnetic nanoparticle-based delivery system for BCNU in the treatment of gliomas.Biomaterials. 2011 Jan 1; 32(2):516-27.

[192.] Plassat V, Wilhelm C, Marsaud V, Ménager C, Gazeau F, Renoir JM, Lesieur S. Anti-estrogen-loaded super para magnetic liposomes for intracellular magnetic targeting and treatment of breast cancer tumors. Advanced functional materials. 2011 Jan 7;21(1):83-92.

[193.] Bringas E, Köysüren Ö, Quach DV, Mahmoudi M, Aznar E, Roehling JD, Marcos MD, Martínez-Máñez R, Stroeve P. Triggered release in lipid bilayer-capped mesoporous silica nanoparticles containing SPION using an alternating magnetic field. Chemical communications. 2012;48(45):5647-9.

[194.] Hu SH, Chen SY, Liu DM, Hsiao CS. Core/single-crystal-shell nanospheres for controlled drug release via a magnetically triggered rupturing mechanism. Advanced materials. 2008 Jul 17; 20(14):2690-5.

[195.] Hu SH, Chen SY, Gao X. Multifunctional nanocapsules for simultaneous encapsulation of hydrophilic and hydrophobic compounds and on-demand release. ACS nano. 2012 Mar 27;6(3):2558-65.

[196.] Shao P, Wang B, Wang Y, Li J, Zhang Y. The application of thermosensitivenanocarriers in controlled drug delivery. Journal of Nanomaterials. 2011 Jan 1;2011.

[197.] Kost J, Langer R. Responsive polymeric delivery systems. Advanced drug delivery reviews. 2012 Dec 1; 64: 327-41.

[198.] Yokoyama M, Okano T. Targetable drug carriers: present status and a future perspective. Advanced drug delivery reviews. 1996; 21(2):77-80.

[199.] Topp MD, Dijkstra PJ, Talsma H, Feijen J. Thermosensitive micelle-forming block copolymers of poly (ethylene glycol) and poly (N-isopropylacrylamide). Macromolecules. 1997 Dec 29;30(26):8518-20.

[200.] Klouda L, Mikos AG. Thermoresponsive hydrogels in biomedical applications.European journal of pharmaceutics and biopharmaceutics. 2008 Jan 1;68(1):34-45.

[201.] Lu J, Choi E, Tamanoi F, Zink JI. Light-activated nanoimpeller-controlled drug release in cancer cells. Small (Weinheiman der Bergstrasse, Germany). 2008 Apr;4(4):421.

[202.] Yuan J, Duan R, Yang H, Luo X, Xi M. Detection of serum human epididymis secretory protein 4 in patients with ovarian cancer using a label-free biosensor based on localized surface plasmon resonance. International journal of nanomedicine. 2012;7:2921.

[203.] Yan H, Teh C, Sreejith S, Zhu L, Kwok A, Fang W, Ma X, Nguyen KT, Korzh V, Zhao Y. Functional mesoporous silica nanoparticles for photothermal-controlled drug delivery in vivo. AngewandteChemie International Edition. 2012 Aug 13; 51(33):8373-7.

[204.] Yang G, Liu J, Wu Y, Feng L, Liu Z. Near-infrared-light responsive nanoscale drug delivery systems for cancer treatment. Coordination Chemistry Reviews. 2016 Aug 1;320:100-17.

[205.] Rapoport NY, Kennedy AM, Shea JE, Scaife CL, Nam KH. Controlled and targeted tumor chemotherapy by ultrasound-activated nanoemulsions/microbubbles. Journal of Controlled Release. 2009 Sep 15; 138(3):268-76.

[206.] Dromi S, Frenkel V, Luk A, Traughber B, Angstadt M, Bur M, Poff J, Xie J, Libutti SK, Li KC, Wood BJ. Pulsed-high intensity focused ultrasound and low temperature–sensitive liposomes for enhanced targeted drug delivery and antitumor effect. Clinical cancer research. 2007 May 1; 13(9):2722-7.

[207.] Schroeder A, Kost J, Barenholz Y. Ultrasound, liposomes, and drug delivery: principles for using ultrasound to control the release of drugs from liposomes. Chemistry and physics of lipids. 2009 Nov 1; 162(1-2):1-6.

[208.] Geers B, Dewitte H, De Smedt SC, Lentacker I. Crucial factors and emerging concepts in ultrasound-triggered drug delivery. Journal of controlled release. 2012 Dec 28; 164(3):248-55.

[209.] Ge J, Neofytou E, Cahill III TJ, Beygui RE, Zare RN. Drug release from electric-field-responsive nanoparticles.ACS nano. 2012 Jan 24; 6(1):227-33.

[210.] George PM, LaVan DA, Burdick JA, Chen CY, Liang E, Langer R. Electrically controlled drug delivery from biotin-doped conductive polypyrrole. Advanced Materials. 2006 Mar 3; 18(5):577-81."

[211.] Im JS, Bai BC, Lee YS. The effect of carbon nanotubes on drug delivery in an electro-sensitive transdermal drug delivery system.Biomaterials. 2010 Feb 1; 31(6):1414-9.

[212.] Murdan S. Electro-responsive drug delivery from hydrogels. Journal of controlled release. 2003 Sep 19; 92(1-2):1-7.

[213.] Abidian MR, Kim DH, Martin DC. Conducting-polymer nanotubes for controlled drug release. Advanced materials. 2006 Feb 17; 18(4):405-9.

[214.] Dang Y, Guan J. Nanoparticle-based drug delivery systems for cancer therapy. Smart Materials in Medicine. 2020 Jan 1;1 :10-9.