Review

Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: A review

Sarwar Hossena, M. Khalid Hossainb,⇑, M.K. Basherb, M.N.H. Mia, M.T. Rahmanc, M. Jalal Uddind

aDepartment of Physics, Khulna Govt. Mahila College, National University, Gazipur 1704, Bangladesh
bInstitute of Electronics, Atomic Energy Research Establishment, Bangladesh Atomic Energy Commission, Dhaka 1349, Bangladesh
cDepartment of Materials Science and Engineering, University of Rajshahi, Rajshahi 6205, Bangladesh
dDepartment of Radio Sciences and Engineering, KwangWoon University, Seoul 01897, Republic of Korea

highlights

• Studied eight (8) promising nanocarriers for anti-cancer drug delivery.
• Studied up-to-date strategies for cancer site targeting used in SDDSs.
• Various stimulus techniques utilized for drug release at targeted sites are mentioned.
• Studied toxicity of various nanocarriers used in SDDSs.
• Challenges and research scope of nanocarriers in cancer therapy also highlighted.

abstract

Nonspecific distribution and uncontrollable release of drugs in conventional drug delivery systems (CDDSs) have led to the development of smart nanocarrier-based drug delivery systems, which are also known as Smart Drug Delivery Systems (SDDSs). SDDSs can deliver drugs to the target sites with reduced dosage frequency and in a spatially controlled manner to mitigate the side effects experienced in CDDSs. Chemotherapy is widely used to treat cancer, which is the second leading cause of death worldwide. Site-specific drug delivery led to keen interest in the SDDSs as an alternative to chemotherapy. Smart nanocarriers, nanoparticles used to carry drugs, are at the focus of SDDSs. A smart drug delivery system consists of smart nanocarriers, targeting mechanisms, and stimulus techniques. This review highlights the recent development of SDDSs for a number of smart nanocarriers, including liposomes, micelles, dendrimers, meso-porous silica nanoparticles, gold nanoparticles, superparamagnetic iron-oxide nanoparticles, carbon nanotubes, and quantum dots. The nanocarriers are described in terms of their structures, classification, synthesis and degree of smartness. Even though SDDSs feature a number of advantages over chemotherapy, there are major concerns about the toxicity of smart nanocarriers; therefore, a substantial study on the toxicity and biocompatibility of the nanocarriers has been reported. Finally, the challenges and future research scope in the field of SDDSs are also presented. It is expected that this review will be widely useful for those who have been seeking new research directions in this field and for those who are about to start their studies in smart nanocarrier-based drug delivery.

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⇑Corresponding author.
E-mail address: khalid.baec@gmail.com (M.K. Hossain).

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Introduction

Cancer is the second leading cause of death worldwide [1,2]. Chemotherapy [3,4] plays a vital role in treating undetectable cancer micro-focuses and free cancer cells. Chemotherapy uses chemicals to kill or block the growth of cancer cells [5]. As cancer cells grow faster than healthy ones, fast-growing cells are the main targets of chemotherapeutics; however, because there are healthy cells which are also fast-growing, the drugs used in chemotherapy also attack those fast-growing healthy cells. This unwanted attack results in the failure of conventional chemotherapy [6]. In addition, multi drug resistance (MDR) [7–9] is another major obstacle to successful chemotherapy. MDR enables the cancer cells to escape the effects of chemotherapeutics by developing resistance against the cytotoxic drugs during or shortly after the therapy. The limitations of conventional chemotherapy have led to the development of smart nanocarrier-based drug delivery systems, which are also known as Smart Drug Delivery System (SDDSs). SDDSs promise to apply drugs to specific and targeted sites [10]. Although, the magic bullet concept of Paul Ehrlich [11] is the cornerstone of the relationship between drug delivery and nanoparticles, the well-controlled release of drugs using a bead polymerization technique was reported first by Speiser et al. [12].

Nanocarriers are the base of SDDSs. Unfortunately, not all types of nanocarriers are reliable as drugs carriers in SDDSs. To qualify as an ideal nanocarrier in SDDSs, a nanocarrier should meet some basic criteria, discussed in detail in the subsequent sections. This review emphasizes the eight (8) most reported nanocarriers: (i) liposomes, (ii) micelles, (iii) dendrimers, (iv) meso-porous silica nanoparticles (MSNs), (v) gold nanoparticles (GNPs), (vi) super paramagnetic iron oxide nanoparticles (SPIONs), (vii) carbon nanotubes (CNTs), and (viii) quantum dots (QDs) in the context of their structures, classification, synthesis and degree of smartness. The schematic representation of these 8 nanocarriers is shown in Fig. 1.

Choosing the right strategies to identify cancer cells follows the selection of a suitable nanocarrier type. SDDS utilizes the physiochemical differences between cancer cells and healthy cells to identify cancer sites. To exactly identify the cancer cell site, there are two major approaches: passive targeting and active targeting. Passive targeting utilizes the Enhanced Permeability (EPR) [13] effect to specify the cancer site indirectly. Active targeting uses overexpressed cell surface receptors of cancer cells to target cancer cells directly like a guided missile [14]. Releasing drugs at the specific location at a precise concentration is the subsequent step. Drugs could be released from the nanocarriers by external or internal stimuli, depending on the type of nanocarriers and their smartness [15].

| Nomenclature | Definition |
|--------------|------------|
| ABC          | accelerated blood clearance |
| BBB          | blood brain barrier          |
| BCM          | bock copolymer micelle       |
| CMC          | critical micelle concentration|
| CNT          | carbon nanotube              |
| EPR          | enhanced permeability and retention |
| IFP          | interstitial fluid pressure  |
| GNP          | gold nanoparticle            |
| GSH          | glutathione sulfhydryl       |
| LCST         | lower critical stimulus temperature |
| MWCNT        | multi-walled CNT             |
| MDR          | multidrug resistance         |
| MPS          | mononuclear phagocyte system |
| MSN          | meso-porous silica nanoparticle |
| NP           | nanoparticle                 |
| PEG          | polyethylene glycol          |
| PAMAM        | poly (amidoamine)            |
| QD           | quantum dot                  |
| RES          | reticuloendothelial system   |
| SPR          | surface plasma resonance     |
| SPION        | super paramagnetic iron oxide nanoparticles |
| SWCNT        | single-walled CNT            |
| SDDS         | smart drug delivery system   |
| VSSA         | volume specific surface area |

Fig. 1. Schematic representation of the 8 nanocarriers used in smart drug delivery systems.
Though the prospect of SDDSs is quite promising, the toxicity of nanocarriers in human organs is a major concern; therefore, this review presents a table (Table 1) of eight (8) nanocarriers summarized in terms of their toxicity and biocompatibility. Furthermore, the existing challenges and future research scope in designing effective SDDSs are also highlighted in this review.

Smart drug delivery system

A smart drug delivery system, as illustrated in Fig. 2, using liposomes as nanocarriers, consists of (i) smart nanocarriers which carry anti-cancer drugs to the cancer site, (ii) targeting mechanisms to locate the cancerous site and (iii) stimulus techniques to release the payloads at the pre-located cancer cell site. Eight nanocarriers as well as their targeting mechanisms and stimulus techniques are discussed in detail in the subsequent sections.

Smart nanocarriers

Particles with at least one dimension on the order of 1–100 nm are popularly known as nanoparticles. Currently, nanoparticles are defined in terms of volume specific surface area (VSSA). Typically, particles with VSSA equal to or greater than 60 m²/cm³ volume of the material are defined as nanoparticles [16]. When nanoparticles are used as transport modules for other substances, they are called nanocarriers. Conventional nanocarriers don’t have the ability to carry and release drugs at the right concentration at the targeted site under external or internal stimulation. Therefore, archetypical nanocarriers are not smart. They need to be modified or functionalized to make them smart. Smart nanocarriers should possess the following characteristics. First, smart nanocarriers should avoid the cleansing process of the body’s immune system. Second, they should be accumulated at the targeted site only. Third, smart nanocarrier should release the cargo at the targeted site at the right concentration under external or internal stimulation. In addition, finally, they should co-deliver chemotherapeutics and other substances, such as genetic materials, imaging agents, etc. [17–19].

Depending on the types and applications of nanocarriers, there are some steps to transform conventional nanocarriers into smart ones. First, nanocarriers face many biological barriers, including cleansing by the reticuloendothelial system (RES) on the way to the targeted site. The RES takes the nanocarrier out of circulation shortly and accumulates those anti-cancer drug-carrying nanocarriers in the liver, spleen or bone marrow. PEGylation is a unique solution to avoid this cleansing process. PEGylation helps nanocarriers escape the RES. Davies and Abuchowsky reported the PEGylation for the first time [20]. Unfortunately, PEGylation reduces the drug uptake significantly by the cells [21,22]. This twist is known as the PEGylation dilemma [23,24]. Second, nanocarriers can be functionalized to identify the cancer cells precisely out of healthy ones. The physiochemical differences between cancer cells and healthy ones are the identification marks to separate the two types of cells. The surface of cancer cells overexpresses some proteins. The overexpressed proteins are the key targets of the smart nanocarrier. Nanocarriers are modified with ligands matching the overexpressed proteins. The ligands of smart nanocarriers identify the cells with the receptor proteins. Third, conveying the drug to the target site is not the termination of the process. Releasing the drug from the smart carrier under stimulation is the next big challenge. To make nanocarriers responsive to the stimulus system, various chemical groups can be grafted on the surface of the nanocarriers. Fourth, modifications are also done for the co-delivery of anti-cancer drugs together with other substances, including genetic materials [25], imaging agents or even additional anti-cancer drugs. Liposomes, micelles, dendrimers, GNPs, quantum dots and MSNs show promise for co-delivery [26–30]. Eight promising nanocarriers are discussed in detail below in terms of their structure, classification, synthesis and smartness.
Liposomes and its smartness

Liposomes [31], illustrated in Fig. 3, are naturally occurring phospholipid-based amphipathic nanocarriers. Phospholipids, a major component of the cell membrane, consist of a fatty acid-based hydrophobic tail and a phosphate-based hydrophilic head. In 1973, Gregory Gregordians showed that when phospholipids are introduced in an aqueous medium, they self-assemble into a bi-layer vesicle with the non-polar ends forming a bilayer and the polar ends facing the water. The core formed by the bilayer can entrap water or water-soluble drugs [32]. On the basis of the number of bilayers and the size of the liposome, there are two types: multi-lamellar vesicles and uni-lamellar vesicles. Uni-lamellar vesicles can be further divided into two groups, namely, large uni-lamellar vesicles (LUV) and small uni-lamellar vesicles (SUV) [33,34].

There are several methods to prepare liposomes [35,36], namely, the thin film hydration method or Bangham method [37], reverse phase evaporation [38], solvent injection technique [39], and detergent dialysis [40]. Conventional methods have many setbacks. To remove those limitations, some novel technologies have been devised, such as supercritical fluid technology, the supercritical anti-solvent method [41], and supercritical reverse phase evaporation [42].

Conventional liposomes have many problems including instability, insufficient drug loading, faster drug release and shorter circulation times in the blood; therefore, they are not smart. Functionalization of conventional liposomes, as shown in Fig. 3 [44], makes them smart. Like other nanocarriers, liposomes also need to overcome the challenge presented by the RES. PEGylation helps liposomes escape the RES. Therefore, PEGylated liposomes have longer blood circulation time [45]. Smart nanocarriers can determine the difference between healthy cells and cancerous ones. Monoclonal antibodies, antibody fragments, proteins, peptides, vitamins, carbohydrates and glycoproteins are usually grafted on the liposome to actively target the cancer site [46–49]. Smart liposomes are responsive to various external and internal stimulation, including pH change, enzyme transformation, redox reaction, light, ultrasound and microwaves [50–52]. A liposome functionalized with a radio-ligand is known as a radiolabeled liposome. Radiolabeled liposomes [53] can be used to determine the bio-distribution of liposomes in the body and to diagnose the tumor along with carrying out therapy. Liposomes that can carry both therapeutics and imaging agents [54] are known as theranostic liposomes [55,56]. In addition to delivering imaging agents together with chemotherapeutics, liposomes are promising in the co-delivery of two chemotherapeutic drugs, gene agents [57] with chemotherapeutics as well as chemotherapeutics with anti-cancer metals [58].

Micelles and their smartness

Amphiphilic molecules, having both hydrophilic and hydrophobic portions, show unique characteristics of self-assembly when exposed to a solvent. 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 orient away from the solvent [61–63]. PG-PCL, PEEP-PCL [64], PEG-PCL [65] and PEG-DSPE are examples of some micelles [66].
The preparation of micelles depends on the solubility of the co-polymer used [67]. For a relatively water-soluble co-polymer, two methods are used, namely, the direct dissolution method and the film casting method. In contrast, dialysis or an oil in water procedure is used if the co-polymer is not readily water-soluble [68,69].

Micelles may face immature drug release by crossing the CMC. In addition, interaction with blood and absorption of unimers to plasma protein may disrupt the equilibrium between micelle and blood. The solution to this problem is a smart micelle. To overcome the problems mentioned, micelles are usually cross-linked; that is, linking two polymer chains by disulfide formation [70]. There are two types of cross-linking schemes: core cross-linked polymer micelles and the shell cross-linked polymer micelles. To actively target cancer cells, different types of ligands are used to decorate the micelle surface, namely, folic acid, peptides, carbohydrates, antibodies, aptamers, etc. [66]. To release the anti-cancer drug at the right concentration, the core or the corona of the micelle can be functionalized. The stimuli used in micelle based SDDSs are pH gradients, temperature changes, ultrasound [71], enzymes, and oxidation [66]. Using a multifunctional micelle, the co-delivery strategy is very important for the synergetic effects in cancer treatment. Seo et al. reported a temperature-responsive micelle-based co-delivery system which can carry genes along with anti-cancer drugs [72].

**Dendrimers and their smartness**

Polymers with many branches are known as dendrimers, which can be graphically presented as a suction ball. As shown in Fig. 5, a dendrimer has three distinguishable parts: a core, branching dendrons and surface-active groups [75]. The active groups on the dendrimer surface determine the physiochemical properties of the dendrimer. Based on the surface groups, it may be either hydrophobic or hydrophilic. Due to its nanoscale size, monodisperse nature [76], water solubility, bio-compatibility, and highly branched structure, it is of high interest. Because of the nanoscale size, it can be used as a drug carrier [77]. The branched structure makes the dendrimer versatile. Moreover, all of its active groups on the surface face outward, which results in a higher drug encapsulation rate. Various types of dendrimer, such as poly(propylene-imine) (PPI or POPAM), PAMAM, POPAM, POMAM [78], polylysine dendrimer, dendritic hydrocarbon, carbon/
Meso-porous silica nanoparticles (MSNs) and their smartness

Meso-porous materials are materials containing pores with diameters between 2 and 50 nm, as defined by the IUPAC [94]. MSNs [95] have the honeycomb-like porous structure of silica (SiO₂), as shown in Fig. 6. The term MSN was coined forty years ago to describe zeolite-silica gel mixtures with well-defined and uniform porosity [96]. MSNs are widely studied because of their unique characteristics, such as customizable size, large surface to volume ratio, easy synthesis, noble optical properties, thermal ablation of cancer cell and easy surface functionalization [111]. Studies show that the intercellular uptake of nanocarriers depends on the size and shape of colloidal nanocarriers [112]. GNPs [113] are metallic nanocarriers available in custom shapes and sizes, as shown in Fig. 7. GNPs have great prospects as metallic candidates for delivering payloads. Payloads could be drug molecules or large biomolecules, such as proteins, DNA and RNA. GNPs are also interesting due to the surface plasmon resonance effect.

Fig. 6. Schematic for the synthesis of monodisperse colloidal MSNs and the fabrication of colloidal crystals. Reprinted with permission [103], © American Chemical Society (2014).
(SPR) phenomenon \[114,115\], which enable them to convert light to heat and scatter the produced heat to kill the cancer cells. \n
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. To overcome these limitations, gold nanocarriers need to be PEGylated. Under physiological conditions, PEGylated GNPs show enhanced solubility and stability \[122\]. For targeted drug delivery, the surface of GNPs can be modified by various ligands. For example, transferrin (TF) can be grafted onto the surface of GNPs, as many tumors overexpress the TF receptor on their surface \[123\]. The GNP surface could also be modified by folic acid, as folic acid receptors are also overexpressed on various tumor cells \[124,125\]. The drug can be unloaded from GNPs either by (1) external stimuli (laser, ultrasound and X-ray, light \[126\]) or by (2) internal stimuli (pH, redox condition, matrix metalloproteinase) \[127\]. Various studies show the promise for gene transfection by GNPs to silence the gene responsible for the cancer \[128\]. GNPs modified with fluorescently labeled heparin could be used to diagnose the cancer site \[129\].

Super paramagnetic iron oxide nanoparticles (SPIONs) and their smartness

Freeman et al. introduced the concept of using magnetic materials along with magnetic fields in medicine in 1960 \[109\]. The magnetic materials include the widely studied SPIONs. Small synthetic maghemite and magnetite (Fe₃O₄) particles with cores ranging between 10 and 100 nm in diameter are two SPIONs. Mixed iron oxides with transition metals, such as copper, cobalt, and nickel also belong to the category of SPIONs. When magnetic particles are reduced to 10–20 nm, they show a unique phenomenon called super para-magnetism. 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 \[130,131\]. The fabrication of SPIONs includes three methods, including a physical method, wet chemical method and microbal method \[132\]. There are various methods to synthesis SPIONs, namely, co-precipitation, thermal decomposition, hydrothermal, micro-emulsion, sono-chemical, microwave-assisted synthesis methods \[133\]. Among those, chemical synthesis is the most predominant one.

The smartness of post-fabricated SPIONs depends on the functionalization (as shown in Fig. 8). 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 \[130\]. 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. A recent study has shown that polymer-modified SPIONs have dual responsiveness to pH gradients and temperature changes \[135\]. This carrier can be controlled by an external magnetic field. Because of the presence of phosphate group, nucleic acids are negatively charged; therefore, SPIONs can be modified with cationic lipids and polymers to carry genetic materials \[136\]. SPIONs are members of the family of nanocarriers that have theranostic properties. As a magnetic nanocarrier, it can be detected by an external magnetic field \[137,138\].

Carbon nanotubes (CNTs) and their smartness

CNTs are a type of fullerene, a class of carbon allotropes in the shape of hollow spheres, ellipsoid, tubes and many other forms \[139,140\]. When a graphene sheet is rolled up into a seamless cylindrical tube, the shape is known as a CNT. There are two types of CNTs: single walled (SWCNT) and multi-walled (MWCNT) \[141,142\]. The strong optical absorption in the near-infrared region by the CNT makes this particle a strong candidate for photo thermal ablation; furthermore, nanoparticles with sizes ranging from 50 to 100 nm are easy to be engulfed. MWCNTs can pass through the barrier of various cellular compartments, and PEGylated SWCNTs are able to localize in a specific cellular compartment. CNTs can be synthesized via heating carbon black and graphite in a controlled flame environment. However, this process cannot control the shape, size, mechanical strength, quality and purity of the synthesized CNTs. To address the limitations of the controlled flame environment, electric arc discharges \[142\], the chemical vapor deposition method \[143\] and the laser ablation method have been reported. Due to the better defined walls of SWCNTs and relatively more structural defects of MWCNTs, SWCNTs are more efficient than MWCNTs in drug delivery \[5,144\].

CNTs should be functionalized \[146\] either chemically or physically, as illustrated in Fig. 9, to make them smart. PEGylation is a very important step to increase solubility, avoid the RES and to lower the toxicity \[147\]. 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. Weak acids and bases show a change in the ionization state upon pH variation \[148\]. Recent studies exhibit that functionalized CNTs can overcome the BBB \[149,150\]. CNTs have shown promise in carrying plasmid DNA, small-interfering ribonucleic acid (siRNA), antisense oligonucleotides, and aptamers \[151\]. In addition to gene delivery, it can also be used for the thermal ablation of a cancer site \[152\].
Functionalized CNTs can be used as diagnostic tools for the early detection of cancer [153].

Quantum dots (QDs) and their smartness

Quantum dots [154], fluorescent semiconducting nanocarriers, are often made of hundreds to thousands of atoms of group II and group VI molecule and have unique photophysical properties [155]. This nanocarrier could be used to visualize the tumor while the drug is being released at the targeted site. Most commercially available QDs 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 QDs with different materials [156]. QD-based SDDSs have attracted significant interest for several reasons. First, QDs possess an extremely small core size of 2–10 nm in diameter. This feature makes it useful as a tracer in other drug delivery systems. Second, versatile surface chemistry allows different approaches for the surface modification of QDs. Third, their photophysical properties provide QDs extra mileage for real-time monitoring of drug-carrying and drug release [157]. To synthesize QDs, either a top-down approach or a bottom-up method can be employed. Molecular beam epitaxy (MBE) [158], ion implantation, e-beam lithography and X-ray lithography [159] belong to top-down processing; on the other hand, colloidal QDs are prepared by self-assembly in solution following chemical reduction, which is a bottom-up approach [160]. Functionalization of archetypical QDs also bears a significant importance similar to other smart nanocarriers. As reported for other nanocarriers, QDs also experience non-specific uptake by the RES. 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 [162]. Recently, Iannazzo

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**Fig. 8.** (a) Schematic representation of the ‘core–shell’ structure of magnetic nanocarriers and multi-functional surface decoration, (b) illustration of super paramagnetic MNP response to applied magnetic fields. Reproduced with permission [134], under CC BY 3.0 license.
et al. showed the bright prospects of graphene QD-based targeted drug delivery. They covalently linked QDs 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, as shown in Fig. 10 [163]. QDs are specially known for cancer imaging due to their inherent fluorescence. A folic acid complex has been used to diagnose ovarian cancer [164]. To combat MDR, co-delivery of chemotherapeutics and siRNA was developed [165]. Bio-conjugated and polymer-encapsulated QD probes for cancer imaging and targeting were studied by Gao et al. [166,167].

**Cancer cell targeting mechanism**

If the anti-cancer drug-carrying smart nanocarrier survives the cleansing process of our body’s immune system, the smart
nanocarrier then finds the cancerous area of the body. A smart drug delivery system utilizes two types of targeting: passive targeting and active targeting [168,169]. Passive targeting employs the EPR effect [170] to locate cancer sites. Active targeting utilizes the ligand-receptor technique to locate the ultimate target – the individual cancer cell.

Passive targeting

Accumulation rate of drug-loaded 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 lymphatic system is the drainage system of the body. A deficiency of the lymphatic system leads to the retention of the nanoparticles in the tumor. This retention is known as the enhanced retention effect. Both the phenomena are collectively known as the EPR effect [171]. Using this EPR effect, the concentration of anti-cancer drugs in the tumor could be increased many times compared to the healthy tissue of the body. Interstitial fluid pressure (IFP) is another barrier in the way of successful accumulation of drug-loaded nanocarriers in the solid tumor [172,173]; however, efficient modifications of nanocarriers can overcome many biological barriers, including IFP and the RES [174].

Active targeting

Active targeting means guiding the drug-carrying nanocarriers to the cancer cells such as guided missiles [175]. Cancer cells and normal cells can be separated in terms of cell surface receptor and antigen expression. Cell surface receptors are embedded proteins in the cell membrane responsible for trans-membrane communication. Cancer cells show the amplification or overexpression of various cell surface receptors otherwise known as cell markers, such as folic acid and cell surface antigen. Drug-loaded nanocarriers are conjugated with targeting ligands. These ligands identify their matching target overexpressed on the cancer cell surface. Folate, transferrin, antibodies, peptides and aptamers are some investigated ligands.

Stimulus for drug release

Exogenous and endogenous are the two types of stimuli. An extra-corporal signal to release drugs from nanocarriers, such as a magnetic field, ultrasound waves, an electric field, a temperature change is known as exogenous stimulus. A signal produced from inside the body to release anti-cancer drugs is known as an endogenous stimulus. pH change, enzyme transformation, temperature and redox reactions are the examples of endogenous stimuli [176].

Endogenous stimulus

Endogenous stimulus is also known as intrinsic stimulus. In the case of endogenous stimulus, the triggering signal comes from the internal pH level, enzyme activity and redox activity of the body. Different types of endogenous stimuli are discussed below in detail [177].

The pH-responsive stimulus

According to the Warburg effect, the tumor cells predominantly produce energy due to enhanced glycolysis followed by lactic acid fermentation in the cytosol [178]. This extra acid production leads to lower pH in cancer cells. The pH-responsive drug delivery system is interesting because the pH level varies from organ to organ, even from tissue to tissue. The extracellular pH in tumors has an acidic environment compare to more slightly basic intracellular pH [179]. Therefore, pH has been established as an effective physiological property for smart drug delivery to tumor sites by many studies. This acidic extracellular pH results from poor blood flow, hypoxia and lactic acid in tumors [180]. The extracellular pH range is approximately 6–7 [181]. In addition to this pH gradient across the cell, there is a pH change across cell compartments. The lysosomal pH level is approximately 5, whereas the cytosol has a pH level of 7.2 [182]. The pH-sensitive nanocarriers usually store and stabilize anti-cancer drugs at physiological pH, but rapidly release the drug at a pH trigger point, which ensures that intracellular drug concentration reaches a peak. 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.

Redox sensitive stimulus

Glutathione sulfhydryl (GSH) is a highly effective antioxidant. It consists of three amino acids. GSH is found at higher concentrations in all mammalian tissue [183]. GSH controls the reductive microenvironment. The concentration of GSH in a tumor site is at least 4 times higher than in normal cells. The intra-cellular concentration of GSH is 1000 times higher than in the blood stream [70,184]. GSH, a functional group with the structure R-S-S-, can reduce the disulfide bonds of nanocarriers. Reduction of disulfide bonds leads to the release of an encapsulated drug [185]; for example, the disulfide bond of cross-linked micelles could be reduced by the cell-site GHS. The reduction of disulfide bonds leads to the precise cargo unload from nano-vehicles [186].

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. Enzymes are catalysts for biochemical reactions produced by living organisms. Enzymes play a vital role in cell function regulation; therefore, they are very important targets for drug delivery. Enzyme-triggered strategies utilize the overexpressed enzyme of the extracellular environment of tumor sites. This strategy is not applicable for intracellular drug release because the intracellular enzyme concentrations of cancer cells and healthy cells are almost same [187]. Proteases, an enzyme that breaks down protein and peptides, is an ideal candidate for releasing drugs from liposomes [188,189].

Exogenous stimulus

In extrinsic stimulus systems, contrast agents are used to visualize the accumulation of nanocarriers in cancer sites. The accumulated drug-loaded nanocarriers are stimulated by an external factor, such as a magnetic field, ultrasound waves, light and electric fields [190] to release drugs at the right concentration.

Magnetic field responsive stimulus

In magnetically induced systems, an extracorporeal magnetic field is used to accumulate drug-loaded nanocarriers in tumor sites after the injection of nanocarriers. Core-shell structured
nanoparticles coated with silica, polymer or magnetoliposome (magnehite nanocrystals encapsulated in liposomes) are some ideal candidates for magnetic stimulus [191,192]. Magnetically guided nanocarriers can also carry genetic materials. 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 [193–195].

Thermo-responsive stimulus

In this method, drug-loaded nanocarriers release their payloads in response to temperature change. At a predetermined temperature, the nanocarriers change their conformation, solubility or hydrophilic and hydrophobic balance. There are some nanocarriers which release their cargo whenever they go through a temperature change. Thermo-sensitive nanocarriers show the lower critical solution temperature (LCST) phenomena [196,197]. Polymer aqueous solutions show one phase below LCST and phase separation above the temperature. Micelles with thermo-responsiveness are being widely studied [198,199]. Thermo-sensitive hydrogels and poly (N-isopropyl acrylamide) (PNIPAAm) show temperature above the temperature. Micelles with thermo-responsiveness are being widely studied [198,199]. Thermo-sensitive hydrogels and poly (N-isopropyl acrylamide) (PNIPAAm) show temperature responsive sol-gel transitions [200].

Light-triggered stimulus

The recent development 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. The stimulus is achieved by making the nanocarriers sensitive to light [201–203]. CNTs and GPNs 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 [204].

Ultrasound-responsive stimulus

Ultrasound is under intense investigation to release drugs from nanocarriers because of its non-invasiveness characteristics, deep penetration into the body and non-ionizing irradiation [205]. By using ultrasound, both thermal and mechanical effects can be induced in the nanocarriers to release the loaded-drug. The release of drugs from temperature-sensitive liposomes was investigated by Dromi el al. in 2007 using high intensity focused ultrasound waves [206,207,208].

Electric field-responsive stimulus

This stimulus system uses an electric field to release payloads. The thermo-responsive, light-triggered and ultrasound-responsive stimulus systems discussed already require large or specialized equipment to release drugs. On the contrary, electric fields are easy to generate and control [209]. 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 and the molecular weight of the drug. Biotin is a dopant that has been studied experimentally [210]. MWCNTs can be used as a conductive additive to increase electrical conductivity [211]; in addition, polyelectrolyte hydrogels are also in consideration [212,213].

Toxicity study of eight nanocarriers

Currently, the toxicity of nanocarriers in the human body is the most important issue for investigation. To give the current status of toxicity research on nanocarriers loaded with anti-cancer drugs to the relevant researchers, a study is presented in Table 1.

Table 1
Different nanocarriers in terms of toxicity and bio-distribution.

| SDDS name        | Toxicity                                                                 | Bio-distribution of nanocarrier and renal excretion | Refs.        |
|------------------|-------------------------------------------------------------------------|-----------------------------------------------------|--------------|
| Liposome-based SDDS | * Cationic liposome affects the in vitro growth of different cell lines, such as L1210, HepG2, A549, etc. | Majority accumulates in the liver followed by spleen. | [214–224]    |
|                   | * In vivo study shows DNA damage due to the cationic surface charge.     | Rapid clearance with urine.                         |              |
| Micelle-based SDDS | * Kawaguchi investigated the toxicity of polymeric micelles, which show no pathological abnormalities. | The Kawaguchi experiment finds that polymeric micelle-based drug carriers trigger transient immunogenicity in the MPS system. | [59,225–231] |
|                   | * Many investigations show that polymeric micelles are less toxic.       | Polymeric micelles based on poly (ethylene oxide) and α-carbon substituted poly (ε-caprolactone) are found to be non-immunogenic to dendritic cells—the antigen presenting cell of the mammalian immune system. |              |
| Dendrimer-based SDDS | * Dendrimers, such as PPI, PAMAM, and PLL, exert significant in vitro cytotoxicity due to their surface catatic groups, but significantly lowered cytotoxicity is observed with the PEG-modified dendrimer. | The in vivo toxicity screening of well characterized cationic polymeric micelles shows that particles could be found in major organs, such as lung, liver, kidney. | [75,88,232–241] |
|                   | * Naha et al. study shows that PAMAM has adverse effects on mammalian cells. | Peptide Amphiphile accumulates primarily in bladder then pass through the urine. |              |
|                   | * Proper surface modification can reduce cytotoxicity.                   | Dendrimers show no or little immunological response. |              |
|                   |                                                                         | Roberts et al. investigated the immunogenicity of the PAMAM dendrimer. |              |
|                   |                                                                         | They are present in the intracellular compartment of kidney, liver and lung. |              |

(continued on next page)
### Factors affecting the toxicity of nanocarriers

Table 1 shows that all the engineered nanocarriers exhibit some degree of toxicity. The toxicity of the nanocarriers depends on their size, shape (tube, films, rods, etc.) [282] surface charge and the presence or absence of a shell. In addition, the route of administration of drugs [283] and the dose of drugs also determine the toxicity of nanocarriers [284]. Size is the most important parameter in toxicity assessments of nanocarriers. The toxicity and the size of nanocarriers are inversely related; that is, the smaller the size of the nanocarriers, the higher the toxicity and vice versa [250,285]. Shape also has a very important role in toxicity. For example, spherical gold nanocarriers are almost safe for the human body, while rod-shaped ones are very toxic [286,287]. The surface charge of nanocarriers is another challenge to SDDS design, as the surface charge largely determines the interaction between the body and nanocarriers. Nanocarriers with positive charges, or cationic nanocarriers, show greater toxicity compared to ones with negative surface charges [214,288]. A shell around the nanocarriers plays a vital role in reducing the toxicity of nanocarriers. Research shows that intravenous (IV) administration brings more medical complications than oral administration.

### Challenges and the future research scope

Every opportunity comes with some challenges. SDDSs are no exception. The barriers in the way of successful SDDSs is the toxicity of nanocarriers in the human body, cost-effectiveness of the system, the diversities and heterogeneities of cancer, and lack of specific regulatory guidelines [289–291].

To kill the cancer cell, nanocarriers carry and release the anticancer drugs at the targeted sites. The concern is with the ultimate fate of the drug-carrying nanocarriers. Depending on the chemical composition, size, shape, specific surface area, surface charge as well as the presence and absence of a shell around the nanocarrier, conventional nanocarriers accumulate in different vital organs such as the lungs, spleen, kidneys, liver and heart. A comprehensive study of the bio-distribution of nanocarriers is summarized in Table 1 above. Table 1 shows that the majority of nanocarriers are not discharged from body; instead, they accumulate in the vital organs mentioned above [292]. This deposition leads to toxicity, which is a gigantic barrier in the way of the success of SDDSs. Many in vitro and in vivo studies of toxicities in the cases of animals have been performed; unfortunately, toxicity studies in the human body are very limited. The research scope for toxicity studies is still wide open [293,294].

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### Table 1 (continued)

| SDDS name | Cytotoxicity | Toxicity | Immunogenicity | Bio-distribution of nanocarrier and renal excretion | Refs. |
|-----------|-------------|----------|----------------|---------------------------------------------------|-------|
| Meso-porous silica nanoparticle-based SDDS | • In vitro cytotoxicity is controversial. | • Functionalized mesoporous silica nanoparticles do not affect the viability of primary immune cells from the spleen in relevant concentrations. | • Silica nanoparticles have a toxic effect on the liver. | • MSNs mainly distribute in the liver and spleen; minority can be found in the lungs, kidneys and heart. | [46,100,106,242–249] |
| $\text{Meso-porous silica nanoparticle-based SDDS}$ | • Pasqua et al. showed that MCM-41 and two of its functional analogs kill human neuroblastoma (SK–N–SH) cells. | • Potential adverse effects on the immune system are not clear and need further research. | • Silica nanoparticles have a toxic effect on the liver. | • PEGylated MSNs with smaller particle sizes possess longer blood circulation and lower graded products in the urine. | |
| Gold nanocarriers-based SDDS | • Silica nanoparticle cytotoxicity is size dependent; smaller particles have higher toxicity. | • The immunological study of the RAW264.7 macrophage did not indicate any immunological toxicity. | • GSH coated GNP nanocarriers have lower accumulation in the kidneys and liver compared to bare GNPs. | • Mostly excreted with urine and no systemic toxicity. | [175,250–260] |
| Gold nanocarriers-based SDDS | • In vitro cytotoxicity screening of K562 leukemia cells shows that they do not exhibit an acute toxic effect based on the MTT assay—colorimetric assay for assessing cells’ metabolic activity. | • Villiers et al. also showed non-immunological toxicity. | • Mostly excreted with urine and no systemic toxicity. | • Mostly excreted with urine and no systemic toxicity. | |
| Gold nanocarriers-based SDDS | • Experiment on RAW264.7 also shows no considerable cytotoxicity based on the MTT assay. | • In vivo experiment showed size dependent toxicity; that is, nanoparticles with certain sizes show lethal toxicity while other sizes of nanoparticles show no considerable toxicity. | • Mostly excreted with urine and no systemic toxicity. | • Mostly excreted with urine and no systemic toxicity. | |
| Gold nanocarriers-based SDDS | • On the other hand Goodman in 2004 shows that cationic GNanocarriers show toxicity. | • Pan et al. in 2009 shows size dependent cytotoxicity. | • Mostly excreted with urine and no systemic toxicity. | • Mostly excreted with urine and no systemic toxicity. | |
| Gold nanocarriers-based SDDS | • The immunological study of the RAW264.7 macrophage did not indicate any immunological toxicity. | • The generation of ROS could trigger immunological toxicity. | • Mostly excreted with urine and no systemic toxicity. | • Mostly excreted with urine and no systemic toxicity. | [130,261–265] |
| Gold nanocarriers-based SDDS | • Villiers et al. also showed non-immunological toxicity. | • Primarily found in the spleen and liver. | • Mostly excreted with urine and no systemic toxicity. | • Mostly excreted with urine and no systemic toxicity. | |
| SPION-based SDDS | • SPIONS are toxic to brain cells with different coatings. | • CNTs functionalized with peptides do not trigger anti-peptide antibodies. | • Well individualized MWCNTs with shorter lengths and higher degrees of oxidation escape the RES in organs (liver, spleen lungs) and clear through renal excretion. | • Well individualized MWCNTs with shorter lengths and higher degrees of oxidation escape the RES in organs (liver, spleen lungs) and clear through renal excretion. | [266–272] |
| CNT-based SDDS | • Interaction of functionalized SWCNTs with CHO and 3T3 cells exhibited no toxicity. | • CNTs functionalized with peptides do not trigger anti-peptide antibodies. | • Well individualized MWCNTs with shorter lengths and higher degrees of oxidation escape the RES in organs (liver, spleen lungs) and clear through renal excretion. | • Well individualized MWCNTs with shorter lengths and higher degrees of oxidation escape the RES in organs (liver, spleen lungs) and clear through renal excretion. | |
| Quantum dot-based SDDS | • QD-induced cytotoxicity is not observed in many in vivo and in vitro experiments. | • Immune response could be suppressed by CdSe/ZnS QDs. | • Salykin et al. report that QDs primarily deposit in the lung and atri-ums of heart. | • Not excreted with urine. | [273–281] |
Cancer varies in diversity and heterogeneity; that is, the types of cancers are still undetermined. Moreover, the physical nature of cancer may vary from person to person. Therefore, personalization of anti-cancer treatment is also a major challenge. DNA/RNA-based anti-cancer treatments have a bright future to make medication personalized and safer. Thus, the development of nanocarriers as carriers of DNA/RNA to remove cancer cells could be a promising research area [295–297].

In the way of finding of cancer cells, conventional nanocarriers face many biological challenges, such as the RES, accelerated blood clearance (ABC), etc. To address those hurdles, conventional nanocarriers are modified using various processes, including PEGylation, grafting ligands on the surface of nanocarriers; in addition, the nanocarriers need to be functionalized in order to release the drugs at target sites under stimulation. These modifications lead to increased manufacturing steps, which in turn lead to an increased cost of the final product. The cost-benefit balance should be positive for any launched product to be sustainable in the market [298–300].

Securing approval from regulatory authorities is the ultimate challenge in the way of the commercialization of SDDSs. The FDA and European medicines authority (EMA) have very strong roles in the approval process. Twenty-three years after the first smart nanocarrier-based anti-cancer drug, Doxil, has been reported in 1995 the number of FDA-approved nanocarrier-based anti-cancer drugs is very limited, though there are many products in the pipeline. For regulatory approval, the manufacturers are supposed to prove the safety of the products for the human body both in the short term and long term. Therefore, it is very time consuming and laborious to launch a product following all the necessary steps. The lack of specific guidelines sometimes complicates the approval process. Therefore, an accord among researchers, industry and regulatory authorities is necessary to overcome these barriers [301,302].

Conclusions and future perspectives

Nanocarriers, a wonder of modern science, play vital roles in biomedical applications, especially in anti-cancer drug delivery. To conquer the limitations associated with conventional chemotherapy, smart nanocarrier-based drug delivery systems, also known as SDDSs, have been introduced. However, there are still many challenges ahead for SDDSs to be effectively applied as a promising alternative to chemotherapy for cancer treatment; therefore, the technology behind SDDSs is under continuous research. The toxicity of the nanocarriers is a major barrier in the way of a successful SDDS. Studies have been conducted to either optimize the toxicity of existing nanocarriers or to develop some other new nanocarriers with lower toxicity. This review considers the gravity of toxicity and makes a bio-distribution assessment of the eight most common nanocarriers used in SDDSs. Our study on toxicity along with bio-distribution shows that almost every nanocarrier, from liposomes to QDs, show some degree of toxicity. The toxicity suggests that more extensive research is needed for SDDSs. The associated challenges and future research scope in SDDSs, which may favor the enduring perspectives and development of nanocarrier-based SDDSs for cancer treatment, have also been discussed.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics requirements

This article does not contain any studies with human or animal subjects.

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Hu S-H, Chen S-Y, Liu D-M, Hsiao C-S. Core/single-crystal-shell nanospheres for controlled drug delivery via a magnetically triggered rupturing mechanism. Adv Mater 2008;20:2690–5.
Ferritin has been shown to have a therapeutic role in a variety of diseases, including cancer, where it is used as a vaccine vector for therapeutic proteins and as an adjuvant for immunotherapies.

Knudsen et al. investigated the therapeutic potential of ferritin nanoparticles in a mouse model of cancer. The nanoparticles were engineered to deliver a payload of a therapeutic cargo, such as a chemotherapy drug or a vaccine antigen. The results showed that the nanoparticles were able to effectively deliver the payload to the tumor site, leading to improved therapeutic outcomes.

Jin et al. studied the killing activity of ferritin nanoparticles in various cancer cell lines. The nanoparticles were engineered to express a cytotoxic cargo, such as a prodrug that is activated upon internalization by cancer cells. The results showed that the nanoparticles were able to selectively kill cancer cells while sparing normal cells, demonstrating their potential as a targeted therapeutic agent.

In conclusion, ferritin nanoparticles represent a promising therapeutic platform for cancer and other diseases, with potential applications in targeting and delivering therapeutic cargoes to specific cell types.

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**Note:** This information is based on the abstract and is intended to provide a general understanding of the research. For a complete understanding, please refer to the original publications.
M. Khalid Hossain has received his Master of Science (M.Sc) degree in Applied Physics, Electronics and Communication Engineering from the Islamic University, Kushtia, Bangladesh in 2009. During his M.Sc program, he mainly focused on the preparation of amorphous Fe_{73.5}Cu_{1}Nb_{3}Si_{13.5}B_{9} magnetic ribbon by a rapid quenching method; then, the nanostructure and ultra-soft magnetic properties were developed by heat treatment. He has been a research scientist of the Institute of Electronics, Bangladesh Atomic Energy Commission (BAEC), Dhaka, Bangladesh since 2012. His research interests include-energy materials, micro/nano fabrication, thin films, photovoltaic devices and advanced functional materials. He has published 17SCI(E) articles as author and co-author in various reputable peer reviewed journals.

M. Khairedul Bashar received his B.Sc. and M.Sc. degree in Applied Physics, Electronics & Communication Engineering from the University of Chittagong, Chittagong, Bangladesh in 2007 and 2008, respectively. He also completed a M. Phil degree in Material Science from the Bangladesh University of Engineering and Technology, Dhaka, Bangladesh. After completing M.Sc., he joined the Bangladesh Atomic Energy Commission as a scientist in 2012. He is now working as a research scientist in the Institute of Electronics, Bangladesh Atomic Energy Commission. His research interest mainly focuses on nanostructured materials and energy materials.

M. Nasrul Haque Mia received his B.Sc. and M.Sc. degree in Applied Physics, Electronics & Communication Engineering from the Islamic University, Kushtia, Bangladesh in 2003 and 2004, respectively. After completing his M.Sc., he joined the Bangladesh Atomic Energy Commission as a scientist in 2009. He is now working as a research scientist and divisional head of the VLSI technology laboratory in the Bangladesh Atomic Energy Commission. His research interest mainly focuses on nanotechnology and biomedical applications. He has published 17SCI(E) articles as author and co-author in various reputable peer reviewed journals.

M. Tayebur Rahman received his B.Sc. (Eng.) and M.Sc. (Eng.) degrees in Materials Science and Engineering from the University of Rajshahi, Bangladesh in 2014 and 2015, respectively. During his B.Sc. program, he explored the area of nanotechnology in medicine sectors, and, during his M.Sc. program, he fabricated ceramic nanoparticles (Fe_{2}O_{3}, TiO_{2} and NiFe_{2}O_{4}) dispersed in HDPE and UPR polymer matrix as novel nanocomposites to evaluate the mechanical, thermal, optical, and electrical properties. Currently, he is working as a research fellow in the Bangladesh Atomic Energy Commission (BAEC) and Bangladesh Council of Scientific and Industrial Research (BCSIR). His research interest mainly focuses on nanomaterials for bio-medical applications, nanocomposites, thin films and photovoltaic devices.