Gels Horizons: From Science to Smart Materials

K. S. Joshy
Sabu Thomas
Vijay Kumar Thakur *Editors*

Nanoparticles for Drug Delivery

Springer

Gels Horizons: From Science to Smart Materials

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Preface

This book discusses most of the well-investigated biomaterials, nanomaterials quantum dots, ceramic materials and hybrid nanomaterials designed for drug delivery and cancer therapy. It recapitulates the confront and opportunities offered by such nanomaterials for an advanced drug delivery. Some biomaterials developed for most intensively studied diseases, such as cancer, are presented in detail. Recent advances in the field of tailored drug delivery systems (DDS, e.g. quantum dots, ceramic-based nanomaterials, stimuli-responsive hybrid nanosystems lipid, polymeric and biopolymers) and their applications for controlled delivery of drugs have been discussed in detail, and finally, future opportunities of nanomaterials and hybrid nanosystems for advanced drug delivery can be found within this volume.

The book entitled *Nanomaterials for Drug Delivery* contains eight chapters, as follows:

Chapter 1, "Nanomaterials for Cancer Therapeutics", prepared by Saravanan Krishnan et al., presents an up-to-date overview of recent developments in the application of nanoparticles based cancer therapeutics. Various multifunctional nanoparticles used to provide effective cancer therapy are illustrated with suitable examples. Moreover, the FDA- or EMA-approved nanomedicines and other approval awaiting (under clinical trials) nanomedicines for cancer therapy are highlighted

Chapter 2, "Biomaterials and Its Advances for Delivering Anticancer Drugs", prepared by Rajakumari et al., provides insights about the wide range of polymers which help to engineer the anticancer molecules. It also emphasizes the different mechanisms for releasing the anticancer drugs in an effective manner. The recent advances about the materials used for cancer therapy and commercially available products are also discussed. The effect of engineered biomaterials for treating the cancer patients is mostly expected to increase in future

Chapter 3, prepared by Priya Vijayaraghavan et al., entitled "Stimuli-responsive Hybrid Polymeric Nanoparticles for Targeted Drug Delivery", provides an overview of the use of designing polymeric nanoparticle responding to various stimuli for the applications in medical applications. A combination of various triggers and polymeric nanoparticles creates unique and smart therapeutic materials. Surface modification of polymeric nanoparticles sensing various chemical and physical

signals of the human body is one key aspect towards building up site-specific drug delivery vehicles. So far, most of the drug delivery systems reported has extremely intricate designs which may perhaps be possible to hinder the cost-effective and scaled-up production. Hence, the possibility of stimuli-responsive nanoparticles towards clinical acceptance has been thoroughly discussed in this chapter

Chapter 4, entitled "Hybrid Nanoparticles in Image-Guided Drug Delivery", prepared by Finosh G. T., presents the multidisciplinary approach of combining drug delivery and image-guided diagnostics which led to the evolution of theranostic approaches which exhibit significant translational potential.

Chapter 5, prepared by Narendra Pal Singh Chauhan, entitled "Ceramic-Based Hybrid Nanoparticles in Drug Delivery", reviews the different kinds of hybrid ceramic nanoparticles for drug delivery applications.

Chapter 6, "Biomaterials for Anticancer Drugs", prepared by Remya V. R. et al., gives an overview of the current state of the art in cancer, oral chemotherapy and different biomaterials for anticancer drug and their advantage over conventional anticancer drugs. This chapter will be a remarkable one for understanding the usage of different types of biomaterials for the enhancement of bioavailability of anti-cancer drug delivery system.

Chapter 7, prepared by Durgadas Cherukaraveedu, entitled "Quantum Dots in Drug Delivery", investigates the use of "quantum dots" in enormous opportunities in future for the theranostic approaches and their extraordinary features for biomedical applications. The bright future of nanomedicine can definitely address the unmet clinical concerns in the cancer drug delivery by exploring the brightly emitting quantum dots.

Chapter 8, entitled "Nanotechnology and Its Implication in Antiviral Drug Delivery", prepared by Joshy K. S. et al., provides an insight into the life cycle and infection of HIV and various nanoparticulate delivery vehicles used for anti-retroviral drugs. Biocompatible polymeric nanoparticles, liposomes and hybrid nanosystems have been thoroughly discussed. Such nanostructured materials hold great promise for the future of HIV treatment and can be expected to improve the quality of life of HIV victims.

Kottayam, India — K. S. Joshy
Kottayam, India — Sabu Thomas
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Contents

Editors and Contributors

About the Editors

K. S. Joshy is a post-doctoral researcher at the International and Inter University Center for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kerala, India. His research interests include synthesis and characterization of nanoparticles with application for drug delivery. He has authored 10 research articles in high-impact journals, one book chapter and has been a co-editor on one book.

Sabu Thomas is currently Professor and Pro-Vice Chancellor in Mahatma Gandhi University, Kerala, India, in addition to being the founder director of the International and Inter University Centre for Nanoscience and Nanotechnology. After his B.Tech. in polymer science and rubber technology from University of Cochin, he went on to do his Ph.D. from Indian Institute of Technology, Kharagpur. Professor Thomas is the Chief Editor of *Nano-Structures & Nano-Objects* and has received many national and international awards, including Fellowship of the Royal Society of Chemistry, MRSI award, SESR award, the Dr. A. P. J. Abdul Kalam Award for Scientific Excellence, an honorary degree by Université de Lorraine, and multiple fellowships by prestigious societies and universities. Professor Thomas' research has spanned many areas of nanocomposite and polymer science and engineering, and he has edited more than 70 books, holds five patents and has authored over 750 research publications.

Dr. Vijay Kumar Thakur is currently a faculty member in the School of Aerospace, Transport and Manufacturing at Cranfield University. Prior to this, Dr. Thakur worked as a Staff Scientist in the School of Mechanical and Materials Engineering at Washington State University, U.S. Some of his other prior significant appointments include being a Research Scientist in Temasek Laboratories at Nanyang Technological University, Singapore and a Visiting Research Fellow in the Department of Chemical and Materials Engineering at LHU–Taiwan. He did his post-doctoral study in Materials Science and Engineering at Iowa State University

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Chapter 1
Nanomaterials for Cancer Therapeutics

Saravanan Krishnan, Blessy Joseph, Jemy James, and Sabu Thomas

Abstract Cancer is a fatal disease which occurs due to abnormal and uncontrolled growth of cells in the form of tumor. To meet the societal requirements of a proper diagnosis of cancer and effective cancer treatment, researchers put their continuous efforts using cutting-edge technology to develop novel cancer theragnostics. Nanotechnology has revolutionized the field of medicine through point-of-care cancer diagnosis and site-specific drug delivery for treating cancer. The use of nanoparticles as drug carriers might improve the therapeutic efficacy by means of targeted drug delivery. This chapter presents an overview of recent developments in nanoparticles-based cancer therapeutics. Various multifunctional nanoparticles that are developed for effective cancer therapy are illustrated with suitable examples. Moreover, the FDA- or EMA-approved nanomedicines and other approval awaiting (under clinical trials) nanomedicines for cancer therapy are elaborated.

Keywords Cancer · Nanoparticles · Multifunctional · Therapy · Drug delivery

1 Introduction

Cancer remains the major cause of human death worldwide. Further, technological advancements have made diagnosis of cancer much easier, and also decreases the overall mortality rate. Chemotherapy, radiation, immunotherapy, etc., are few of the the active strategies used in cancer treatment. However, lack of specificity

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remains a major problem with all these conventional techniques. As a step toward controlling the progression of cancer, it is important to devise targeted drug delivery systems for effective cancer therapy. The use of nanoparticles as drug carriers can significantly alter the pharmacokinetic and pharmacodynamics of the drugs. As compared to conventional cancer treatment modalities, the use of nano-biomaterials in cancer has unique advantages like (i) can carry high load of chemotherapeutic agent, (ii) multiple drug release, (iii) site-specific drug delivery, (iv) controlled drug release, (v) protect the drug from degradation and improve the solubility. Site-specific targeting is an important aspect in the design of nanoparticle based drug delivery system. Passive targeting and active targeting are the two approaches of targeted drug delivery. Passive drug delivery is a size-dependent process, whereas active targeting involves surface modification of nanoparticles with one or more agents like vitamins (folate), peptides (e.g., RGD), proteins (antibody), sugars (glucose), aptamers and few others. With the advent of nanotechnology, there are several nanoparticles-based cancer therapeutics being developed and evaluated for their performance in cell line and animal model studies. This chapter presents the recent advances in the developments of nanoparticles-based therapeutics and their mechanism of action.

2 Molybdenum-Based Nanoparticles

Wang et al. [1] reported that the bifunctional bioceramic 3D scaffold containing molybdenum disulfide nanosheets prepared by hydrothermal method showed positive effect in treating malignant bone tumors, by removing the tumor tissues and bone defect regeneration. Increased photothermal temperature resulted from NIR-responsive bifunctional scaffold causes cancer cell death. More importantly, this scaffold promotes the attachment, proliferation and differentiation of bone mesenchymal stem cells along with induction of bone regeneration mechanism.

In another study, the biocompatible nanocomposite containing molybdenum disulfide and graphene oxide has shown to selectively target the lung cells [2]. Moreover, this nanocomposite offers enhanced drug loading capacity with tumor killing effect and also prevents the metastasis of cancer cells to the lungs, as evidenced by studies with B16 murine melanoma cancer cells in lungs of mice (Fig. 1).

3 Iron and Other Magnetic Nanomaterials

Ma et al. [3] reported the synthesis of Fe–$CaSiO_3$ composite scaffold (30CS) by ball milling method and 3D printing technique, as efficient biomaterial for treating bone cancer. This bioscaffold offers few promising features like improved mechanical support and enhanced tumor killing efficacy through synergic combination of

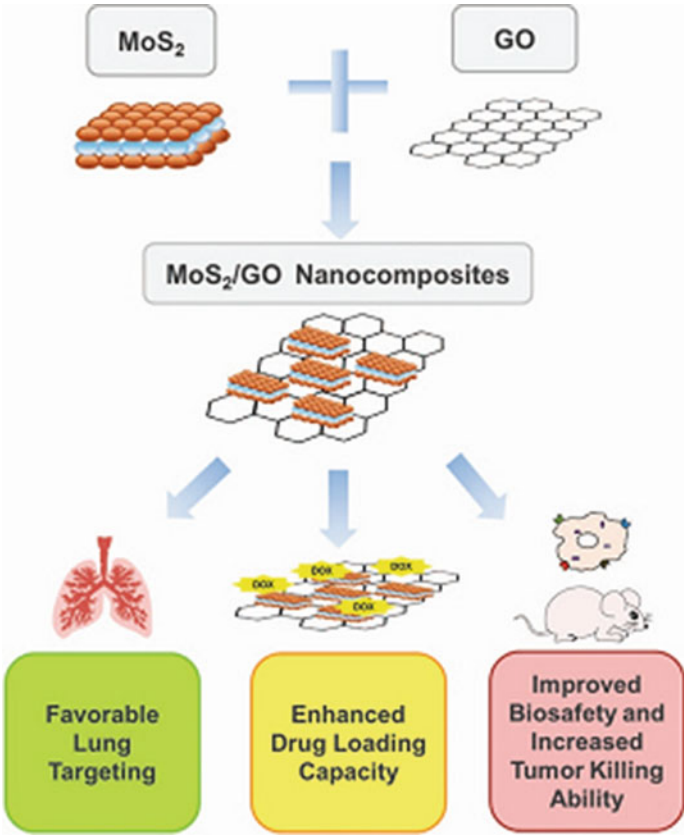

Fig. 1 Schematic depicting the application of molybdenum disulfide and graphene oxide nanocomposites with targeted therapeutic efficacy in treating lung cancer [2]

photothermal and ROS therapy as shown in Fig. 2. Calcium metasilicate induces the proliferation and differentiation of bone marrow-derived mesenchymal stem cells (rBMSCs) and further boosts the cellular machinery involved in bone formation.

Like other nanoparticles, magnetic nanomaterials have also been developed and simultaneously been explored toward the design of novel cancer theragnostics. An example is the iron diselenide nanoparticles developed and evaluated for combined multimodal imaging and photothermal therapy in treating cancer [4]. Evidently, it is interesting to note that this nanomaterial acts as both contrast agent for tumor imaging and photothermal agent for cancer therapeutic applications. Moreover, this magnetic nanomaterial $FeSe_2$ did not show any toxicity during the long-term toxicity studies in mice which also emphasize its therapeutic role in establishing a promising anti-cancer therapy. In a separate study, the design of nanoformulation of magnetoliposomes which is composed of maghemite nanoparticles and

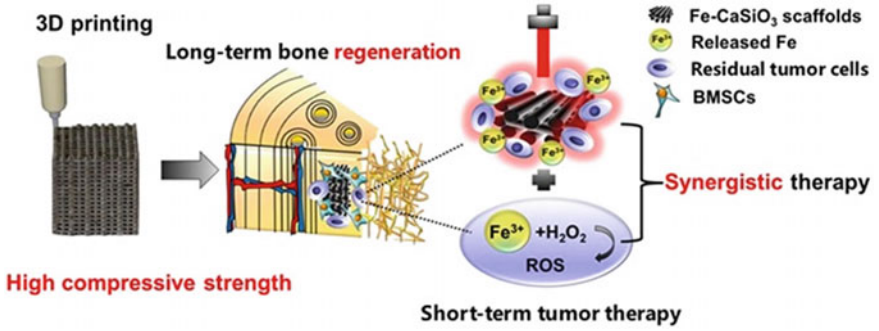

Fig. 2 Schematic depicting the application of Fe-$CaSiO_3$ composite scaffold (30CS) for treating bone cancer [3]

phosphatidylcholine liposomes is reported [5]. Further, cytotoxicity assay of this nanomaterial carried out against human blood cells, human non-tumor colon and colon cancer cell lines which demonstrates that magnetoliposomes acts as an excellent biocompatible nanomaterial with maximum cellular uptake at 24 h. Moreover, the proof of functionality of this nanoformulation is also evidenced by the cell migration effect observed in colon cancer cells, due to applied external magnetic field.

In another study, iron oxide nanoparticles were reported to improve the drug solubility and cytotoxicity against cancer cells [6]. Toward this, synthesis and evaluation of galbanic acid-coated Fe_3O_4 magnetic nanoparticles against prostate cancer cell lines (androgen-dependent and androgen-independent) are reported. It is already established that galbanic acid is cytotoxic only against androgen-dependent prostate cancer type. Here, the galbanic acid-coated Fe_3O_4 magnetic nanoparticles showed appreciable cytotoxicity against androgen-independent prostate cancer cell lines. Nanocomposite that mimics the tumor cell may have significant role toward achieving precise cancer therapy. To this end, a bioinspired nanosystem, namely SPIO@DOX-ICG, which camouflages the cancer cell membrane is designed by Huang and his research group [7]. This biocompatible nanosystem comprise of specific antigens and adhesion molecules present on the cancer cell surface, due to which it accumulates selectively in the tumor region.

Dual functional nanoparticle systems can also be used as nanovehicles to target the cancer cells with high specificity. Recently, Liu et al. [8] reported the preparation of Tat-functionalized Ag–Fe_3O_4 nanocomposites to treat breast cancer under in vitro and in vivo conditions. In this study, silver nanoparticles act as carriers of doxorubicin and further gets released in pH-dependent manner. Cell penetrating peptide (Tat) and external magnetic field together increase the cytotoxicity of drug-loaded nanoparticles. Analysis of anti-tumor efficacy revealed that Tat-FeAgNP-Dox demonstrated excellent inhibition of tumor cellular growth and

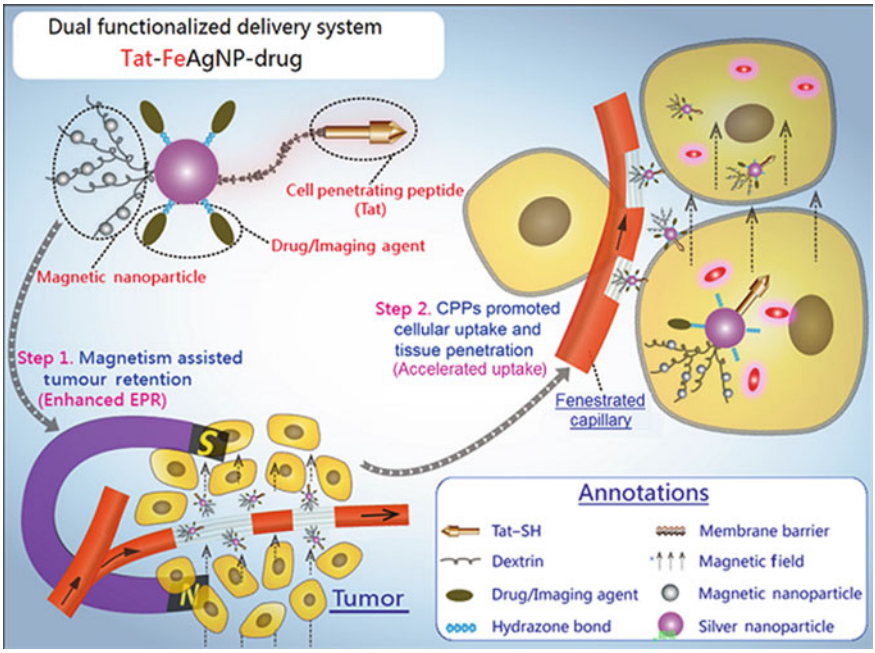

Fig. 3 Schematic showing the mechanism of anticancer efficacy of dual functional nanocomposite (Tat-FeAgNP-Dox) in breast cancer cells [8]

significantly reduces the specific growth rate of tumor by 29.6%. Iron oxide nanoparticles increase the retention from circulation, whereas Tat peptide increases the penetration of this nanocomposite in tumor cells as shown in Fig. 3.

4 Chitosan-Based Nanoparticles

Naqvi et al. [9] reported the preparation of niclosamide-loaded chitosan nanoparticles (Nic-Chi Np's) and also evaluated the therapeutic efficacy against breast cancer cell line (MCF-7) and human lung cancer cell line (A549). Accumulation of reactive oxygen species and the induction of apoptosis are the possible mechanisms of action of Nic-Chi Np's against these cancer cell lines. Toward understanding the mechanism, semiquantitative RT-PCR studies showed that the pro-apoptotic genes (Bak, Bax, Bad, P^{53}, caspase) are upregulated and anti-apoptotic genes (Bcl-2 and Bcl-xL) are downregulated (Fig. 4).

Recently, a facile method to encapsulate chitosan (CS)/polylactide (PLA) nanoparticles with drug tamoxifen and further explore its role in the treatment of breast cancer is reported [10]. Drug-loaded nanoparticle system kills both the hormone-positive breast cancer cells and hormone-triple negative breast cancer

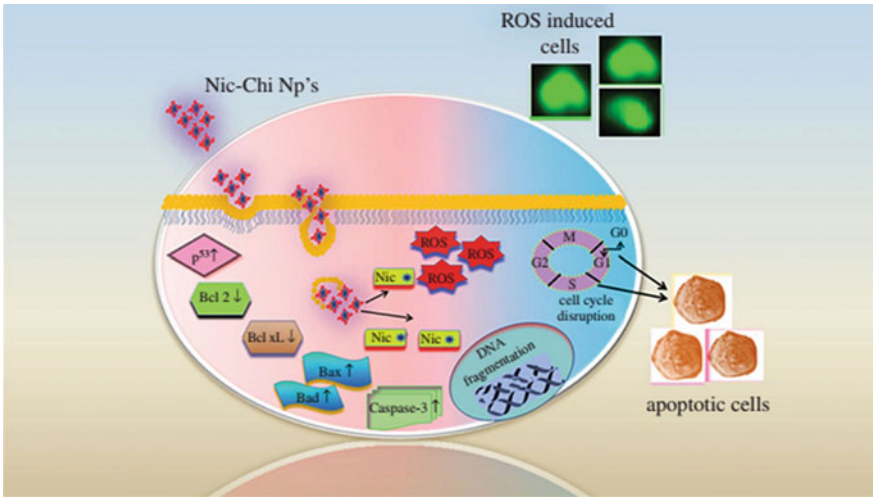

Fig. 4 Schematic showing the mechanism of niclosamide-loaded chitosan nanoparticles in cancer cells [9]

cells. In another study, synthesis and characterization of chitosan–tripolyphosphate nanoparticles encapsulated with chlorine e6-decorated doxorubicin are reported for the NIR-responsive drug release associated with the treatment of breast cancer [11].

5 Polymer-/Polyamino Acids-Based Nanoparticles

Polymer nanoparticles-based cancer theragnostic agents can also be programmed to demonstrate better anti-cancer efficacy. In a study by Au et al. [12], an approach of targeted cancer therapy lying between the fast releases of tumor apoptosis inducing agent and the slow release of therapeutic agent is devised. Experiment with paclitaxel-loaded microspheres showed better site-specific drug delivery and drug retention in the tumor site than the commercial Taxol drug. In a study by Gelperina et al. [13], a doxorubicin drug-loaded polymer nanoparticle coated with surfactant Tween 80 is reported to effectively pass through the blood-brain barrier and treats the brain cancer.

In the realm of developing novel nanomaterials as drug delivery vehicles in cancer therapeutics, self-assembled polyelectrolytes-based nanoparticles are recently reported [14]. In this study, the anti-cancer drug methotrexate is loaded onto these self-assembled PAH/fucoidan nanoparticles and further evaluated on MCF-7 cells and HeLa cells. Apparently, this biodegradable and biocompatible self-assembled polyelectrolyte nanocomposite effectively inhibits both the cancer cells due to the sustained release of cancer drug. In other study, the use of drug-loaded hybrid nanoparticles comprising poly(lactide-co-glycolide) (PLGA)

and bovine serum albumin (BSA) are covalently linked with pH-sensitive peptide (acidity-triggered rational membrane peptide, ATRAM) is for efficient targeting of cancer cells is established [15].

Synthesis of biodegradable and biocompatible polymeric nanoparticles PLA-PEG-PPG-PEG using poly(lactic acid) or PLA, poly(ethylene glycol) or PEG, and poly(propylene glycol) or PPG is reported [16]. These polymeric nanoparticles can be further modified into multifunctional nanostructures by encapsulating with one or more agents (peptides and antibodies) for site-specific targeting and cancer therapy. Semiconducting polymer nanoparticles of poly(diketopyrrolopyrrole-terthiophene) (PDPP3T NPs) were fabricated using *N*-isopropylacrylamide (NIPAM) and acrylic acid (AA) as monomer along with bis (2-methacryloyl) oxyethyl disulfide (BMOD) as crosslinker [17]. This type of semiconducting polymer nanoparticles (SPNs) has found tremendous success in recent years as promising theragnostic agent owing to their good optical properties, high photostability and outstanding biocompatibility. PDPP3T@PNIPAMAA interpenetrating networks (IPNs) made from the SPNs (Fig. 5) were evaluated for photothermal therapy. It exhibited excellent photothermal properties and also showed an increase in temperature from 27 to 60 °C at a laser power density of 0.75 W/cm^2. In vivo studies showed significant tumor necrosis when combined with chemo-/photothermal therapy, while PDPP3T@PNIPAMAA-DOX IPNs without irradiation only caused partial apoptosis of tumor cells.

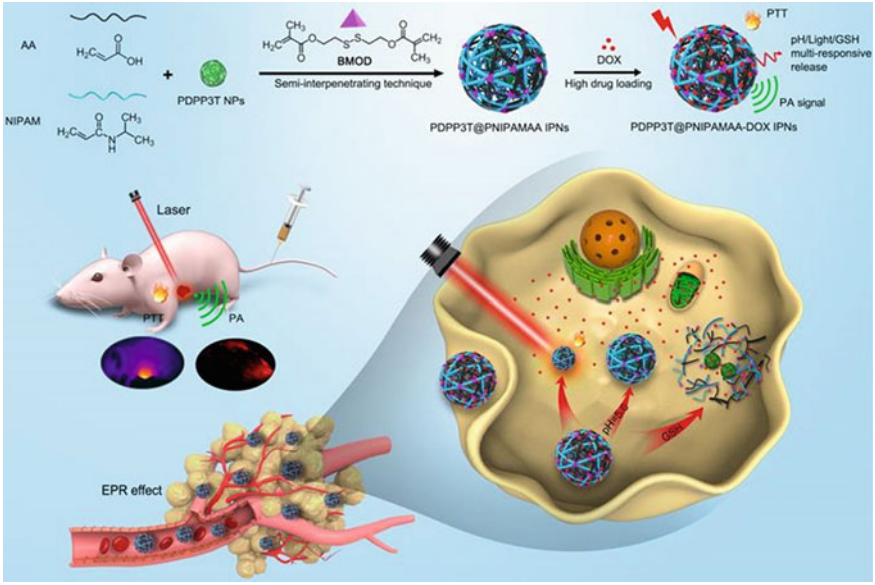

Fig. 5 Schematic illustration to show the semi-interpenetrating synthesis of PDPP3T@PNIPAMAA-DOX IPNs and the PAI-guided chemo-/photothermal combined therapy [17]

Among different nanocomposites, those involving the combination of inorganic and organic nanoparticles, oxide nanoparticles, for developing cancer therapeutics are also known. A very recent example is the paclitaxel drug-loaded polymeric micelle tagged with lanthanum oxide nanoparticles reported for the extended anti-cancer drug delivery [18]. Besides the action of anti-cancer drug, lanthanum oxide nanoparticles also kill the cancer cells by generating reactive oxygen species.

Synthesis and evaluation of RGD-decorated biodegradable polytyrosine nanoparticles (cRGD-PTN) for the controlled release of doxorubicin in colorectal cancer in vivo (Fig. 6) are recently reported [19]. Interestingly, cRGD-PTN nanoparticles showed maximum loading of doxorubicin up to 54.1 wt% and nanoparticles release the drug due to degradation of poly-L-tyrosine. Subsequent studies showed that colorectal cancer cells selectively uptake cRGD-PTN-DOX nanoparticles by receptor-mediated endocytosis, release the DOX into nuclei and thereby induce increased anti-tumor activity as compared to non-targeted PTN-DOX and liposomal DOX. In addition, cRGD-PTN-DOX nanoparticles have showed 5 times better tolerance than that of liposomal DOX and thereby culminate the side effects observed at 6 or 12 mg DOX equiv./kg in HCT-116 tumor-bearing mice.

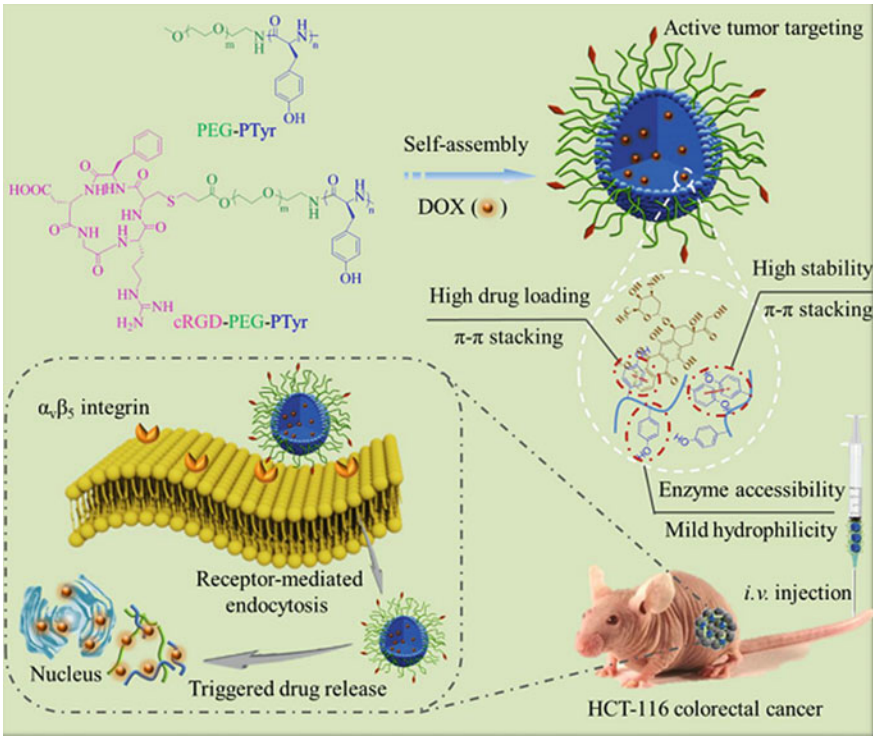

Fig. 6 Graphical illustration of synthesis of DOX drug-loaded cRGD-decorated polytyrosine nanoparticles (cRGD-PTN-DOX) and controlled DOX release in HCT-116 colorectal tumor in mice [19]

Similar to solid nanoparticles, nanogels are also reportedly used as carriers to deliver the anti-cancer drug. Aguirre et al. [20] evaluated the synthesis of thermo-responsive poly(*N*-vinylcaprolactam), pH-responsive poly(2-(diethylamino) ethyl) methacrylate and both thermo- and pH-responsive nanogels for the release of doxorubicin in cervical and breast cancer cell lines. Slow release of drug doxorubicin by the nanogel confirms this nanosystem acts as an effective nanocarrier in developing cancer therapeutics.

6 Plant Viral Nanoparticles

The use of plant viral nanoparticles for cancer therapy is also established. Plant virus, namely potato virus X (PVX), is reportedly used to deliver the HER2 receptor in HER2 receptor-positive breast cancer cells as compared to free HER2, with remarkable cytotoxic activity [21]. Moreover, ZnO nanoparticles conjugated with hydrophobic peptides show higher cytotoxicity against colon cancer cells, than either peptide or nanoparticles alone. Earlier study has elaborated the utility of plant viral nanoparticles (27 kDa) conjugated to Herceptin (trastuzumab) monoclonal antibody (55 kDa) as a nano-drug conjugate (82 kDa), for the site-specific targeting of breast cancer cells [23].

7 Gold Nanoparticles

Selective entry and accumulation of gold nanoparticles in nuclear site of cancer cells are achieved by conjugating Au NPs to arginine–glycine–aspartic acid (RGD) peptide and lysine–lysine–lysine–arginine–lysine (KKKRK) [24]. Gold nanoparticles are also known for treating cancer through radiosensitization effect. Chen et al. showed that gold nanoparticles functionalized using cysteamine and thioglucose displayed better cellular uptake and improved cytotoxicity response to radiation in MCF-7 (breast cancer cell line) as compared to non-malignant breast cancer cell line [25]. In another study, the use of thiolated PEG-functionalized gold nanoshells have been tested in vivo for treating cancer therapy [26]. As compared to the control group, gold nanoshells-treated group shows significantly larger sized necrotic regions which could be due to the thermo-radiotherapy effect attributed by gold nanoshell.

Nanoparticles-based photothermal therapy has many advantages as compared to conventional cancer treatment modalities. This is exemplified by the separate study where interventional nanoparticles-based photothermal therapy and clinical iodine-125 (^{125}I) interstitial brachytherapy (IBT) in orthotopic xenograft model of human pancreatic cancer is reported [27]. In this study, a nanocomposite composed of anti-urokinase plasminogen activator receptor antibody, polyethylene glycol and indocyanine green-modified gold nanoshells is applied in the localized tumor

region. More significantly, 25% high median survival rate is recorded for the interventional nanoparticle-based photothermal therapy as compared to the clinical IBT treatment.

The role of albumin-conjugated gold nanoparticles (Au NPs) in mediating selective photothermal therapy against solid liver tumor under ex vivo is reported [28]. Site-specific delivery and accumulation of albumin-conjugated Au NPs into the malignant liver tissue in the ex vivo-perfused liver specimen of hepatocellular carcinoma patient indicate its selectivity in photothermal ablation. Song et al. described the fabrication of polysaccharide (dextran or pullulan) with gold nanorods for preparing self-destructible Au@PSa nanocomposites, an efficient nanomaterial for photothermal cancer therapy [29]. More significantly, pullulan-associated gold nanorods are capable of selectively targeting the liver cells and also induce pronounced effect of photothermal cancer therapy owing to the strong absorption of Au NRs in NIR region as shown in Fig. 7.

The role of paclitaxel-loaded biocompatible gold nanoparticles prepared by chitosan is evaluated for the anti-cancer drug delivery and tumor imaging

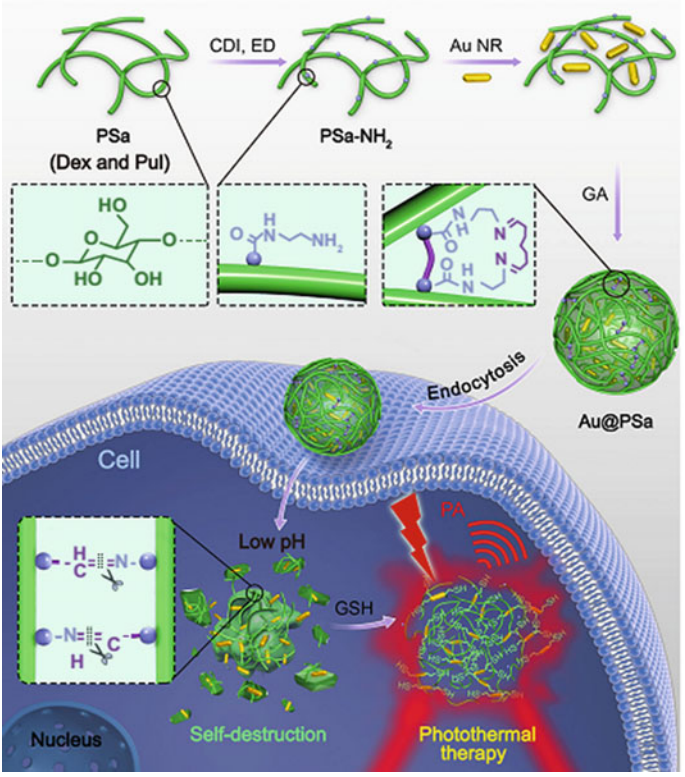

Fig. 7 Schematic representing the preparation of Au@PSa nanocomposites for effective photothermal cancer therapy [29]

applications [30]. This drug–nanoparticle complex showed continuous and pH-dependent drug release pattern. Also, this nanoparticle–drug complex induced strong cytotoxic effect in human breast cancer cell line (MDA-MB-231) through the possible mechanism such as induction of apoptotic pathway, ROS generation and alteration in membrane potential of mitochondria.

Ramasamy et al. [31] employed the triple combination of elements like gold, silicon dioxide and selenium for the preparation of nanosized Se@Au@mSiO$_2$/DOX in treating multidrug-resistant breast cancer under NIR-responsive chemo-photothermal therapy, as shown in Fig. 8. Here, the inhibition of tumor cell growth occurs by two ways, *viz*., (i) cell cycle arrest and (ii) induction of apoptosis by suppression of cellular signaling pathways like Src/FAK/AKT. Hematology and biochemical analysis substantiated that Se@Au@mSiO$_2$/DOX did not show neither any signs of organ damage nor toxicity effect.

In a recent work by Messersmith et al. [32], the preparation of polydopamine-coated nanoparticles of various metals like gold, silver or iron oxide for applications in cancer therapy is reported. Very recently, an approach to improve the chemotherapeutic performance by subjecting the drug nanoparticles to intravenous administration for minimum of 2 h is reported. For instance, hepatocellular carcinoma is treated using this approach showing improved benefit/rate ratio and decreased side effects [33].

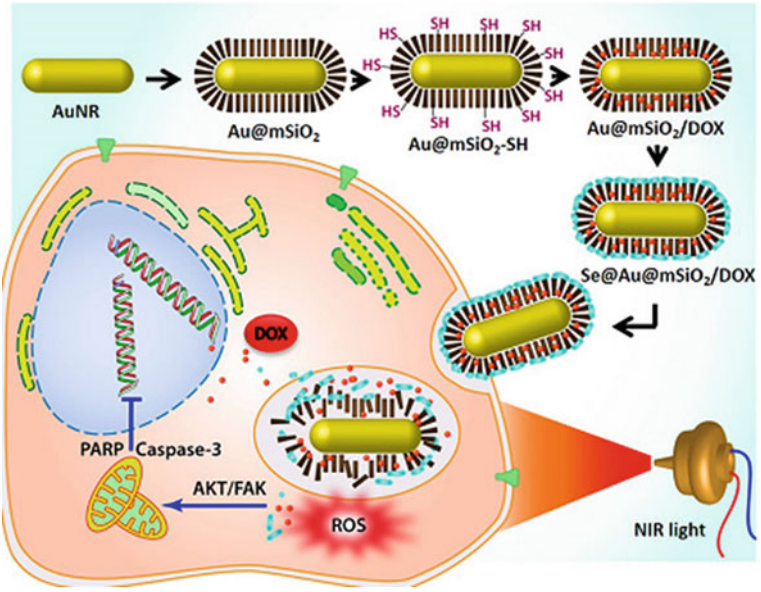

Fig. 8 Schematic depicting selenium-capped Au@mSiO$_2$/DOX (Se@Au@mSiO$_2$/DOX) for the treatment of metastatic breast cancer [31]

8 Quantum Dots

Light-emitting nanoparticles like quantum dots are reportedly used in cancer treatment through photodynamic therapy since these particles absorb light energy and emit light of suitable wavelength to activate the anti-cancer drug. ZnS-coated DsSe quantum dots have been selectively targeted to the blood vessel within tumor region by conjugation with a specific antibody [34]. It is important to design the drug delivery system with high efficiency to target specifically the cancer cells and deliver the drug. Recently, single-stranded oligonucleotide-based aptamers (S15-APT) are used as ligands for site-specific tumor cell targeting and also conjugated to quantum dots [35]. Evaluation studies indicated that nano-aptamer conjugate is selectively internalized by the human lung cancer A549 cells and not taken up by normal human bronchial epithelial BEAS2B, cervical carcinoma (HeLa) and colon adenocarcinoma CaCo-2 cells. Systematic studies revealed A549 cells uptake the S15-APT-quantum dots by clathrin-dependent receptor-mediated endocytosis with a low dissociation constant and high binding affinity.

Nanoparticles-based cancer therapeutics has also been recognized to work effectively against MDR-positive cancer cells. Sangtani et al. [36] reported that the quantum dots–peptide–drug bioconjugate acts against multidrug-resistant cancer cells. In this report, cell peptide facilitates their entry into cells by endocytosis pathway and the peptide–drug conjugate gets cleaved by esterase enzyme localized in the same cellular compartment as shown in Fig. 9. Cell uptake studies showed

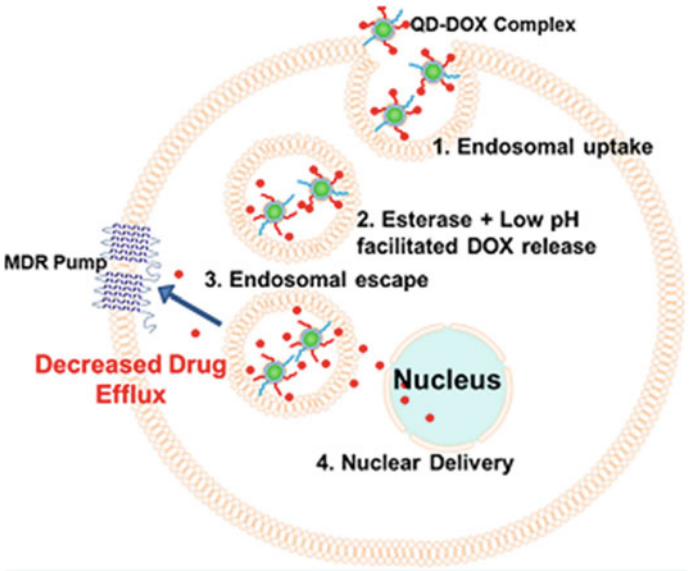

Fig. 9 Mechanism of action of quantum dots–peptide–drug bioconjugate against the multidrug resistance in cancer cells [36]

that the NP–drug conjugate accumulates more in MDR-positive cancer cells, particularly in the nucleus. As compared to free drug, the NP–drug complex showed better inhibition (40%) of MDR-positive cancer cells.

9 Recent Examples of Other Nanoparticles-Based Cancer Therapeutics

In a separate study, the potential of human serum albumin nanoparticles prepared by emulsion-solvent evaporation method is tested for loading anti-cancer drug paclitaxel [37]. Moreover, evaluation studies of these nanoparticles against breast cancer cell line (MCF-7) showed decreasing trend in cell viability with increasing doses of cancer drug (8, 20.2 and 31.4 μg/mL).

A facile approach employed the Fischer esterification reaction to functionalize the chlorotoxin peptide on the surface of nanocellulose crystals is reported [38]. Cellular uptake of the nano-peptide conjugates in U87MG glioblastoma cell line highlighted the scope of these novel nanosystems as drug carriers for targeted anti-cancer therapy.

With the advancement of technology being developed for cancer theragnostics, new techniques such as sonodynamic therapy are considered as an alternative to photodynamic therapy, which helps to overcome the depth penetration barrier faced by PDT. Here, metal–organic framework-derived carbon nanostructure (PMCS) is utilized as a sonosensitizer [39]. Apparently, the carbon nanostructures are assisted in the cavitation process and, as a result, higher amount of ROS generated kills the tumor cells with 85% efficiency. Poudel et al. [40] investigated the use of black phosphorus nanosheets prepared by batch-by-batch free route, as base material for the combined chemo-photothermal therapy of breast cancer. In this study, doxorubicin, poly-L-lysine and hyaluronic acid are mixed with black phosphorus to form a biocompatible composite which is further evaluated under in vitro and in vivo, for site-specific delivery of doxorubicin to breast cancer cells.

Recently, nanobubbles are engineered to perform as an effective nanocarrier for targeted drug release and also provide therapeutic action against cancer cells [41]. Nanobubbles are prepared from oleylamine-/IR-780-loaded hollow structures, folate and the ^{Gd}DTPA-BSA@5-FU complex. Interestingly, this nanobubble demonstrated pH-/light-responsive drug release and charge-switchable behaviors which increases the overall anti-cancer efficacy. Especially, better anti-tumor properties and accumulation of nanobubbles in tumor regions are observed during the chemo-photothermal therapy in MGC-803 tumor-bearing mice. Human annexin V-modified carbon nanotubes selectively target the vasculature seen in tumor cells and from complex nanostructures [42]. This nanosystem destroyed the cancer cell upon irradiating them with a suitable energy source. Local heat generated by the nanostructure destroys the tumor vessels which supply nutrition to the tumor cells.

Liposome-based nanoparticles is also reportedly used for site-specific targeting and cancer therapy. Ashley et al. [43] showed that the nanostructure composed of porous silica core with lipid bilayer and one or more agents like siRNA and peptide are effective for targeted drug delivery and subsequent cancer therapy. For instance, these nanostructures functionalized with cMet peptide have excellent binding to hepatocellular cancer cells owing to the intrinsic affinity of peptide to liver cancer cells.

10 Nanoparticles-Based Cancer Therapeutics in the Market

As a next step in translational research, it is important to understand the commercial utility of the cancer nanotherapeutics. Product clearance from regulatory agencies like Food and Drug Administration (FDA) and European Medicines Agency (EMA) is mandatory for commercialization purposes. Table 1 shows the partial list of the nanoformulation approved by FDA or EMA for the treatment of various types of cancer. Cancer nanomedicine as a product has to be properly evaluated and tested under different phases of clinical trials, in order to get the regulatory approval. Some of the examples of nanomedicines which are currently under clinical trials are represented in Table 2.

Table 1 Some of EMA- and FDA-approved nanoformulation for cancer therapy

S. no.	Classification	Clinical product	Manufacturer	Nanoformulation	Approved cancer target
1	Inorganic	NanoTherm	MagForce	Iron oxide	Glioblastoma
2	Polymers	Genexol-PM	Samyang Corporation	mpEG-coated PLA micelle loaded with paclitaxel	Metastatic breast cancer
3	Lipids	Onivyde	Merrimack	Liposomal irinotecan	Pancreatic cancer
4	Lipids	Doxil	Barenholz	PEGylated liposome-based doxorubicin	Epithelial ovarian Kaposi's sarcoma
5	Lipids	Marqibo	Spectrum	Non-PEGylated liposome-based doxorubicin	Philadelphia chromosome-negative acute lymphoblastic leukemia
6	Lipids	Myocet	Teva UK	Non-PEGylated liposome-based doxorubicin	Metastatic breast cancer

Table 2 Examples of nanoparticles-based cancer therapeutics under clinical trials

S. no.	Classification	Clinical product	Manufacturer	Nanoformulation	Application	Clinical trials
1	Lipids	ThermoDox	Celsion Corporation	PEGylated liposome-based doxorubicin	Hepatocellular carcinoma	Phase III
2	Lipids	Oncoprex	Genprex	FUS1 (TUSC2) encapsulated liposome	Lung cancer	Phase I/II
3	Lipids	PROMITIL	Lipomedix Pharmaceuticals	PEGylated liposomal mitomycin-C	Solid tumors	Phase I
4	Polymers	Cynviloq IG-001	Sorrento	Paclitaxel polymeric micelle nanoparticle	Breast cancer	–
5	Polymers	NC-4016 DACH-Platin micelle	NanoCarrier	Polyamino acid, PEG and oxaliplatin micellar nanoparticle	Advanced solid tumors or lymphomas	Phase I
6	Inorganic	AuroLase	Nanospectra Biosciences	PEG-coated silica–gold nanoshells for near-infrared light-facilitated thermal ablation	Solid primary and/or metastatic lung tumors	–
7	Inorganic	Magnablate		Iron nanoparticles	Prostrate cancer	Phase 0
8	Inorganic	NBTXR3 PEP503	Nanobiotix	Hafnium oxide nanoparticles	Squamous cell carcinoma	Phase I

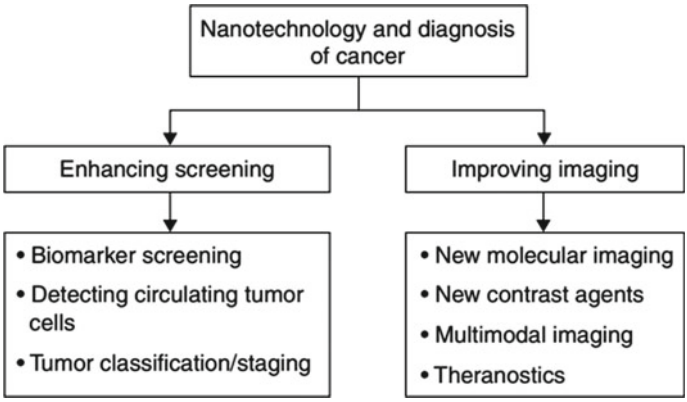

Fig. 10 Nanotechnology contributions to improving diagnosis of cancer [45]

11 Nanodiagnostics for Cancer Treatment

Early diagnosis of cancer is the most essential step in today's world. Cancer diagnosis mainly involves screening the cancer biomarkers and also imaging the related body parts. It is very crucial to identify the changes involved in the early stages of cancer. Thus, sensitivity of diagnostics is an important factor. Every cancer involves certain specific markers like cancer-associated proteins, circulating tumor DNA, circulating tumor cells and exosomes, and the goal of diagnosis is to analyze these markers [44]. Nanotechnology provides unique and highly sensitive detection of cancer-related molecules (Fig. 10) [45].

Nanotechnology has opened up new avenues for detecting infectious diseases and cancer. An interesting work was reported by the scientists at Sanford Burnham Prebys Medical Discovery Institute. Here, quantum dots were used to image the tumor in mice and an etchant was used to block signals from non-cancerous tissue. QDs were delivered intravenously into mice along with a tumor-penetrating peptide. An etchant Ag–TS (silver ions stabilized with thiosulfate) was used to quench the fluorescence of QDs that may remain in the blood stream. This in turn makes the system more specific to cancer cells [46]. Screening of biomarkers also helps to analyze the progression of cancer, and nanotechnology makes the biomarker detection much easier.

12 Conclusion

This chapter presents the recent developments in the nanoparticles-based cancer therapeutics employing a wide range of nanoparticles. Nanoformulation involving one or multiple nanoparticles of organic to inorganic type has been used for

developing effective cancer nanotherapeutics. The applicability of nanomedicines in cancer therapy is initially evaluated through a series of in vitro and in vivo toxicity and efficacy studies. This is further supported by the FDA or EMA regulatory clearance for these nanomedicines in treating cancer with high therapeutic efficacy. Besides, many nanomedicines developed are under clinical trials. Nanoparticles-based anti-cancer drug delivery systems successfully developed respond to various stimuli such as receptor, acoustic, magnetic field, pH regulated, temperature and radiation. Besides the active drug molecule, the nanoparticles itself influence the cancer treatment regimen to certain extent and also dependent on its intrinsic properties (optical, electrical, magnetic). Selectivity of the nanoparticles-based cancer therapeutics is induced by the surface conjugation of nanomaterials with ligands like peptides, vitamins, receptors, etc. In recent years, the use of multifunctional nanomaterials through functionalization of nanostructures with one or more agents, for developing potential cancer therapeutics or theragnostics, is well recognized. These multifunctional nanostructures show improvement in selectivity, specificity and efficiency of the nanomedicine in cancer therapy and thus lead to increased anti-tumor effectiveness of the cancer nanotherapeutics.

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Chapter 2
Biomaterials and Its Advances for Delivering Anticancer Drugs

R. Rajakumari, Sabu Thomas, and Nandakumar Kalarikkal

Abstract Most of the anticancer drugs affect both the cancerous cells and the normal cells. The most common treatment chemotherapy is always associated with the poor selection of the targeted cancer cells and also the drug resistance. Therefore, to enhance the therapeutic efficacy of anticancer drugs, nano-drug delivery systems have been designed and implemented. To limit the challenges associated with the conventional chemotherapy, there are strategies to combat it. The strategies are functionalising the material, functionalisation with multiple targets, in vivo imaging and dual/multiple drug delivery system. This chapter provides insights about the wide range of polymers which helps to engineer the anticancer molecules. It also emphasises the different mechanisms for releasing the anticancer drugs in an effective manner. The recent advances about the materials used for cancer therapy and commercially available products are also discussed. The effect of engineered biomaterials for treating the cancer patients is mostly expected to increase in the future.

Keywords Anticancer drugs · Biomaterials · Targeted delivery system · Release · Functionalisation · Chemotherapy

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1 Introduction

Cancer is the most major disease in the world with huge number of death due to exposure of carcinogenic substances, change in diet, age, suppression in the immune system and other factors [1]. In the recent years, a lot of progress has been taken place in developing a targeted delivery system. By these effective treatments, the survival rate of patients will be increased and still some of the disadvantages occurs. The chemotherapy treatment acts non-specifically in the cancerous cells and also in the normal cells because of the toxic side effects. Moreover, a high dose is required for some of the patients at regular intervals to improve the therapeutic efficacy in the targeted area [2, 3]. The recent advancements of the biomaterials incorporated delivery system provide the specific release of the anticancer agents only in the cancerous cells by subsequently improving the life of patients and its side effects are eliminated [4].

There have been a lot of developments in the recent years for the treatment of cancer are formulations of controlled delivery system, targeted delivery systems and nano-drug delivery system. Formulating a biomaterial with a controlled or targeted release is quite challenging task and needs a multidisciplinary approach [5, 6]. There are certain parameters to develop the formulation and they are incorporating the sufficient drug within the biomaterial for the controlled and prolonged release to achieve better efficacy. Secondly, to protect the drug in the human environment (in vivo) to increase the biological activity. Thirdly, formulating a drug by predicting its release behaviour to improve its therapeutic efficacy which ranges from weeks to years. Fourthly, the drug component and the biomaterials should be biocompatible and nontoxic within the system. Fifthly, the developing material should avoid the discomfort before and during administration. Finally, the drug-biomaterial formulation should be affordable to the patients which are most important factor to taken into account before designing the formulation [7, 8].

There is strong growth in developing biomaterials for the controlled/targeted release of anticancer drugs by imbibing different types of mechanisms which is not confined to diffusion, swelling, magnetic and chemical-based mechanisms [9–11]. There are formulations which consist of phospholipids with bilayer structures that lead to the preparation of liposomes and it is one of the nanocarrier delivery systems. This then expanded into many carriers such as micelles, nanospheres, nanomaterials, dendrimers and inorganic nanoparticles in the rapidly increasing field of nano-drug delivery system. The biomaterials and the drug can also be modified by microfabrication technology to formulate patches consisting of microneedles which pierce the skin without pain to deliver the drug. This transdermal delivery system allows the drug to improve the permeability in skin, it should dissolve, should be biodegradable and should not leave any waste. Very recently, there are smart and intelligent biomaterials have been developed which responds to the environmental factors (pH, enzymes, temperature and pressure) for releasing the drug. Likewise, there are biomaterials which can be triggered by UV-Vis light, NIR light, sound, electrical currents and by means of magnetic pulse for delivering the drugs in controllable pace [12–16].

In this chapter, the importance and the need for the incorporation of biomaterials in the drug delivery system are explained. An outline of the natural, synthetic and combination of both natural and synthetic materials used for the development of the targeted delivery system is also highlighted. The recent advancements in the design, development and preparation of hybrid materials are also described. Lastly, the significance of the polymeric materials incorporated in the targeted system and commercially available products are also presented.

2 Classes of Biomaterials for Anticancer Activity

There is a broad array of polymers used as carrier for the anticancer compounds and this includes natural, synthetic and hybrid classes (Fig. 1). In the synthetic class, organic and inorganic materials are used, and this section deals with the physical, chemical properties and mechanisms of drug delivery of individual class of carriers. The natural source of biomaterials comes from both the animals and the plants which includes collagen, alginates, hyaluronic acid, silk fibroin, chitosan and others. The synthetic classes of biomaterials include poly(ethylene glycol) (PEG), polylactides, polyglycolide and its derivatives. Then, the hybrid materials include PEG-alginates, PEG-proteins and others [17].

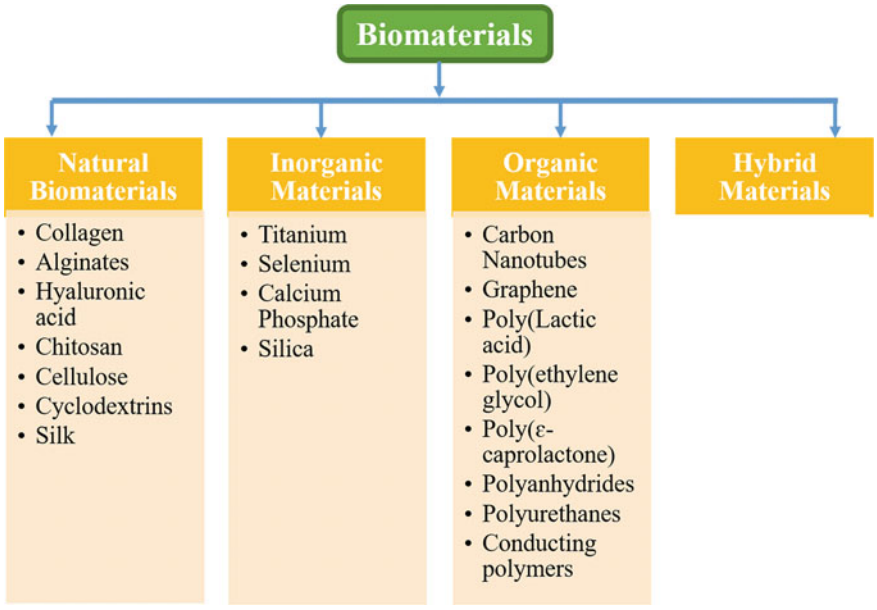

Fig. 1 Classification of biomaterials

3 Natural Biomaterials

In the tumour stroma, there are natural proteins which occur in the tumour stroma which increases the formation of tumour in the cancerous cell through interactions of physicochemical properties. Those proteins include fibrin, collagen and laminin, and to improve the biochemical nature of the extracellular matrix (ECM) proteins, these natural biomaterials are used and they are explained below;

3.1 Collagen

The most important biomaterial is hydrogels and they occur in the crosslinked chains of collagen with a high amount of absorption of water and also it facilitates the exchange of nutrients. This is one of the natural proteins found in abundance in the ECM protein which occurs in the tumour stroma and it provides mechanical strength to the tissue [18]. Moreover, the biochemical and mechanical properties of the hydrogels are improved by changing the crosslinking behaviour or the individual polymer chains. The bioactive components, growth factors and metalloproteases are incorporated in the hydrogel matrix for the encapsulation of the drugs. Therefore, these hydrogels are formulated by mechanical, chemical and structural means in particular to change the behaviour of the cells and to provide targeted delivery [19]. The hydrogels were prepared with the collagen which are formed through a physical crosslinking and they are used for the encapsulation of the anticancer drugs. Through enzymatic crosslinking the collagen-based gels have been prepared with the enzyme transglutaminase. These hydrogels are used against the MDA-MB-231 metastatic cells which are breast cancer cells and it forms tissue hypoxia and necrosis. In the case of MCF-7, a non-metastatic breast cancer cells it exhibits epithelial–mesenchymal transition (EMT) markers. Owing to its fibril nature, they have been widely used to study the migration of bioactive moieties through the diameter of fibril, pores and crosslinking density. The elastic modulus and the alignment of the fibres in the collagen matrix are responsible for the release behaviour [20]. For example, an increase in the collagen density leads to mechanical stiffness which leads to invasion of malignant cells. This kind of collagen hydrogels is used against the epithelial organoids and tumour spheroids which invades through adhesion by integrin [21].

3.2 Alginates

They are natural biomaterial which are derived from the seaweeds and it has been used as gel for the controlled delivery of anticancer drugs. They have α-L-guluronic and β-D-mannuronic acid in the structure and it involves in the ion-exchange

reaction for the release of the bioactive components. The advantages of using alginates and agarose as carrier are they have high porosity and high water holding capacity [22]. Agarose is also similar to alginates which has D-galactose and 3, 6-anhydro-L-galactopyranose in its structure. The physicochemical properties of these biopolymers such as molecular weight, pH, ionic strength, mechanical strength, porosity can be tuned by modifying the concentration of the two structural units. These two polymeric gel can be used as encapsulating agent for the cancer drugs because of its thermal stability. Alginates incorporated bioactive moieties are used against breast cancer cells, leukaemic cells and squamous cell carcinoma. The alginates have very good mechanical stiffness which ranges from 21 kPa to 105 kPa and this characteristic property destroys the tumourigenic potential of hepatocellular carcinoma. Agarose is used against the renal carcinoma cells and MCF-7 cancer cells [23–25].

3.3 Hyaluronic Acid (HA)

It is a high molecular weight biopolymer and it consists of the repeating units of D-glucuronic acid and D-*N*-acetyl glucosamine. Because of its presence in the ECM matrix, this HA have been widely used as carrier for the anticancer moieties. The molecular weight of hyaluronic acid (0.5–2 MDa) and its interaction with the tissues are the main determining factors for the release of the active moieties in the cells. In a study, the ultra-high molecular weight (6–12 MDa) of HA leads to an invasion of cancer cells due to the decrease in activity of degrading enzymes of HA. The molecular weight of HA is reliant on the comparative activity of HA synthases and they are denoted as HAS1, HAS2 and HAS3 which specifically synthesis HA of different molecular weights [26]. The hyaluronidase activity (HYAL1, HYAL2) is the one in which it breaks the HA high molecular weight into small chains HA in the ECM matrix. In an another study, they have found that the higher levels of HA low molecular weight along with the higher levels of HAS1, HAS2, HYAL1, HYAL2 exhibited an invasion of breast cancer cells [27].

Anticancer drugs encapsulated HA hydrogels (0.5–1.3 MDa) forms a cluster formation by the hyaluronidase enzyme which involves in destroying the cancer cells. HA with the molecular weight of 500 kDa along with the thiol and acrylate groups forms the hydrogel bilayer constructs which were used to invade the prostate cancer cells. HA with molecular weight >1 MDa forms a reticulated hydrogels which is combined with the adipic dihydrazide were used to destroy the primary tumours based on its secretion of hyaluronidase. HA hydrogel with molecular weight $\sim$1.5 MDa along with the tyramine were used to attack CD44 and CD133 of U87 astrocytoma cells. Therefore, for choosing HA, the physicochemical and biological properties should be optimised cautiously to study the cell reaction through tissue-matrix interactions [28–30].

3.4 Chitosan

This is obtained from the polymer chitin and they are used for many biomedical applications starting from sutures to implants [31]. The chitosan films were impregnated with the paclitaxel and it is implanted in the tumour site to obtain the sustained release behaviour. The release profile shows an initial burst effect and this chitosan offers a high loading capacity of about 31% W/W. The further release behaviour shows the sustained delivery of paclitaxel and the film lost its integrity by the biodegradation mechanism. There is no inflammatory response of this biopolymer films and its biodegradation behaviour helps in the delivery of implantable anticancer drugs [32]. Chitosan is used in many anticancer treatments and the examples include chitosan-doxorubicin for chemo-immunotherapy [33], chitosan-cisplatin used for pleural mesothelioma [34] and chitosan-letrozole for the breast cancer treatments [35].

3.5 Cellulose

This is another kind of biocompatible biopolymer used as carrier for biomedical applications [36]. In a clinical study, cisplatin was administered for treatment of glioblastoma multiforme. For this, they have used biodegradable carbomethylcellulose biopolymer is incorporated with the cisplatin drug and they have administered as chemotherapy (polymer-drug) for 17 patients. After the removal of the tumour cells, the polymer-drug plates were implanted into the tumour area and they have found that the total survival rate of patients increased (427.5 days), whereas for patients from the control group is 211 days [37]. In another study, cellulose sulphate is encapsulated in the genetically modified cells and they were implanted in the tumour site for the treatment of pancreatic cancer. The cytochrome P450 2B1 enzyme modified the cells and it could able to modify the cancer drug ifosfamide to its toxic metabolites. By this method, the tumour cells were ablated completely and it shows an example of in situ mechanism [38].

3.6 Cyclodextrins (CD)

It consists of 6–8 glucopyranoside unit which are interconnected and they are used as carriers for many bioactive molecules [39, 40]. It contains a hydrophilic part in the outer region and the hydrophobic part in the inner region and this type of shape creates an inclusion complex between the CD and the hydrophobic anticancer drugs. β-CD are covalently linked with the amino acid poly-L-lysine and anticancer

drug risedronate which is used for the treatment of bone cancer [41, 42]. Manchun et al. demonstrated about the dextrin nanogels incorporated doxorubicin and they have formulated by an emulsion method. Using a cross-linker glyoxal and formaldehyde, the doxorubicin was bonded (acid labile bond) to the CDs. They have also found that the release of doxorubicin is a pH responsive and it delivers the drug at pH-5 which is the pH of the cancer cells. The obtained nanogels were effective for destroying the colorectal cancer cells nuclei and the side effects were reduced [43, 44].

3.7 Silk

Silk fibroin is used as a suitable biomaterial since long time for biomedical applications [45, 46]. There are a lot of advantages and some of them are it has extremely good mechanical and elastic properties, good immune behaviour, biocompatible, biodegradable and very low adherence to bacterial cells. These proteins can be developed into films without any difficulty, and the films act as a carrier for the anticancer moieties. In a study, they have prepared silk fibroin hydrogels and doxorubicin was incorporated into it and they observed a good loading efficiency. The self-assembling nature of the silk showed extraordinary anticancer activity [47, 48]. One of the reported works suggests that the cell-specific and site-specific delivery of doxorubicin was achieved by the silk-doxorubicin matrix films. These films are used for the treatment of advanced stage of breast cancer and their results of the in vivo studies proves that it showed an exceptional improvement in inhibiting the cell growth when compared to the control. In addition, they have also identified huge reduction in the tumour cells weight and the tumour spread was also reduced with no toxic effects in the normal cells [49–51]. For treating the not resectable neuroblastoma cells, the silk fibroin films were loaded with doxorubicin and crizotinib. It forms a crosslinking between the drug and the film which showed an outstanding results in treating the unresectable neuroblastoma cells. It is also reported that it exhibited an excellent activity in the in vitro and in vivo studies when compared to the intravenous dose of drugs. Moreover, it also displayed a good release profile with desirable kinetics and can be directly placed over the tumour surface [52–54]. It was also reported in a study that they have combined the surgery along with the drug loaded silk films to treat the neuroblastoma cancer cells. It was stated that the drug release was observed in the sustained manner, and thereby during shrinkage of cells, it was removed surgically. Recently, silk fibroin nanospheres were fabricated along with the incorporation of floxuridine for the prevention and treatment of cancer cells. Nanogels silk elastin was loaded with floxuridine for the treatment of hepatocellular carcinoma [55, 56].

4 Inorganic Biomaterials

4.1 Titanium and Selenium

The titanium is one of the most used metals in the development of implants owing to its many advantages like good mechanical strength [57], resistant to corrosion properties, biocompatible and time-dependent biodegradable behaviour [58]. The implant consists of a layers of titanium oxide and it is implanted over the surface of the cancerous bone. The orthopaedic implant will replace the cancerous bone cells and it is the common method adopted to treat bone cancer. The titanium alone cannot able to prevent the cancer cells, and hence the anticancer drugs are incorporated in the titanium dioxide layers by surface modification technique [59–61]. For supporting the above-said statement, Perla et al. found two strategies to develop the new type of bone implants. The first one is modifying the surface of the implants by using nanosize range of particles particularly to improve the adhesion and growth rate. The second one modifying the surface through chemical means by using metal particles exhibiting anticancer properties. The one such inorganic material which has anticarcinogenic potential is selenium. They observed improved adhesion of osteoblasts cells in the surface modified selenium and nanoparticles matrix. It was reported that selenium nanoparticles found to be a promising material for the anticancer orthopaedic implants [62].

Tran et al. used nanoselenium along with the titanium and found that it inhibits the growth of cancerous cells from recurrence simultaneously improving the growth of bone. In the in vivo experimentation, the Se-coated Ti nanoparticles were observed to be a promising material for the tumourous bone cells and also for the healthy cells [63–65]. Chen et al. came up with a new modification in the surface of the titanium. They have formulated a chitosan coated over the surface of nano-titania tubes and deposited selenium on the surface of nanotubes. They have studied its efficacy by implanting this material and observed that it prevents the growth of cancerous cells and improves the proliferation of healthy cells. In addition, they have also shown that selenium exhibits sustained release behaviour of about twenty-one days. Titanium nanowires and titanium nanotubes are incorporated with doxorubicin drug for treatment of brain cancer (doxorubicin implants) [66]. Gulati et al. demonstrated that this novel nano-metal-drug conjugates were successful in the prevention of brain tumour. The loading efficiency and the release profile of the doxorubicin showed better characteristics. The added advantage of this method was it could able to bypass the blood-brain barrier which actually prevents the release of doxorubicin from the blood and thereby releases the drug in the brain [67].

4.2 Calcium Phosphate

The calcium phosphate biomaterial is very similar to the bone mineral in its composition and this biomaterial itself acts as an anticancer agent. This biomineral also offers several advantages and they are osteoconductive, biocompatible and biodegradable based on its porosity, bioactive, nontoxic and stable. The most commonly used calcium phosphate-based biomaterials are tricalcium phosphate, hydroxyapatite and amorphous calcium phosphate [68–72]. Cisplatin is incorporated in the bone mineral and studied its release behaviour. The release pattern followed the sustained release behaviour and it was observed for nearly 12 week period under in vitro conditions. The in vivo behaviour of this implanted material of about 3 months shows good compatibility and better release profile [73]. Then, in another study, they have used hydroxyapatite material which is incorporated with adriamycin and it was found that hydroxyapatite (2 mm diameter) can load about 0.08 of adriamycin. The in vivo studies revealed that the implanted composites exhibited sustained release behaviour and used in the treatment of early stage hepatic cancer whereas for the late stage it was unresectable. After resection of tumour, the bone mineral containing high concentration of anticancer drug was placed in the tumour site for improving the cells present in the site. Likewise, the calcium phosphate mineral loaded with *cis*-diaminedichloroplatinum and the release profile was observed to be 0.1 mg/day. After implantation of over six weeks, the platinum release was 3200 μg/g tissue which was found accumulated in bone marrow whereas it was not present in other organs. When the platinum is administered intravenously, the concentration of platinum is very low in bone marrow 0.2 μg/g tissue and it was lower than that of liver 3.5 μg/g tissue and kidneys 3.5 μg/g tissue [74]. The composites showed that the concentration of platinum at the tumour site is higher than that of other tissues and organs. This idea was taken by Tanzwa et al. prepared a composite containing calcium phosphate loaded with caffeine and the cisplatin. Here, the cisplatin release was improved in the tumour site because of the presence of caffeine which holds the cisplatin in the tumour site [75]. Recently, Chen et al. developed a polycaprolactone scaffold along with chitosan, nanoclay and β-tricalcium phosphate loaded with doxorubicin for the controlled delivery of the drug in the tumour site [76].

4.3 Silica

This biomaterial is related with the breast implants and they are also used for drug delivery applications. They are hydrophobic material which are used as membrane-based reservoir systems [77]. The first work on silicone-based anticancer drug delivery was introduced by Ueno. The selected anticancer drug 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) is incorporated in the different types of

silica, silicone and silicone-nylon refillable systems. In this work, they have selected silicone balloons as a reservoir for the drug and it is used for the treatment of ocular malignancies [78].

Nanoporous silica was developed by Bell et al. and he reported that because of its solubility, biocompatibility, biodegradability and low toxicity, and it has very wide range of biomedical applications [79]. The applications include biosensors [80], chemical sensors [81], radiotherapy [82], drug delivery and biotechnological applications [83–86]. The porous silica nanoparticles are used for delivering anti-cancer drugs like doxorubicin [87, 88], cisplatin [89], celastrol [90] and camptothecin [91]. Therefore, the biodegradation pathway of nanosilica particles paves the way to remove safely from the body [92]. Tzur et al. investigated the porous nanosilica films loaded with the anticancer agent mitoxantrone dihydrochloride for the local drug delivery. The drug was loaded into the nanostructured silica by means of alkylation and thermal hydrosilylation using undecylenic acid and dodecene. And the drug was adsorbed and covalently linked to the porous nanosilica scaffold. The release pattern exhibited no burst effect initially followed by the sustained delivery of mitoxantrone in the breast cancer site. They have also denoted that it can be further developed either into injectable nanosilica particles or implantable material [93, 94].

5 Synthetic Biomaterials

5.1 Carbon Nanotubes (CNTs)

There has been extensive research in using the carbon nanotubes structures as a nanocarrier for numerous biomedical applications. The CNTs are said to be a universal carrier for a large number of bioactive molecules [95]. The CNTs containing immobilised drug can be combined with the nanoparticles containing magnetic properties and this hybrid structures releases the drug via the external magnetic field for targeting the cancer cells [96]. Functionalising the CNTs and surface modifications are another way of releasing the drug in the target site. The oxidised CNTs are difunctionalised using folic acid and iron nanoparticles which are useful in dual targeting [97, 98]. Doxorubicin drug is incorporated into the dual targeted nanocarrier CNTs and found the controlled release behaviour. The in vitro studies prove that the difunctionalised CNTs-doxorubicin act against the HeLa cells. It was also reported that CNTs exhibit improved doxorubicin loading capacity and it provides 6 times better release profile than the free drug. When the CNTs functionalised with folic acid and it is particularly useful in targeting the lymphatic systems through the external stimuli magnetic field. The externally place magnet will target the lymph nodes and releases the drug cisplatin and 5-fluorouracil in a controlled fashion [99, 100]. The natural bioactive compound quercetin is incorporated in the CNTs nanocarrier and they are formulated by polymerisation of methacrylic acid around CNTs. Then, the quercetin drug was found to be covalently

conjugated which showed a better release profile. The in vitro studies proved that it acts against the HeLa cells effectively than the free quercetin. The quercetin was particularly loaded in nanocarrier CNTs particularly to improve the stability and release profile [101].

5.2 Graphene

An interesting nanomaterial which provides many advantages since its inception and they are graphene-based materials (GBMs) and in particular graphene oxide (GO) and reduced graphene oxide (rGO) [102]. The GO and rGO attracted much interest in the last few years for the development of drug delivery systems and in many biomedical applications [103]. There are lot of studies reported that it has toxic potential based on its size and amount used. But the side effects produced from GBMs are very low compared to the chemical molecules. Huge number of reports studied that GBMs was used as nanocarrier for many anticancer drugs [104–107]. Zhang et al. study reported that GO functionalised with folic acid in particular to target the MCF-7 cells. Doxorubicin and camptothecin are loaded in the GO through hydrophobic and π–π interactions. The effects showed that it targets specifically to the cancer cells with higher loading and better release properties [108]. Wu et al. studied the effects of doxorubicin-GO-Adramycin complex and found a good loading capacity of about 93.6%. They revealed that doxorubicin undergoes a pH mediated release in a controlled fashion and found effective in killing breast cancer cells. The pH mediated release is that the hydrogen bonding between the GO and doxorubicin is dissociated and protonated $–NH_2$ groups in the doxorubicin molecule [109].

5.3 Poly(Lactic Acid) (PLA)

PLA has a lot of advantages and they are biocompatible, biodegradable, easily processable and nontoxic. PLA and its product poly(D,L-lactide-coglycolide) (PLGA) have been used since its inception in many pharmaceutical products for biomedical applications and these polymers are approved by FDA [110]. Zhao et al. used recombinant drug interleukin-2 and it is conjugated with PLA/PLGA microspheres along with dextran. The microspheres were prepared with a core/shell morphology with the loaded drug and this was used for the treatment of paracrine cancer. When the interleukin-2 was administered multiple injections, it has been proved that the rate of growth inhibition of the cancer cells was higher. The L-lactide and g-lactide with the dextran molecules form the stereocomplex which undergoes gelation and releases the drug in controlled fashion [111]. PLA nanofibres along with sodium dichloroacetane and diisopropylamine dichloroacetate loaded with the oxaliplatin and studied its release profile. It was reported that it

has good loading efficiency and release profile. The in vivo studies showed that prolonged release behaviour of oxaliplatin in tumour site and it also completely inhibit the growth and limits the recurrence of tumour in the liver. The suppression rate of the tumour was observed to be 95% and its asymmetric structure enables in diffusion of oxaliplatin in normal cells and other tissues [112, 113].

5.4 Poly(Ethylene Glycol) (PEG)

Mostly, the anticancer drugs are incorporated in the PEG as hydrogel formulation [114–116]. Hydrogels are powerful structures and are widely used in smart drug delivery systems because its delivers the drug inside the system through the changes in the pH, light, temperature and sound. They also have all the advantages in which the carrier molecules should possess and they biocompatible, biodegradable and nontoxic. When the drug is incorporated in the system, it changes from the liquid state to gel state by means of chemical interactions such as hydrogen bonding, crosslinking, hydrophobic–hydrophilic, charge, sterocomplexation, photo-polymerisation and molecular recognition. When the drug loaded hydrogels are implanted in the tumour site, it releases the drug via diffusion coefficient mechanism. PEG are formulated into a hydrogel delivery system for many biomedical applications [117–120]. 5-fluorouracil is loaded into the PEG hydrogels which are used to prevent the growth the malignant tumours. The in vivo studies shows that when the drug was administered via bolus injection, the release rate was very poor and leads to short half-life. Whereas the hydrogel formulation showed that it increases the drug residence time and half-life of the drug was observed to be satisfactory [121]. In order to increase the desired properties of PEG, it is to be copolymerised with the other molecules such as poly(methyl methacrylate) (PMMA) [122], poly(vinyl ether) [123], poly(styrene) [124]. In a study, they have incorporated polycaprolactone (PCL), PLGA into the PEG system and it undergoes crosslinking through gelation process. The crosslinking takes place when the temperature is increased and resulted in aggregation of the hydrophobic portion of the molecule [120]. In a study by Cheng et al., they have formulated hydrogels composed of triblock copolymers consists of poly(γ-ethyl-L-glutamate)–poly (ethylene glycol)–poly(γ-ethyl-L-glutamate) and incorporated the drug paclitaxel. The in vivo studies demonstrated that within 3 weeks of time, it completely prevents the growth of tumour without damaging the other tissues and cells [125]. In another study, PEG was formulated in the micellar structures along with the 2,2-bis (methylo)propionic acid loaded with the drug paclitaxel. The in vivo experimentation showed that it inhibits the growth of tumour cells. Nanoparticle delivery system was developed by combining PEG and poly(propylene succinate). Then, it is loaded with the drug cisplatin and it was found to be controlled delivery of drug in the tumour site and thereby preventing the growth of malignant cells [126].

5.5 Poly(ε-Caprolactone) (PCL)

This polymer also possesses many advantages like biocompatible, biodegradable, nontoxic and no side effects [127, 128]. This is widely used in situ forming drug delivery system and this polymer along with its copolymer poly(ε-caprolactone fumarate) loaded with tamoxifen is formulated into injectable preparation. The in vitro studies show that it shows a higher loading efficiency, excellent release rate and it prevents the growth of breast cancer cells against MCF-7 cells. They have also reported that the composites do not display no toxicity, no cytotoxicity in normal cells and tissues [129]. PCL was also formulated into implants together with its copolymers such as derivative poly(ethylene glycol)-block-poly(ε-caprolactone). This PCL and copolymer nanoparticles were loaded with hydroxypropyl-β-cyclodextrin and docetaxel drugs. These implants were placed over the patients having breast adenocarcinoma and found outstanding anticancer activity. Therefore, these PCL-based nanoparticle implants were proven to be suitable for the anticancer therapy [130]. Pereira et al. developed PCL incorporated methotrexate and found it effective for the treatment of Ehrlich solid tumour cells [131]. PCL was formulated into nanofibres and the natural bioactive compound curcumin was incorporated into it. This curcumin loaded PCL fibres were tested against MCF-7 and A459 cells and found better entrapment efficiency which leads to be effective in killing the breast cancer cells and lung cancer cells [132]. PCL along with curcumin was developed into micellar formulation and both the in vitro and in vivo studies displays that they are very effective in treating colon cancer cells [133]. Recently, Wong et al. developed a formulation containing dual functions in which it serves in treating the cancer cells and as well as in tissue regeneration. In this study, PCL was loaded with doxorubicin where it acts in dual functions such as locally delivering the drug in the tumour site and cells get attached for generating new tissues. They have suggested that this kind of drug loaded nanofibres formulation will be very useful in post-surgery of the limb salvage process for repairing the tissues [134].

5.6 Polyanhydrides

This polymer is one perfect example in the category of surface eroding polymers owing to its high water content of the anhydride bonds over the surface and highly hydrophobic in the bulk of the polymer [135]. In this type of polymers, the release of the drug is directly proportional to the erosion rate of the polymer. So, to achieve the control in release of a drug is possible only when the surface of the biomaterial starts degrading. The in vivo experiments suggest that polyanhydride can be easily excreted from the body via urine and faeces as CO_2 [136]. This biomaterial was together mixed with its copolymer poly[bis(pcarboxypenoxy) propanesebacic acid] for the local delivery of cancer drugs which was also approved by the FDA. In this matrix, the drug camptothecin was incorporated to study the effects in treating

gliosarcoma. The results showed that the release rate was prolonged for about 1000 h [137]. Poly(ester anhydride) along with oligomers of poly(sebacic acid) and ricinoleic acid was studied for its possibility of selecting as drug carrier. To the above polymers, the cisplatin drug was loaded and studied that it was very effecting in inhibiting the growth of cancer cells. The above-said polymers are incorporated with 5-fluorouracil, paclitaxel and methotrexate to find out the release rate. The release profile was found to be very effecting and showed prolonged release [138–140]. Recently, curcumin was loaded in the poly(anhydrides) for the prevention of growth against breast cancer cells, osteoblasts cells and HeLa cells. This polymer has also been used for improving the immune response inside the body by the vaccine delivery formulation [141].

5.7 Polyurethanes (PU)

This is one of the synthetic polymers which also has good biocompatibility, biodegradability, good mechanical strength and nontoxic [142, 143]. Chen et al. developed polyurethanes nanocomposite implants loaded with the drug paclitaxel. It releases the drug with tunable on and off switching mechanism for delivering to the tumour site. The temperature-responsive PU nanocomposite membrane releases the drug by heating at 44 °C (switching on) and drops at 37 °C (switching off) results in temperature-responsive release [144]. Another work reported about the solvent casted PU along with paclitaxel drug to make stent-based delivery system for the treatment of tumours in the gastrointestinal area. The PU-paclitaxel stent could able to inhibit the growth of tumour in a better way and its release was inversely proportional to the paclitaxel loading. The major threat to a patient who underwent tumour removal surgery is that it increases the growth in other normal cells [145]. To cure this problem, Manabe et al. came with a new device, i.e. infusion pump with elastomeric tube which delivers the drug gemcitabine directly into the resected tumour site and the tube is used for reloading the drug. The controlled delivery of the gemcitabine drug inhibits the growth, slows down the growth and also prevents regrowth of the tumour [146].

5.8 Conducting Polymers

Mostly, these kinds of polymers are used in electronics, but these kinds of polymers also used as fascinating materials for the drug delivery system [147, 148]. The conducting polymers are not biodegradable and its degradability is increased by chemical modification. So that the polymers become biodegradable with the in vivo enzymes reaction. These polymers are biocompatible, which allows ion-exchange

reactions, electrically conductive which undergoes charging and discharging process [149, 150]. With the help of electric potential, the drugs with anionic charge get immobilised during the process of oxidation and the drugs get released during reduction process which is called as charging-discharging potential of polymer [151]. There are many reported works of this kind of polymer as reservoir for many drugs (ibuprofen [150], salicylate [152], dexamethasone [153] and ciprofloxacin [154, 155]) where they get released inside the system with the help of electrical stimuli. Few years back, scientists have started using this type of polymers as reservoirs for delivering anticancer drugs. They have used a conducting polymer polypyrrole loaded with methotrexate along with oleanolic acid making the system electrochemically active. The kinetic analysis exhibited that methotrexate release was sustained by means of both temperature and electrical stimuli [4]. In another study, authors have used a different type of conducting polymer poly (3,4-ethylenedioxythiophene) as reservoir for releasing methotrexate drug. The in vitro experimentation proved that it acts against the A-549, HeLa and KB cell lines and it showed a controlled release profile. Therefore, these kinds of polymers are used as promising material for the development of formulation containing anticancer drugs [156].

6 Hybrid Materials

By combining two polymers HA and methylcellulose, it forms injectable gel-like structures. This mixed polymers go through the process of gelation technique through hydrogen bonding interactions [157]. Another example is that mixing of sodium carboxymethyl cellulose along with chitosan to encapsulate doxorubicin which can be formulated into microspheres or hydrogels. Because of the porous nature of carboxymethyl chitosan (oxidised hydrogel) shows no cytotoxicity in the umbilical endothelial cells, compatible in the blood and degraded by the lysozyme. This behaviour enables the doxorubicin delivery as an advantageous method for broad spectrum of vascular embolisation. In the microsphere formulation, owing to its porous nature doxorubicin were easily loaded. The in vitro and the in vivo studies proved that doxorubicin was delivered by enzyme degradation [158].

Haupt et al. studied the treatment for colorectal cancer using chitosan and guar gum. Celecoxib as an individual component delivers with the increased side effects with most majorly complications in the gastrointestinal tract (GIT). Along with the hybrid polymers, the celecoxib delivery results in the decrease in the growth of tumour cells and simultaneously reduces the toxic reactions [159, 160].

The CD complexes were combined with the polyelectrolytes in a multilayer fashion for the effective covering of bone implants and this is said to be an in situ prevention of bone tumour. The CD is combined with hydroxyapatite (HA) for the prolonged delivery of chemotherapeutic agent for the treatment of bone reformation. Chai et al. also revealed that there is improvement in the loading of cisplatin

and it is due to the presence of CDs over the surface of HA. It is also noted that it undergoes a prolonged release of cisplatin in the bone defects to reconstruct the bone structure which also exhibits good biocompatibility [42].

The recent studies showed that the nanosilica material can be used as implantable electronic delivery systems. Li et al. fabricated silica wafers incorporated with anticancer moieties cisplatin, carboplatin and platinum. The silica wafers consist of hydroxyapatite, silica and calcium phosphate impregnated with anticancer moiety for the treatment of bone cancer. The implanted material in the tumour site reveals that it delivers the drug via pulsatile delivery with the application of external stimuli involving electric current/radiation [161].

Kakran et al. developed a system containing GO combined with other polymers such as Tween 80, Pluronic F38, maltodextrin. They are loaded with the natural bioactive component ellagic acid via π–π stacking and identified its release kinetics. The cytotoxicity of the formulation is tested against MCF-7 and HT-29 cells and found good anticancer activity because of the antioxidant nature of drug ellagic acid [162]. In a study by Zhang et al., GO was conjugated with the dextran and the anticancer drug was incorporated into the system. They have proved that the GO-drug conjugates exhibited a reduction in the tumour site against cervical cancer cells. And also found that the GO was gradually cleared from the system without causing toxicity [108]. Liu et al. found that GO when combined with polymer polyethylene glycol (PEG) proves to be a promising material for delivering anticancer drugs. GO-PEG conjugates provide very good stability under physiological conditions and the drug molecule camptothecin along with SN38 were attached via π–π stacking. They have reported that this conjugate PEG-GO-SN38-Camptothecin is highly efficient than the FDA approved water soluble pro-drug used for the treatment of colon cancer [163].

Hydrogels were prepared using PLGA, PLA and PEG which is loaded with the anticancer drug topotecan. There are hydrophobic interactions between the polymer and the drug was observed which increases the pKa value of carboxylate group present in the topotecan. Because of this property, the loading percentage of drug was increased and its efficacy is also increased. The in vivo studies proved that when the hydrogels placed as implants in the tumour site it completely inhibits the growth and recurrence [164].

PCL along with chitosan was prepared in the form of core-shell nanoparticles to load the drug. The drug loaded in this formulation was mitomycin-C and they were very effective in treating bladder tumours. PCL along with the PEG diacrylate microneedles loaded with the drug were useful in obtaining the membranes with different structural surface design. They found that the drug release was very slow and delivered in controlled manner for about 112 days. The in vitro studies were studied against the human dermal fibroblasts cells and observed that scaffolds served as platform for attachment of cells [165].

7 Triggerable Biomaterials

There are biomaterials which are responsive to the different triggers and release the drugs effectively (Fig. 2). The triggers can respond to the stimulus such as physical, chemical and biological agents in which the biological and chemical stimuli are present within the body, whereas the physical ones present externally. By this way, the delivery of drugs can be controlled effectively and targeted to the particular site [17]. The following part briefs about the different classes of responsive biomaterials and its use in anticancer drug delivery.

7.1 Magnetic Responsive Biomaterials

The magnetic properties of the material act as a triggering agent for the controlled delivery of drugs. This idea has been extended to design a system for releasing the active moieties to specific organs by combining two techniques [166]. The magnetic resonance imaging techniques and the drug loaded polymers were paired together for the therapeutic treatment and active targeting. In a study, the doxorubicin loaded alginates were taken and incorporated magnetic beads into the material for targeting the diseased organ. This triggering agent can be combined with pH-responsive materials to offer double benefits in delivering the drugs. In a work, they have combined the magnetic particles in the polymeric matrix which

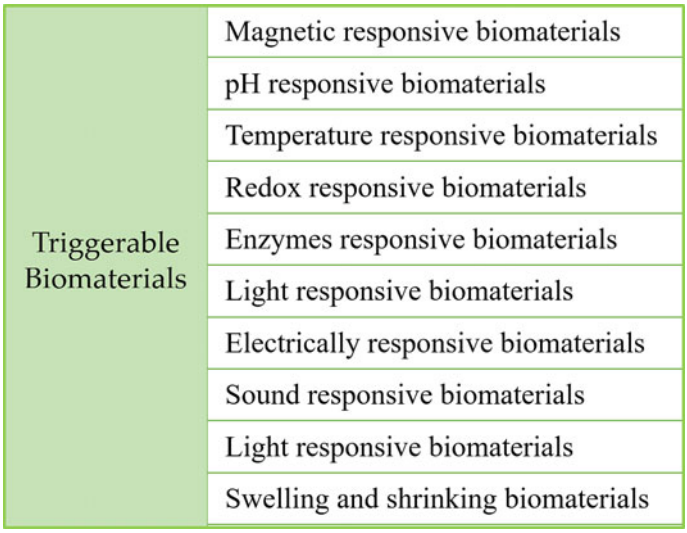

Fig. 2 Triggerable biomaterials

contains drug molecules. Then, they have used MRI imaging to correctly identify the exact location in which the drug was delivered [167–169].

The advantage of including a magnetic material within polymer-drug matrix will be more beneficial because of its easy recovery. When an implant is inserted in a patient, it is necessary to determine the response of the implant. If there is any weak immune response or undesired rejection, to remove the implant from the patient/living system becomes critical. In such a case, this magnetic pulsing technique could be helpful in removing the material from the organ or from the blood circulation. Therefore, drug-polymer with the magnetic particles in the system expands the scope to develop a value-added formulation. It is important to note that some of the magnetic responsive polymer systems have been approved by FDA [170, 171].

7.2 pH-Responsive Biomaterials

There are pH values that exist within the human body and they are different for tissues, organelles and fluids. For example, acidic pH exists in stomach and vaginal areas (pH < 7). The neutral pH occurs in the ocular surface (pH 7.1) and in the blood (pH 7.4). In addition, pH values will differ in disease environment and in the barriers of organ. Therefore, a good approach to increase the efficacy of cancer drugs which involves in the polymeric delivery system which can react at particular pH [172]. To develop a pH sensitive product, functional groups to be included which can protonate or deprotonate in the polymeric matrix. Mostly, amine containing polymers which are derived from dimethyl aminoethylmethacrylate will be protonated to yield a cationic group of materials. Another example in this case is carboxylate containing polymers which includes poly(acrylic acid) will be deprotonated to yield anionic materials under basic environment. Therefore, the charge of these polymers could be easily changed and these materials can react to changes in the pH in the form of swelling, shrinkage, dissociated or degraded. By these strategies, these type of polymeric materials can release the drug moieties in the target organs and tissues [9, 173]. There are various pH-responsive polymers which are used for masking the taste, delivery nucleic acid and doxorubicin delivery (Fig. 3). Most commonly this pH-responsive materials have been used for targeting the tumour environment because they exist at lower pH (5.7). And the surrounding environment occurs at pH of 6.8–7 because of acidosis in the area. Hence, polymeric multifunctional nanocomposites (acid sensitive) were used for the controlled delivery of anticancer drugs. In the cancer environments, the folic acid receptors will be overexpressed and it can be used for functionalising the molecule for improved targeting. The acid-responsive polymer diaminoketal with the drug increases the cellular uptake compared to the free drug alone. A well-known example poly(ethylene glycol) has been used for the controlled delivery of drugs for tumour targeting. These pH-responsive polymeric materials continue to be an area of interest for delivering the anticancer drugs [174, 175].

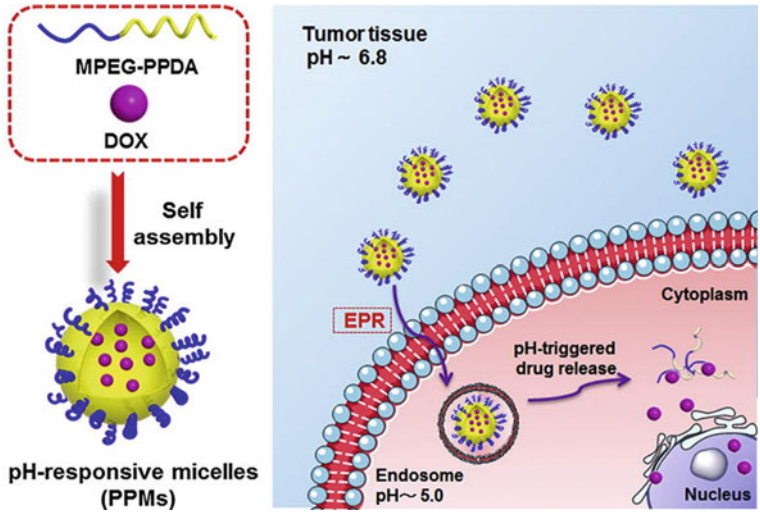

Fig. 3 pH-responsive biomaterials. Copyright permission obtained from Journal of Colloid and Interface Science

7.3 *Temperature-Responsive Biomaterials*

These kinds of polymers can be used for delivering and targeting the tissues and organs. Our human body exists in a temperature of 37 °C, and the room temperature is 25 °C [176]. This difference is advantageous in case of temperature-responsive polymers because these materials flow at ambient temperature and it gels at body temperature. These kinds of polymeric materials were developed by sol-gel techniques for the improved targeting. Examples of these type of polymers are cellulose, chitosan, poly(*N*-vinylcaprolactam), poly(*N*-alkyl acrylamides), poloxamers and xyloglucan. The strategies for formulating this type of materials are modifying the end group molecules, varying the post polymerisation process and changing the concentration of monomers. These strategies could be useful for the controlled delivery and for improved targeting [177–179].

7.4 *Redox Responsive Biomaterials*

The human body consists of reducing and oxidising agent which differs in organs, cells and tissues. Glutathione, a reducing agent found at higher concentration in cells than the surroundings. Hydrogen peroxide, oxidising agent found in the inflamed and injured tissues. The differences in these redox reactions between the cells/tissues and the surrounding environment develop a diseased state. Therefore,

it is important to formulate a materials which should balance the redox potential of the body [180].

The materials obtained from disulphides are used to stabilise the reduction trigger in the body. Inside the cells, it is mediated by glutathione molecule in which the disulphide bridges are reduced to form analogues of dithiol (Fig. 4). This interchange of dithiol and disulphide is a reversible reaction which is best suited for anticancer activity. Another example of this kind is that the sulphur-based materials have been used to balance the oxidation triggers. Sulphur exists in many oxidation states and in particular the sulphur-based block copolymers are used for cancer drug delivery, protein and gene delivery [181, 182].

Interestingly, materials with dual activation capacity can balance both of the oxidation and reduction triggers have been explored. The common functional group used are diselenides in which it has the similar chemical structure as that of disulphides. These diselenides can be incorporated into the bioresponsive polymeric system which prevents the triggers caused by the oxidation and reduction process [183].

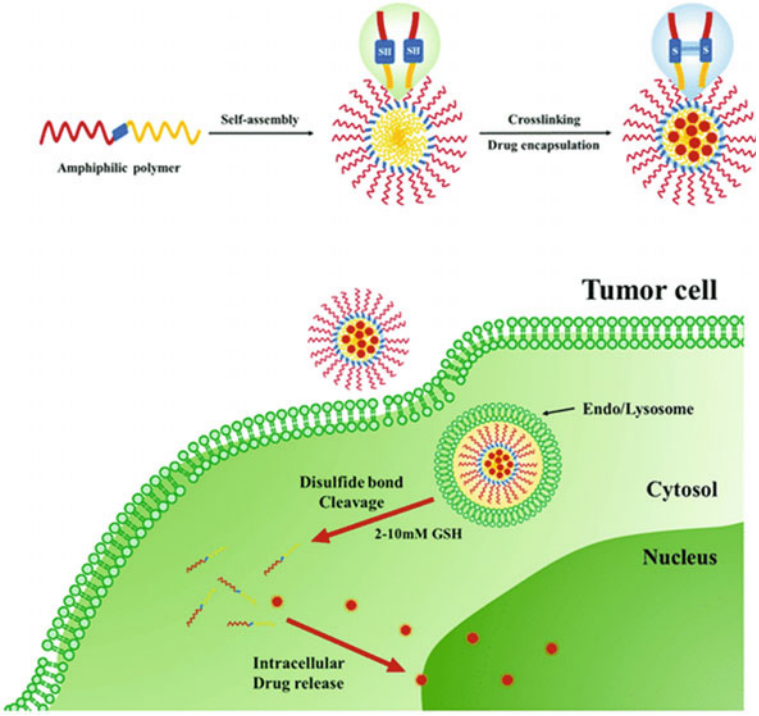

Fig. 4 Redox responsive biomaterials. Copyright permission obtained from Frontiers in Bioengineering and Biotechnology

7.5 *Enzymes and Hydrolysis Sensitive Polymers*

The enzymatic and hydrolytically responsive polymers have been designed and formulated for cancer drug delivery. Hydrolytic susceptible materials are the ones which are degraded by water. The degradation process happens by the nucleophilic addition of water into the functional group (electrophile) of the polymer [184]. The most commonly used electrophilic functional group of the polymers are esters and anhydrides. An example for such kinds of bioresponsive formulation available in the market is Gliadel wafer. This product consists of chemotherapeutic drug carmustine impregnated on the polymer polyanhydride. The Gliadel wafer shows the influence of hydrolysis responsive materials. This chemotherapeutic formulation could also be implanted into brain for the controlled delivery of carmustine to the tumours. Gliadel wafer can also be used in patients with glioblastoma multiforme and it improves the survival rate for about six months [7].

Enzyme sensitive polymers have been developed for tumour imaging and delivering the drugs (Fig. 5). With the disease pathology, some of the enzymes differ from the normal values and they are hyaluronidases, phospholipases, matrix metalloproteins, etc. For the colon tumour treatment, the enzyme responsive polymer along with the drug doxorubicin was developed. It was also found that it minimises the inflammation in the colon than any other systems developed [173, 185].

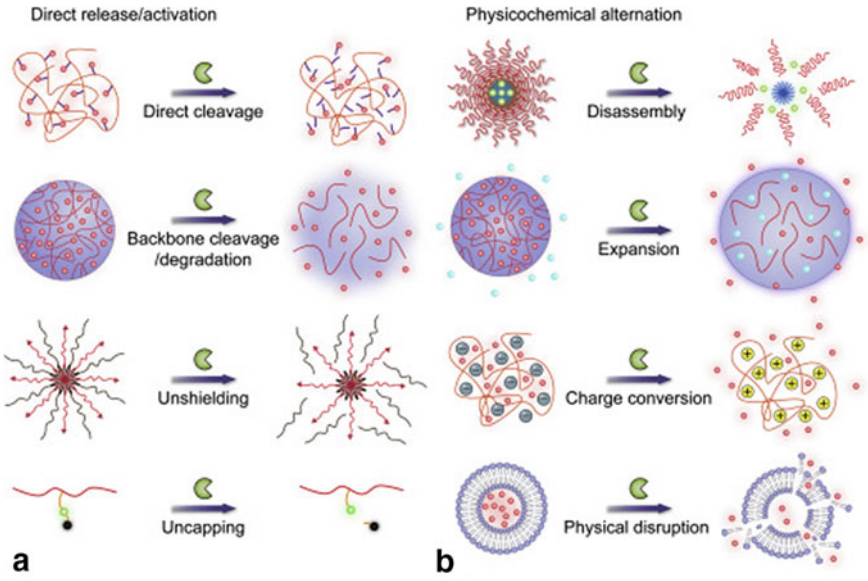

Fig. 5 Enzyme responsive biomaterials. **a** Direct release/activation, **b** indirect release/activation via physicochemical alternation. Copyright permission obtained from Elsevier

7.6 Light Responsive Biomaterials

Light-induced drug delivery has been used to target the cancerous cells by releasing the drugs through the source of light. This is one of the painless and non-invasive technique act as an external stimulus for delivering the cancer drugs [186]. This light stimulation system tuned into a non-invasive trigger for controlling the temporal and spatial delivery of drugs. UV-Visible light irradiation at a particular wavelength will release the drug in the targeted site and this acts as a remote activated system. There are some of the challenges to control the light activation system and they are drug degradation of during light exposure, distance of the light from the polymer-drug system and the thickness of the tissue and the penetration of the light [187]. The important mechanism for the light stimulated delivery is that it undergoes either a ring opening reaction or *cis*-trans isomerisation through the light source. In one of the study, they have used a light sensitive modified azobenzene block copolymer for targeting the melanoma cells. During irradiation, it undergoes a molecular conformation in the azobenzene molecule and by this means it alters the structure to release the drug [188, 189].

7.7 Electrically Responsive Biomaterials

There are various types of electrically sensitive polymers were developed and they have been used for many biomedical applications in particular for targeted delivery of anticancer drugs [190]. Our body is supplied with electrical stimulus, whereas the neurons act as a neurotransmitters for transmitting the information through electrical signals. The electrically responsive polymers are highly conjugated aromatic materials and they will directly form a boundary with the cells when the electrical stimulus is applied. One such example is polypyrrole and they are widely used for electronic applications, bioimaging and targeting the cells. The polypyrrole nanoparticles have also been developed and they have studied its biocompatility in mice. This kind of electrically sensitive polymers has also been combined with temperature sensitive polymers for the dual responsive systems [191, 192].

7.8 Sound Responsive Biomaterials

This is another way to release the drug in the targeted site via auditory stimuli. The challenges associated with this system to release the drug are tuning the properties of materials and functionalising the materials to optimise the release [193]. A study shows that to optimise the release, they have incorporated growth promoting molecules in the ultrasound responsive scaffolds through acoustic responsive polymer. In another study, the drug is impregnated in the fibrin scaffolds and to control the

release, and they have prepared a double layer emulsion using a microfluidiser. Through this microfluidic device, the multilayer delivery systems were created which includes microbubbles and an array of nanoparticle designs [171].

7.9 Swelling and Shrinking Biomaterials

Some of the polymers or biopolymers undergo swelling and contraction with respect to the exterior stimulus. Most common example of biopolymer releasing the anticancer drug is alginates. The anticancer drugs are encapsulated using the alginates by controlling the release profile. Alginates also functionalised by vascular endothelial growth factor (VEGF) to target the specific site in the body. These materials also used for sensing the specific region and the injectable was also prepared using alginates. Many applications are there for using alginates as biopolymer for delivering the drugs [194].

8 Commercially Available Products

There are many products which have been transferred from clinic, approved by FDA and they are commercially available in the market. Most of the formulations are available as ideas in the literature and not executed in commercial market for medical applications (Table 1). **Lupron Depot** is a commercially available drug which contains PLGA microsphere loaded with leuprolide which is used for the treatment of prostate cancer. PLA and PLGA are used in many products because of its versatility, biocompatibility and biodegradability nature which will be degraded into lactides and glycolides [195]. **Doxil** which contains PEGylated (PEG) liposomal formulation encapsulated with doxorubucin was approved by FDA for the treatment and prevention of regrowth of ovarian cancer and Kaposi's sarcoma [196]. **Marqibo** is a recently approved nanoparticle liposomal formulation containing vincristine for the treatment of leukaemia [197]. **Abraxane**, a nanoparticle formulation useful for the treatment of breast cancer [198]. **Zoladex**, a product containing PLGA and drug goserelin acetate for treating prostate and breast cancer cells. This implants duration of action was found to be 3 months and they are in 10 mm length and 1 mm in diameter [199]. **Eligard**, it is an injectable implant containing leuprolide acetate used for the treatment of prostate and breast cancer cells. This implant consists of 2 syringes one is filled with PLGA along with methyl pyrrolidone and the other with the drug. Before injecting at the site, it should be mixed together and injected into the tumour site and it forms implants [200]. **InGell Delta**, PLGA containing dextran and interleukin-2and it forms a stereocomplex which preserves it three-dimensional structure. They exhibit very low initial burst release with good biocompatibility and useful for the treatment of lymphoma [201]. **OncoGel** is a product containing PLGA, PEG loaded with paclitaxel drug and it

Table 1 Commercially available products (anticancer drugs)

Brand name	Drug	Manufacturer	Biomaterial (reservoir)	Application
Lupron depot	Leuprolide	Torrent	PLGA	Prostate cancer, breast cancer
Doxil	Doxorubicin	Boehringer Ingelheim GmbH of Germany	PEG	Ovarian cancer and Kaposi's sarcoma
Marqibo	Vincristine	Eli Lilly and Company	PEG	Leukaemia
Abraxane	Paclitaxel	Abraxis BioScience	PLA	Breast cancer
Zoladex	Goserelin acetate	AstraZeneca	PLGA	Prostate cancer, breast cancer
Eligard	Leuprolide acetate	TAP Pharmaceuticals	PLGA	Prostate cancer, breast cancer
InGell Delta	Interleukin-2	InGell	Dextran and PLGA	Lymphoma
OncoGel	Paclitaxel	Macromed, Inc., Sandy	PLGA and PEG	Brain tumour
Viadur	Leuprorelin	Tolmar	PU	Endometriosis, prostate cancer, breast cancer
Gliadel wafer	Carmustine	Emcure Pharmaceuticals	Poly (carboxyphenoxy-propane/sebacic acid)	Brain tumour, Glioblastoma multiforme

turns into gel form at body temperature. It delivers the drug paclitaxel directly into the brain tumour cells through intralesional injection into the tumour cavity [202]. **Viadur**, osmotic implant which is made up of titanium, PU, elastomeric piston and polyethylene (PE) moderator which provides sustained delivery of drug for about one year in the implant site [203]. **Gliadel wafer** consists of wafers with dime shape and it contains poly(carboxyphenoxy-propane/sebacic acid) loaded with the drug carmustine. They are useful during the post-surgery of the brain tumour, glioblastoma multiforme and release is driven by two types of mechanisms one is surface erosion of biomaterial and drug releases by diffusion [204].

9 Conclusions

The biomaterials (natural, inorganic, organic and hybrid) act as reservoir for delivering the anticancer drugs is the most promising approach to improve the delivery of drugs to the tumour site and thereby reducing its side effects. This approach is advantageous in treating all types of tumour and it can be called as regional chemotherapy. With the expanding research on cancer treatment, the

biomaterials have the potential to deliver the drugs to the targeted site through functionalisation, surface modification, combined delivery and controlled release mechanisms. Hence, the biomaterials mediated drug delivery operate in these three mechanisms such as it inhibits the growth, slows down the growth and also prevents regrowth of the tumour. Moreover, it minimises the harm caused by traditional methods of delivery and it owns the broad spectrum of advantages in the biomedical field. In the last few years, a responsive drug delivery system has been widely considered for the improved permeability, treatment and prevention of cancer growth.

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Chapter 3
Stimuli-responsive Hybrid Polymeric Nanoparticles for Targeted Drug Delivery

Priya Vijayaraghavan, Arjun Sabu, Poliraju Kalluru, and Fredi Francis Cheruvathoor

Abstract Designing polymeric nanoparticle responding to various stimuli is a promising field in medical applications. A combination of various triggers and polymeric nanoparticles creates unique and smart therapeutic materials. Surface modification of polymeric nanoparticles sensing various chemical and physical signals of the human body is one key aspect towards building up site-specific drug delivery vehicles. Although, several reports of targeted drug delivery systems are existing it is quite unfortunate that only a few particles are able to reach the affected tissues. Most of the preclinical trials exploit the enhanced permeation and retention effect, but then again this strategy is questionable in the case of clinical applications. So far most of the drug delivery systems reported has extremely intricate designs which may perhaps be possible to hinder the cost-effective and scaled-up production. Likewise, the other factors that can affect the success ratio towards medical applications may include toxicity of the nanomaterials, weak stability, high drug loading ability, poor degradability, and inadequate biocompatibility. In the future, creating designs by considering and rectifying the aforementioned factors will certainly elevate the stimuli-responsive nanoparticles towards clinical acceptance.

1 Introduction

Polymeric nanoparticles, (PNPs) have recently garnered wide attention, especially in the field of nanoparticle-mediated drug delivery. They are colloidal particles varying in size from 10 to 100 nm in order to facilitate systemic (intravenous)

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administration via diffusion and local (mucosal) administration into the cells. In order to overcome the undesirable in vivo interactions of the therapeutic moieties, efforts are made to design and incorporate the drugs in several biologically safe materials with different sizes, shapes, chemical compositions, and physicochemical properties [1–5]. Some of these materials are liposomes [1], nanoparticles (NPs) [2], polymersomes [3], dendrimers [4], hydrogels [5], nanotubes [6] etc. Depending on the type of delivery vehicle designed, various biomolecules and drugs can be entrapped or adsorbed on polymeric nanoparticles. Generally, highly hydrophilic drugs will largely influence the overall drug release by increasing the water uptake in the polymeric nanoparticles which in turn affects degradation. The advantages of drug encapsulation in the polymer matrix are controlled release, better biocompatibility, improved stability, and targeted delivery.

Hybrid materials are defined as material composed of an intimate mixture of inorganic components, organic components, or both types of components in a scale of less than one micrometer (IUPAC) [7].

Nanodelivery vehicles that can specifically target sites of diseases are an inevitable necessity for drug therapy. To improve this surface functionalization approaches, for example, PEGylation along with functionalizing biologically active ligands on the surface of nanoparticles were adopted. This method can also facilitate phagocytosis by means of enhanced permeability and retention effect through the endothelium of affected areas. However, to a certain extent controlled and on-demand release of drugs from the targeting nanoparticles still remains a difficult task. Hence, the concept of stimuli-responsive drug delivery was introduced to further improve targeted drug delivery to specific tissues (Fig. 1).

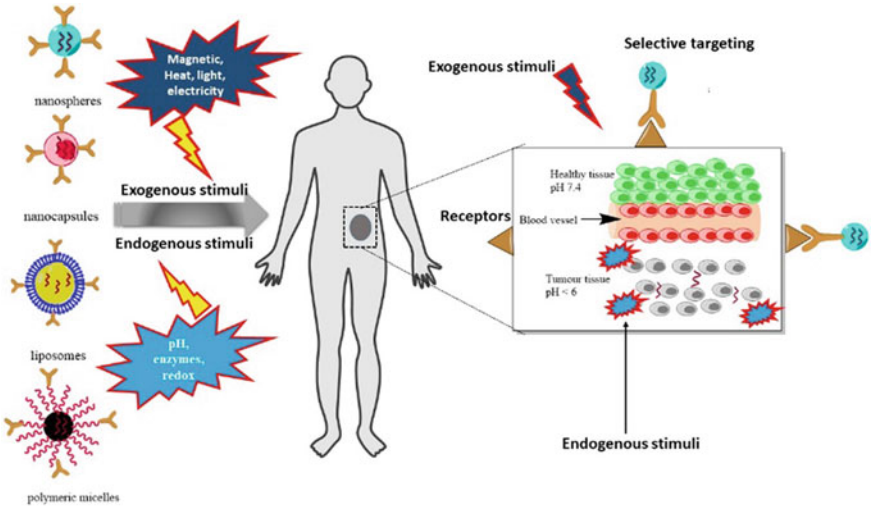


Fig. 1 Diagrammatic representation of various stimuli-responsive drug delivery using different kinds of polymeric nanoparticles

Stimuli-responsive polymeric nanoparticles are small supramolecular nanoassemblies strategically designed to rapidly respond to any change in a specific stimulus in their cellular microenvironment of various diseases. Chemical structure of the polymers is the key factor to the responsive behavior during various triggers and these include abrupt changes in the physical properties including swelling, dissociation, shape, solubility, etc [8]. Various polymerization reactions used to develop appropriate copolymers includes atomic transfer radical polymerization (ATRP), reversible addition fragmentation chain transfer polymerization (RAFT), and nitroxide-mediated radical polymerization (NMP). The types of triggers utilized may include any differences in surrounding temperature, photoirradiation of specific cells by certain the wavelength of light, altered pH gradient, or higher levels of enzymes, etc.

Stimuli-responsive drug-delivery systems are designed for the release of various therapeutic agents triggered by various factors including temperature, magnetic field, ultrasound, light and electric field which are exogenous in nature whereas the endogenous triggers include redox potentials and reactions, pH, and presence of biomolecules and many others.

Various types of triggers are broadly classified under two major groups, exogenous or endogenous triggers.

2 Exogenous Stimuli-Responsive Polymeric Nanoparticles

Under this section, we shall discuss the drug delivery systems susceptible to the changes in externally applied triggers such as temperature, magnetic field, light, and electricity.

2.1 Light Responsive PNPs

Photodynamic therapy uses light as a trigger for the activation of desired reactions and the advantages of these systems are minimal invasion, rapid response, and application to specific area by the irradiation of the target area [9, 10]. Another major application of these photoactivation is the activation of a photo responsive drug system and drug release *via* photochemical reactions and/or conformational changes [11]. Photochromic compounds such as spiropyran, azobenzene, o-nitrobenzyl, coumarin, etc. are introduced into polymeric micelles for the design of hybrid drug delivery systems [12]. In order to improve the morphological stability and loading capability, functional inorganic nanoparticles can also be incorporated into these micelles *via* self-assembly. It can also enhance the properties required for drug delivery by combining the properties of inorganic nanoparticles and polymeric micelles [13, 14]. Light responsive nanocarriers have been designed based on hollow mesoporous silica nanoparticles and spiropyran

copolymer. The irradiation of the system with 365 nm UV light leads to the shifting of the hydrophilic–hydrophobic balance of the amphiphilic copolymer resulting in the breaking away of the polymer from the hydrophobic silica surface and releasing the pre-loaded anti-cancer drug [15]. Semiconductors can also be used in hybrid materials to function as light-responsive moieties and the band gap can be tuned to attain the range of light responsiveness from NIR to UV and visible light [16]. It was reported that by changing the amount of dopant Se, the band gap of homogeneous $AgIn(S_{1-x}Se_x)_2$ could be tuned [17]. The UV-Vis light-based systems possess a severe drawback in terms of tissue-penetration which limits the release of drugs to surface tissues and the absorption of the UV and intense visible light are toxic to normal tissues [18]. These drawbacks can be rectified by using NIR radiation with a wavelength between 750 and 1000 nm having higher penetrating power and lower radiation damage [13, 19]. NIR responsive systems can be designed by embedding NIR active particles as heat dissipater into thermo responsive systems [20]. Hybrid nanoparticles were made from PNIPAM microgels with a high surface charge and Au nanorods on the surface. A phase transition of polymeric chains were induced by the delivery of localized heat to polymeric hydrogels [21]. A similar structure and strategy was applied for controlling the release of Norvancomycin by modulating the intensity of the irradiated NIR [22]. Tumor targeting compounds can be introduced in order to attribute active targeting capability for the light-responsive drug carrier [23]. This will result in the gathering of carriers in a specific targeted site and light irradiation could release the drug in the specific site [24]. Such a hybrid system was reported in which Au NPs with caged folate molecules on the surface, which could selectively target cancer cells when irradiated with light [25]. The folic acid which is caged by a photo cleavable *o*-nitrobenzyl group by binding to α- and γ-carboxylates could bind on the folate receptor on cell surface [26].

AuNRs can be tuned to absorb in NIR region and hence can be used as the photoactive component in hybrid materials. Hybrid nanoparticles having excellent photothermal conversion capabilities with NIR were developed with a stretched hydrophilic PEG as covering polymeric shell and polyamidoamine (PAMAM) dendrimers along with AuNRs as the core which have considerable effect in tumor reduction [27]. Targeted photothermal therapeutic applications were explored by conjugating RGD peptides on the PAMAM shell and using it as a stabilizing agent for the NRs. Upon NIR activation these nanocomposites exhibited efficient activity against the targeted A375 cancer cells both in vitro and in vivo [28]. Owing to their structural properties these polymeric hybrid assemblies with hydrophobic cores can effectively store hydrophobic agents and act as reservoirs for drug delivery. This is utilized to prepare AuNRs modified with polymers as NIR responsive nanovessels to deliver drugs to specific tumor sites. AuNR hybrid micelles were prepared by coating them with poly(ethylene glycol)-*b*-poly(caprolactone) (Lip-PEG-*b*-PCL) copolymers with or without RGD cyclic targeting ligand. DOX was used as drug which was retained in the hydrophobic core without any premature release under normal conditions and under low power NIR, the drug could be swiftly released by heat generation [29, 30].

Modifiying the nanorods with a thermoresponsive polymer will render the system more sensitive towards NIR and it was demonstrated by using AuNRs modified with thermoresponsive polymeric micelles as drug carrying system for DOX and was concluded that localized photothermal heating resulted in an enhanced cytotoxicity and easy release [31]. In a similar work poly(ethylene glycol)-*b*-poly(N-vinylcaprolactam) (PEG-*b*-PNVCL) polymer, which was temperature responsive, formed a corona on the nanorod surface and released the drug with a low power IR(250 mW) [32].

Instead of utilizing the nanocarriers hydrophobic core to load drugs, they can be converted to nanocarrier-drug conjugates *via* covalent bonds which are cleavable biologically. This can prevent the leakage of drugs to the circulatory system. PEG-modified PAMAM dendrimers were wrapped on AuNRs before conjugating DOX via a hydrazine linkage which is acid labile. This system is stable in inner physiological conditions and in acidic/lysosomal conditions; the cleavage of hydrazine linkage took place to release the drug. The synergistic efficacy by this combined photothermal-chemotherapy have greater potential in anti-cancer applications [33].

Mg nanoparticles (MgNPs) and CuS nanoparticles (CuSNPs) can also be used for photo thermal treatment of cancer being wrapped with amphiphilic copolymers which form spherical nanohybrids. Mg being a lighter and abundant element in the human body is benign for biomedical applications. MgNPs were synthesized and functionalized with PLGA-*b*-PEG block copolymer and the thermal sensitivity could be regulated by varying the laser intensity of the laser [34]. In a similar work Cy5.5-modified hyaluronic acid polymeric nanoparticles were used to co-conjugate with CuSNPs, due to the generated hyperthermia effect, the tumor growth was efficiently inhibited.

By the integration of NIR absorbing agents and photosensitizers into one polymeric nanocarrier, a combined PTT and PDT effect can be attained since both the phototherapeutic agents could function by their own independent mechanisms without interfering each other. Following this idea, for PDT, an additional cargo of chlorin e6 (Ce6) is utilized by virtue of its NIR-absorption, rapid elimination from the body, high singlet oxygen generation efficiency, and commercial availability. Multifunctional self-assembled micelles were made by pre-conjugating a PEGylated amphiphilic polymer with the photosensitizer Ce6 and then by addition of a NIR sensitive dye [35]. This hybrid system could be used for the multi modal imaging of tumors in mouse models *via* magnetic, fluorescence, and photoacoustic methods. A synergistic in vitro and in vivo antitumor effect was observed during combined photothermal–photodynamic therapy (PTT-PDT). A similar application *via* sequential combination of PTT with PDT along with dual photoacoustic/NIR imaging modalities was reported by using inside biodegradable PEG-*b*-PAsp(DA) micelles loaded with cypate and Ce6 [36]. In a similar study thiol terminated poly (ethylene glycol)-*b*-poly(styrene) (PEG-*b*-PS) was utilized to modify AuNPs which formed vesicles based on the monolayer polymer by self-assembly [37]. The NIR absorption properties of these plasmonic vesicular assemblies were utilized for PTT of cancer. PTT and PDT guided by multimodal imaging via NIR fluorescence/

thermal/photoacoustic techniques were made possible by the incorporation of Ce6. A pluronic nanogel functionalized with chitosan and loaded with AuNRs and Ce6 was developed for PTT-PDT [38]. Both photothermal and photodynamic treatment applications were enabled by eliminating the quenching of Ce6 fluorescence by avoiding the direct contact with AuNRs facilitated by a modified loading method. Superior performance was observed for the combined PTT-PDT when compared to PTT or PDT alone for antitumor activity.

If the lesions are readily available or accessible from outside the body, conventional photo sensitive systems could be used and if deep tissue drug delivery is required, NIR light with a larger penetration depth and targeting compounds will come in handy.

2.2 Magnetic Responsive PNPs

In general, PNPs are combined with super paramagnetic iron oxides, SPIONS (magnetite: Fe_3O_4 or maghemite: γ-Fe_2O_3) forming a polymer magnetic nanoparticle composite material for stimuli-responsive drug delivery. SPIONS are widely used for magnetic resonance imaging (MRI), magnetothermal therapy, and as various drug delivery vehicles. These polymeric magnetic nanoparticles could generate heat upon alternating current magnetic field (ACMF) which favored the release of drug from the polymer composite material. There are various magnetic nanoparticles, polymeric nanoparticles and their drug-releasing ability upon exposure to external magnetic fields which contributed towards inhibiting cancers. Magnetic field can be used to guide the therapeutic material to the affected tissues. In order to avoid aggregation and improve stability the magnetic nanoparticles are surface functionalized with polymers. Furthermore, lipid-polymer hybrid magnetic nanoparticles are stable, with controlled drug release and improved chemotherapy to kill the cancer cells [39]. Also, few other nanoparticles were employed as targeted drug delivery vehicles under a low magnetic field [40]. In literature, it was reported that titania nanotubes were decorated with magnetic nanoparticles and further conjugated with polymer as a drug carrier [41]. An interesting material called as magnetic liposomes were also reported which could be employed as a drug delivery vehicle to reach the tumor site [42]. Smart magnetic nanoparticles (Fe_3O_4) with polymer could also generate magnetic hyperthermia and drug release [43].

Several methods have been explored to synthesize polymer magnetic nanoparticles to release the drug at the tumor site in a controlled way. Lipid polymer-hybrid nanoparticles [poly (lactic-co-glycolic acid) PLGA), Fe_3O_4 NPs] can be produced by various methods including self-assembly and nanoprecipitation method [39], conjugation method [40], drug encapsulation on polymer NPs [41], magnetic nanoparticles combined with liposomes [42], polymer nanocontainers with poly (methacrylic acid) combined with *N*-isopropyl acrylamide [43], etc.

Although polymer magnetic nanocomposites are an emerging field in biomedical applications, there is a lacking in the targeted delivery of molecular drugs and their

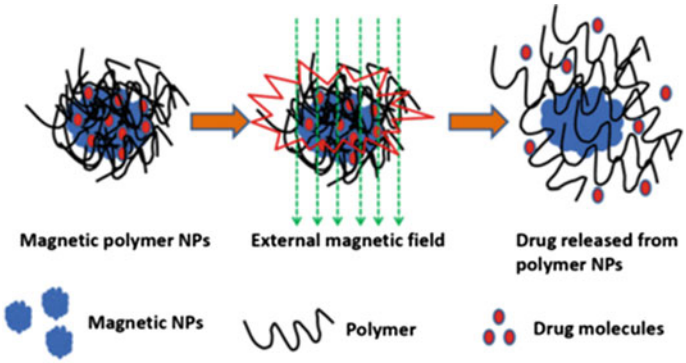


Fig. 2 Schematic representation of magnetic nanoparticles conjugated with polymer matrix and upon external magnetic field the release of drug molecules

controlled release. Figure 2 depicts a general representation of drug delivery using externaly applied magnetic field.

2.3 Thermoresponsive PNPs

Thermoresponsive polymers are a class of smart biomaterials that utilizes the temperature difference between healthy and unhealthy tissues. A local hypo or hyperthermia-induced by any physical way is sufficient for temperature-sensitive drug delivery systems. The phase transition temperature known as critical solution temperature (CST) of polymers is the most essential factor involved in designing temperature sensitive polymeric nanoparticles. Polymers with lower CST (LCST) will become insoluble upon heating. The hydrophobic and hydrophilic bonds of the polymer chain can control the swelling behavior of polymers. As the temperature rises above LCST, a disruption of polymer chain induces the encapsulated drug release. Polymers with the hydrophilic/hydrophobic environment could form micelle at different temperatures with respect to their critical micelle concentration in order to load the drugs into the micelle. They were employed as drug carriers to reach the tumor site. There are several literature reports regarding thermoresponsive polymers as anticancer drug delivery vehicles.

Polymer composite materials have met a significant role in the field of drug delivery and those were differentiated based on their physico-chemical properties and therein, thermoresponsive polymers which were efficient drug carriers to release the drug more effectively. In literature, dendritic polymer nanoparticles, biotinylated double-hydrophilic block copolymer, polycarbonate copolymer have been utilized as a thermoresponsive drug-releasing vehicles and polyurethane to kill the malignant cancer cells [44–48]. Recently there was a report, silk-elastin like

polymer (Poloxamer 407) which could serve as temperature-responsive drug delivery carrier for treatment of painful bladder syndrome [49]. In literature, it is reported that thermoresponsive copolymers conjugated with hydrogels could be utilized for cancer therapy.

Thermoresponsive drug delivery vehicles were synthesized by introducing a different type of polymeric [45], dendritic [44], polymer colloids [48] and hydrogel [50] conjugated composite materials for biomedical applications.

Many studies have reported that thermoresponsive polymer/NPs/colloids/hydrogels were employed as drug carriers and release the drug at 37 °C or above the body temperature. Generally, cancerous tumor would have slightly higher temperature as compared with normal tissue. Based on this concept, in literature it was reported that hydrogel which carry the anticancer drug to the tumor site released the drug in a sustained manner under the physiological condition of the body [50]. Figure 3 shows a diagramatic representation of a thermo-responsive polymer matrix conjugated with anticancer drug molecules reaching the tumor cells. When the temperature of tumor site is more than 37 °C, the drug is released from the heat-responsive polymer matrix. The physico-chemical properties, amphiphilicity, and biodegradation of polymers could be the other essential factors for drug delivery and tissue engineering applications [51].

2.4 *Electroresponsive PNPs*

The electric potential can be used as a trigger with no or minimal invasion. The system can be simple, economic, portable and even microelectrodes can be employed on a minimal invasive manner for body parts in which the conventional triggers are unusable. The application of the hybrid Nanomaterials depends upon the nature of the polymer used and the method of bonding between the drug

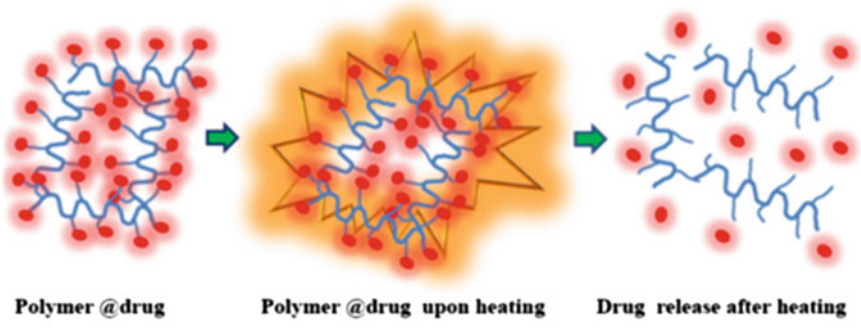


Fig. 3 Schematic representation of temperature-responsive drug release from PNPs

molecule and the material. For example, electro active polymers (EAP) which are responsive to electric field and its subclass intrinsically conducting polymers (ICP) [52, 53] like polypyrroles can be utilized to make thin films that can deliver drugs when triggered by electrodes. Thin films can be used as films with surface nano-structures, ultra-thin films which can bind the substrates with multiple layers, binding the substrates on nano-templates, can be coated as nano-porous membrane for bulk drug reservoirs and as nano-composites. The ICPs which are cationic in nature are incorporated with positive charges along their backbones which makes them capable of holding negatively charged drug molecules and upon the reduction of these the drug molecule can be released [54].

The potentials which will be applied during synthesis and working periods must not activate the release of the drug which will result in the reduced availability and bioactivity while in use. The drug should be highly active towards the biological system so the loading could be low enough. The accumulation of drugs is of major concern and to avoid this, compounds with short half-life should be used. Implants also can be designed in such a way to increase the efficacy of the drug by controlled release to bloodstream where drugs with poor bioavailability are in play. In such cases, the tissues encapsulating the implant will be engaging a high quantity of drug and therefore must be nontoxic to those [53].

Nano structures can hold drug molecules very efficiently. This is made possible by the higher available surface area and due to the presence of pores and other binding modes. Dopants can be used to control the morphology of the thin films. Polypyrroles were known to exhibit a cauliflower-like morphology when electropolymerized on flat electrodes [55]. Suitable dopants can be incorporated during the synthesis so as to attain desired nanostructures. ATP can be used as morphology directing agent for the synthesis of a polypyrrole nanowire textured film and as model drug at the same instance [55]. Use of the dopant sodium *p*-toluenesulfonate afforded the synthesis of nano-tentacles of polypyrrole on the surface and the subsequent incorporation of ATP done by ion-exchange [56]. It was also found that the release of ATP can be controlled by the thickness of the outer protecting film [57].

Nano textured substrates can be covered with thin films which are made from electroactive polymers so that when these films are activated by electric field the drug molecules will be released from the system. The drug molecules can be encapsulated to polymer nano-fibers via electrospinning and other means [58–60]. The films can be deposited as layers on these nano-substrate layers and hence called layer by layer (LbL) method. A nano-porous gold-polycarbonate template with metallic nanopillars was used and was incorporated with dexamethasone by electrodeposition with polypyrrole film [61]. This drug molecule was released by an electric stimulus and is an example of nano-bio electrode as an electrically controlled drug release system. A similar system on platinum electrode with carbon nanotubes was also used for the controlled release of the neutrotrophin-3 from the system by electric stimuli [62]. Electrodes can be synthesized with nanopores when polymers are used as templates and monomer solution with drug molecules can be electropolymerized on to this by colloidal lithography [63–67]. The antipsychotic

drug risperidone was encapsulated with nano-porous polypyrrole film and a non-porous polypyrrole layer was capped over it for the controlled and slow release of the drug upon the application of electric potential [68]. Colloidal lithography was employed to create a nano porous polypyrrole film in which fluorescein was incorporated onto the polymer matrix and dexamethasone to the resultant nano-pores. This approach will lead to the side loading of drugs with different binding characteristics [69]. A similar approach was involved in the synthesis of porous nanowire network of polypyrrole which can bind both lipophilic and hydrophilic drugs [57]. An anodized aluminum oxide electrode was covered with a nanoporous membrane comprising polypyrrole doped with dodecyl benzenesulfonate anion by electro polymerization. The delivery of fluorescein-labeled bovine serum albumin through the membrane was also studied by electrical actuation [67].

The external film cover will reduce the undesirable release of drugs in the target area. This was confirmed when a poly(styrene sulfonate) film was used to encapsulate a dexamethasone doped polyester film on an microelectrode which otherwise will release the drug molecule gradually [70].

Nanomaterials can be incorporated with films in order to make nanocomposites and the electro responsiveness of these thin films can be exploited for targeted electroresponsive drug delivery systems. The nano-materials like carbon nano-tubes can be used in order to increase the conductivity of the film as well and increase the response rate [71] or can be used as a reservoir for loading drugs to the polymer film. Multi-walled carbon nanotubes (MWCNTs) were found useful for this purpose [72]. MWCNTs were filled with dexamethasone and were utilized as small reservoirs and were incorporated into an electro responsive polypyrrole film.

In addition to the film-based systems colloidal or dispersed systems including nanoparticles, micelles, and vesicular structures can also be used for targeted drug delivery. These can be used with minimal effort without extensive fabrication and implants. They are designed in such a way in order to accumulate in the target sites by means of proper surface functionalization. The release of these drugs can be attained by locally installed electrodes like needles. These electrodes can apply potential in such a way that the drug molecules will be driven out of the encapsulated moieties by appropriate potential fields.

Nanoparticles for electrically stimulated targeted delivery which are comprised of a polymer and one or more drug molecule can be synthesized by suitable methods like emulsion, polymerization or copolymerization [73, 74]. These molecules with appropriate functionalization can bind near the target sites. The electrically released molecules can be driven to the electrodes of opposite potential and therefore can be directed to the targeted area more precisely.

The colloidal particles formed by assembling amphiphilic molecules are called micelles. This property of monomeric parts makes them capable of carrying different drug molecules, hydrophobic as well as hydrophilic. These micelles can be disassembled with the application of appropriate electrical field and can release the trapped drug molecule in the targeted site. This method can be utilized to deposit hydrophobic drug molecules in different body locations as desired [75–77].

Similar to the colloidal particles the polymers can also be assembled to polymerosomes or bigger and robust capsules [78, 79]. These vesicular structures can carry both hydrophilic molecules on the hydrophilic parts and hydrophobic molecules in the inner space and encapsulate them. The release of drugs can be actuated by applying suitable electric field and either by disassembly of the system or disruption of vesicular structure to other forms like aggregates [80].

3 Endogenous Stimuli-Responsive Polymeric Nanoparticles

Here, stimuli-responsive nanoparticles that can readily respond to the changes in the internal parameters of the cellular microenvironment such as pH, redox potential, and enzymes are explained.

3.1 Redox-Responsive PNPs

Redox-responsive drug delivery systems mainly rely upon the difference between the redox states in the extracellular circulation fluids and intracellular compartments. The redox potential which prevails between the extracellular(oxidative) and intracellular(reductive) environments mainly depends on the corresponding concentrations of glutathione [81]. Glutathione exists in two states, reduced (GSH) and oxidized (GSSG). The ratio of these within cells indicates cellular oxidative stress. More than 90% of the total glutathione in healthy cells/tissues exists in the reduced form (GSH), and the rest in the disulfide form (GSSG). Normal Glutathione (GSH) levels in intracellular spaces are 100 to 1000 times higher than that in circulatory system, and extracellular media. The normal concentrations in these extracellular environments are reported to be 2–20 μM, whereas the levels within cancer cell range from 2 to 10 mM [82].

Owing to these differences in concentrations and in the redox potentials the redox-sensitive polymer nanomaterials can deliver the payload site specifically as they will be stable in the blood stream and extracellular media and get disassembled in the regions with larger concentrations of GSH, i.e., inside the target cells. The requirements for the design of such systems is the responsiveness to the reduction or oxidation stimuli and for the nanosystems we mainly incorporate the moieties like disulfide, diselenide, or ditellurium bonds which are redox-sensitive [83–86].

Disulfide bonds can be easily cleaved by reducing glutathione into sulfhydryl groups, which results in the decomposition of carriers release the payload. Similarly, diselinide bonds and C-Se bonds can also be utilized in the same way [87–89]. In addition to these other redox responsive systems are also reported. Succinimide-thioether linkage facilitated intracellular release with higher blood

stability and slow-release rate [90]. "Trimethyl-locked" benzoquinone (TMBQ) also exhibits redox sensitivity and are used to deliver anti-tumor drugs which degrade in the presence of $Na_2S_2O_4$ [91, 92].

The redox-sensitive moieties can be used in different modes including

(a) Functionalized to the backbone of polymers and side chains or nanoparticles with drugs, genes, and target groups. Here the attached functionality can be detached easily in a reducing environment.
(b) Existing throughout the backbone. Here the polymeric material will be depolymerized to release the encapsulated drug.
(c) On the surface of nanoparticles in order to connect with other moieties.
(d) Linking moieties with two specific roles like hydrophobic and hydrophilic nature, and
(e) As cross-linking agents.

Different types of redox-responsive polymeric nanotherapeutic systems have been developed in order to address the issues arising from hydrophobic nature of drugs, low bioavailability, in vivo degradation, deactivation by enzymes, side effects on normal tissues, and low therapeutic index.

Redox responsive copolymers: Introducing redox-sensitive groups in copolymers which have good biocompatibility and amphiphilicity drug delivery systems with both hydrophilic and hydrophobic properties for drug encapsulation can be created. They can undergo self-assembly to form nanostructures of varying shapes and sizes based on the ratio of the constituent monomers and linkages. The hydrophobic drugs can be encapsulated by the hydrophilic polymers which cover the surface of the polymeric nanocarriers and prevent toxicity to the other tissues. Recently, redox-responsive polymeric nanocarriers for controlled delivery of doxorubicin were fabricated via covalent linking of the carboxyl groups of alginate and the amino groups of cystamine [93]. Electrostatic interactions between the anionic alginate and cationic doxorubicin facilitated the loading of the drug in the system. Similar strategy was applied for micelles also [94].

Nano-sized hollow polymer capsules with redox-sensitive groups can be excellent candidates due to their simple preparation, excellent biocompatibility, possibilities for surface functionalization, responsiveness, and low cost. Redox-responsive polymeric nanocapsules were synthesized via a template-free strategy utilizing the host–guest interactions between cucurbit[6]uril(CB[6]) and polyamines for the encapsulation of carboxyfluorescein and its release studies [95].

Biodegradable drug delivery carriers avoid the accumulation and toxicity of materials used in drug delivery platforms. Incorporating redox-sensitive groups in biodegradable polymers like polysaccharides and other degradable polymers good biodegradable carriers can be developed. There are recent reports on the preparation of polymeric drug delivery nanocarriers from PEG, thiomalic acid, and caprolactone for Paclitaxel [96].

Amino acids are small biomolecules and are therefore having good biocompatibility. They can also be combined with other monomers and to form copolymers

of good biocompatibility which can be used for gene or drug delivery [97]. The incorporation of redox-sensitive groups enhanced the ability of targeted delivery. Recently, PEG-coated poly(amino acid)s were examined for the delivery of doxorubicin and found that they possessed well-controlled release behavior [98].

The polymer architecture is the main factor for determining their microstructure and properties. Branched polymers have different properties when compared to linear polymers. Their physicochemical properties are much different from linear ones, and many properties suitable for biological applications. Many varieties of branched polymers including dendrimers, star polymers, brush polymers, dumbbell and comb polymers, branched polyethylenimine (PEI), etc. have been prepared. Many of these micro-nanostructures are capable of carrying a payload including genes, bioactive molecules, and drugs. Incorporation of disulphide linkages to the gene carriers afforded the reducible PEI gene carriers which were having reduced toxicity and high gene transfection rate [99]. A similar system was reported by the integration of doxorubicin to a redox-responsive dendrimer made by combining biodegradable PLA, boltorn hyperbranched polymer (H40 star polymer), polyphosphate, and redox responsive disulfide bonds [100].

3.2 pH-Responsive PNPs

The human body is a well fabricated biological system that can maintain a healthy equilibrium of internal acidity and alkalinity. The physiological pH is slightly basic with a value of 7.4. Acid-base homeostasis is a process of homeostatic regulation of pH [101]. Any disruption in the proper balance between the acids and bases in the extracellular fluid can harmfully affect the physiology of the body, leading to various diseases.

pH-sensitive PNPs is a widely investigated area for controlled drug delivery in specific organs including gastrointestinal tract, vagina and to the intracellular organelles such as endosomes and lysosomes [102]. Compared to a healthy tissue there is a difference of pH in the pathological conditions such as inflammation and cancer. Due to the increased metabolic activity, the pH is acidic in endosomes (pH 5.5) and lysosomes (pH 5.0) [103]. pH gradient mainly results from the increased demand for nutrients and oxygen from the irregular angiogenesis in tumors. Thus, resulting in increasing acidic metabolites [103, 104]. This variation in pH gradient can be an excellent opportunity towards advanced pH-responsive drug delivery systems [105]. Innumerable anticancer pH sensitive drug delivery systems have been designed to deliver the drug moieties by exploiting the pH gradient between the healthy tissues (7.4) and the extracellular milieu of solid tumors (6.5–7.2) (Fig. 4).

An efficient pH-sensitive system can be designed by considering two possibilities. One method is by using polymers with ionizable groups which can respond to the environmental pH change by altering their conformation or solubility. The ionization behavior of various polymers at different pH is characterized by the pKa

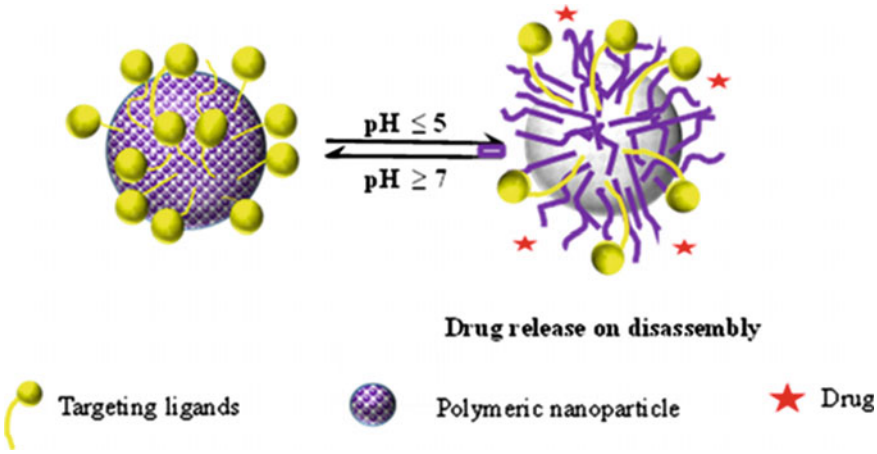


Fig. 4 Schematic representation of pH-responsive drug release from PNPs

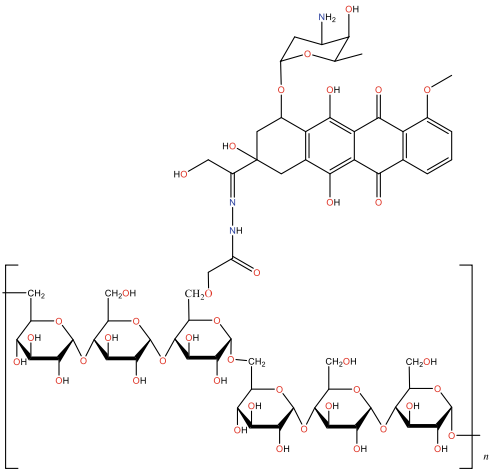
value of a polyelectrolyte which is defined as the pH with equal concentration of the protonated and deprotonated forms [106]. Usually, ionizable polymers are classified under two categories; the first one polyacids or acidic polymers that can release protons at higher pH and the second one is polybases or basic polymers that can accept protons at lower pH value. Few examples of ionizable acid functionalities include carboxylic, sulphonic, boronic acids, etc. [107]. Common basic functionalities include amines, morpholines, pyridines, piperazines, etc. which can undergo protonation or deprotonation at different pH values. Among these, amines, particularly tertiary amines gained extensive importance due to their tunability of pKa and ease of synthesis [108, 109]. Also, it was reported earlier that amines have slightly lower pKa when replaced with long chain hydrophobic units [110].

Ultra-pH sensitive (UPS) polymers consisting of an amphiphilic block copolymer, hydrophilic poly(ethylene glycol) (PEG) and hydrophobic tertiary amine substituted polymethacrylate (PMA), for real-time tumor imaging was reported [111]. These smart nanopolymers can abruptly respond to the pH gradient and strengthen the pH signals of in vivo systems with a small span of time. At physiological pH (7.4), the PEG-*b*-PMA self-assemble as a core shell micelle. In acidic pH, the amines will get protonated by rapidly dissociating micelles into monomers. Here, the system also follows a completely reversible process of dissociation and self-assembly as determined by ambient pH which facilitates the drug release.

Fu et al. modified the UPS polymer system with an amphiphilic copolymer of poly(oligo(ethylene glycol)methacrylate) (POEGMA) and poly(benzyl-L-aspartic acid) (PBLA) with a fluorescent cyaninedye (Cy5.5) conjugated at the chain end of the amphiphilic copolymer [112]. These biodegradable polymers were prepared by reversible addition–fragmentation chain transfer (RAFT) polymerization, ring-opening polymerization, and click reaction. The peptides were further modified with ionizable tertiary amine moieties for pH stimuli-responsive behavior.

Hydrophilic and hydrophobic blocks were covalently bonded by the copper(I)-catalyzed alkyne-azidecyclo addition (CuAAC) "click" chemistry [113]. The amphiphilic copolymer's pKa can be finely tuned by varying the ratio of amino moieties. Polymer chains can self-assemble as stable micelles in neutral pH and dissociate in the feebly acidic pH due to the reversible protonation of ionizable amines. This study promises a simultaneous application to evaluate the subtle change in the pH of tissues and cells and also a theranostic agent for drug delivery and imaging.

Another best example found in the literature is an anticancer drug, doxorubicin (DOX), delivery by using a natural biocompatible polysaccharide pullulan [114]. DOX was functionalized to the polymer support through a pH-sensitive hydrazine bond. At acidic pH (pH 5), DOX was successfully released with less toxicity than free DOX as a result of slow internalization in the 4T1 mouse breast tumor cells. The same strategy was also adapted by Mackay et al. by using an artificial recombinant chimeric polypeptide (CP) to deliver DOX based on the variation in pH [115].



pH-sensitive pullulan-DOX conjugate by Lu et al. [114]

Another method is to fabricate polymeric drug delivery systems with acid-sensitive functionalities that can decompose or destabilize to release the drug molecules bonded to the polymer to the corresponding site. Common acid-sensitive functionalities are hydrazone, acetal, ketal, boronate ester, etc. [116]. An example of a sharply responding polymeric system under a subtle pH change includes the use of poly (2-tetrahydropyranylmethacrylate), poly (THPMA) [117]. Under mild acidic conditions, (pH 5.1), the polymeric system was able to release payloads of paclitaxel, an anticancer drug. Hu et al have reported pH-responsive polypeptide–drug nanoparticles for targeted cancer therapy by using bioactive well-defined elastin-like polypeptides with acid-labile hydrazine linker [118]. These DOX

delivering nanoparticles exhibited less toxicity with better anti-tumor efficacy. Similarly, Wang and co-workers have reported hydrazone-based multifunctional sericin nano particles for sub cellular delivery of chemo drugs [119].

Acetal and ketal groups are also highly acid-sensitive groups that are stable under basic pH. During acid cleavage conditions they can be hydrolyzed to the corresponding carbonyl (aldehyde and ketone) and alcohols [120]. Novel envelop-like mesoporous nanoparticles (MEMSN) were developed for pH responsive delivery of DOX and magnetic resonance imaging (MRI) via acid labile linkages of acetals on the surfaces of mesoporoussilica [121]. Ultra-small lanthanide doped up converting nanoparticle acted as a gatekeeper with the anticancer drug DOX locked inside the pores. Under acidic conditions, hydrolysation of acetals leads to the release of entrapped DOX molecules. Another example for acetal-based drug release was demonstrated by Wang et al. [122]. Amphilic di block copolymers, poly(ethylene oxide)-b-poly(2-((((5-methyl-2-(2,4,6-trimethoxyphenyl)-1,3 dioxanyl) methoxy) carbonyl) amino) ethyl methacrylate) (PEO-*b*-PTTAMA), was synthesized through a reversible addition–fragmentation chain transfer (RAFT) polymerization of a pH-responsive monomer (i.e., TTAMA) using a PEO-based macro RAFT agent. Under neutral pH the hydrophobic cyclic benzylidene acetals were stable. Upon acid trigger, the acetals were hydrolyzed to hydrophilic diols as evaluated by UV/vis spectroscopy, SEM, and TEM. The hydrophobic model drug (Nile red) and hydrophilic chemotherapeutic drug (doxorubicin hydrochloride, DOX · HCl) were loaded into the hydrophobic bilayer and aqueous interior of the polymersomes. Subsequently, the payloads were released according to the pH gradient, and under acidic pH, the drug release was faster.

3.3 Enzyme Responsive PNPs

Enzymes play a very crucial role in all the life-sustaining chemical processes of a living organism. Enzymes are macromolecular biological molecules that significantly accelerate the rate of chemical reactions that take place within each cell. Enzymes selectively react with molecules known as substrates and convert the substrates into different products. In particular, pathological conditions including cancer or inflammation can cause higher enzymatic activity. Therefore, can be utilized to design drug carriers via enzyme facilitated drug delivery depending on the sensitivity towards specific enzyme. For instance, short peptide sequences cleavable by matrix metalloproteins (MMPs), a family of zinc-dependent endopeptidases enzyme which is highly expressed in the tumor cells. MMP cleavable peptides were employed as linkers between the surface functionalized biodegradable polymeric chains [123]. Nanocarriers were stimulated for enhanced intracellular uptake after the cleavage of the polymeric outer layer. An example of plasmin and MMP-responsive nanocapsules were demonstrated in literature [124]. Bovine serum albumin (BSA) and vascular endothelial growth factor (VEGF) were employed as model proteins. On reaction with MMPs nanocapsules demonstrated a

controlled release of proteins. Moreover, the protein release can be tuned by ratio of degradable to non-degradable linkers.

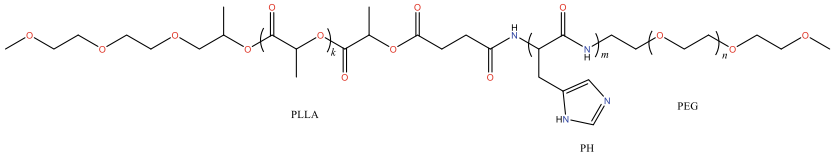
Another study reported the use of mesoporous silica scaffolds attached with polysaccharide derivatives facilitated site-specific transport of DOX after a lysosomal enzyme-mediated breakage of glycoside bonds and reduction of polysaccharide chain lengths [125]. Other than cancer treatments, enzyme responsive drug release can also be applied for the treatment of bacterial infections. Vancomycin releasing lipase sensitive nanogels were reported for stimuli-responsive antibiotic release to hinder the growth of Staphylococcus aureus [126].

Enzyme-responsive polymeric nanoparticles is an emerging field compared to other stimuli-responsive systems. In the future, enzyme responsive drug delivery by utilizing upregulated enzymes can be a promising way to cure diseases.

4 Dual and multistimuli-responsive PNPs

To further improve targeted drug delivery two or more simultaneously applied stimuli have been developed with equal or more importance than a single stimulus. In this segment, we shall discuss few examples of nanoassembilies that take advantage of multiple stimuli.

Magnetic responsivity can be coupled with pH sensitivity by combining super paramagnetic Fe_3O_4 nanoparticles with a pH-sensitive polymer. Such a multi-layered nanocarrier was reported by Cao and group by using super paramagnetic magnetite in the core and triblock copolymer as a triple-layered shell [127]. The outermost layer of the shell of the nanocarrier was prepared by a biocompatible copolymer. The middle and the inner layer were prepared by the polymer consisting of amino groups and hydrophobic molecules. Finally, the third layer of the polymer was rigidly bonded to the magnetite core. The dual drug, chlorambucil (anticancer drug) and indomethacin (anti-inflammatory drug) therapy was established by loading the drugs inside the amino group containing polymeric layer via ionic bonding and hydrophobic interactions. The entrapped drugs were released significantly under acidic pH due to the swelling of the middle layer owing to the protonation of amino groups.



Triblock copolymer synthesized by Liu et al. [127]

Another dual stimulus responsive case is the association of pH stimuli with redox responsiveness. Several pathological locations in the body have a natural co-occurrence of pH gradient and oxidative atmosphere. Hollow nanocapsules

consisting of cysteamine coupled chitosan and dextran sulphate was synthesized by the adsorption on beta-cyclodextrin (beta-CD) functionalized silica spheres followed by cross-linking thiols and removal of silica core [128]. Bovine serum albumin was encapsulated inside the nanocapsules and its release was activated by glutathione reduction followed by a sustainable release by pH gradient.

Other than dual responsive systems, triple responsive systems were also reported in the literature. An example of such a system is a novel targeted drug delivery vehicle with thermal/pH/magnetic responsive behavior [129]. This nanosystem was built with a thermosensitive polymer shell, dextran-g-poly (*N*-isopropylacrylamide-co-*N*, *N*-dimethylacrylamide), and a magnetite core. Chemodrug DOX was attached to the magnetite core through an acid-labile hydrazone linkage. The increase in temperature (LCST = 38 °C) stimulated the disruption of polymer and a lower pH (5.3) lead to the acid-labile hydrazine cleavage which eventually resulted in the release of DOX. Another example of a triple sensitive drug delivery system was also reported [130]. Polyurethane nanocapsules were prepared by interfacial poly addition of monomers and azo group containing diols. Nanocapsules were composed of an aqueous core and polymeric shell. These nanocapsules allowed a controlled release of the encapsulated dye sulforhodamine SR101 in the presence of triggers including temperature, UV light, or pH change.

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Chapter 4
Hybrid Nanoparticles in Image-Guided Drug Delivery

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Abstract The recent advancements in nanotechnology have opened immense opportunities for the management several clinical complications. The multidisciplinary approach of combining drug delivery and image-guided diagnostics led to the evolution of theranostic approaches which exhibit significant translational potential. However, these approaches are still in infantile or conceptual phase where increased research is being carried out globally. Also, very minimal findings are being practiced in clinical arena. The bridging of knowledge from basic biology, disease pathology and materials science to nanotechnology is inevitable for successful theranostic strategies and the field of nanoscience is advancing in multidisciplinary dimensions which would pave the ways for the development of novel theranostic strategies for disease management.

1 Introduction

The concept of personalized medicine largely relies on the understanding of how a person's sole genetic and molecular profile makes them prone to certain diseases and which in turn help to decide the type of medical treatment to be given to that patient. This approach led to a transition from the concept of general medicine (one medicine fits all) practice toward more personalized treatment. Also, this has been emerged as a unique approach for custom-made therapeutics based on interpersonal distinction in drug response. Moreover, these approaches have led to the foundation of an amazing platform called theranostics, which combines diagnosis and therapy based on specific targeted diagnostic tests, thus leading to a promising therapeutic

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paradigm involving diagnosis, drug delivery and monitoring of treatment response. Thus, theranostics approach can be considered as 'P4 medicine,' that is personalized, predictive, preventive and participatory.

The pioneer of the term theranostics is attributed to John Funkhouser and theranostics was defined as the integration of two modalities, that is, therapy and medical imaging. Initially, the concept was mainly focused on cancer therapy, but later it was expanded for other diseases like cardiovascular diseases, inflammatory diseases, autoimmune disorders like type 1 diabetes and neurological disorders. Theranostics covers diagnostic imaging, planning of therapy, classification of diseases, evaluating the stage of the disease and periodic follow-ups during therapy. Theranostics is highly cost-effective, very much efficient and specific medicine protocols involved in theranostics can serve as a guidance in preclinical as well as clinical studies. Theranostics also makes use of genetic information, obtained from human genome project [1], and this helps theranostics to offer precious tool for identifying and selecting patients with a peculiar molecular phenotype with a particular way of response toward particular treatment. This strategy has the potential to boost up drug efficacy by understanding which patients serve to benefit the most from that kind of treatment. This also can adorn the safety profile of a drug, minimizing the unwanted off-target effects to normal tissues, that is often found with various chemotherapies. Thus, theranostics can be considered as a process of diagnostic therapy for individual patients.

2 Principle

The general principle of theranostics deals with drugs and/or techniques that are uniquely combined simultaneously or sequentially to diagnose and treat medical conditions. Mostly, the elements of nanoscience have been employed to combine the diagnostic and therapeutic applications to single platform. Specific diagnostic assays are used as a tool for determining the genetic profile of the disease, subtype of the disease and also to assess the progression status of that disease in a patient. Considering the clinical status of the patient, dosage, route of administration, type of drugs, choice of treatment procedure and the response of the patients treatment form the major challenges. Theranostics exploits specific biological pathways to target specific biomolecule engaged in the pathogenesis/pathology for imaging and also to deliver a therapeutic dose of the drug of interest to the patient. For example, in the case of cancer, specific diagnostic test shows a particular molecular target on a tumor and which allows a therapy agent to specifically target that receptor on the tumor. This integration of multiple moieties into a single agent for imaging and therapeutic interventions offer promising paradigm for advancing treatments against various diseases including cancer. The theranostic brings diagnosis, drug delivery and treatment response monitoring under same platform.

The basic architecture of a theranostic system requires the following components:

1. **A targeting agent**: drives the theranostic system to a molecular target for a specific disease. In solid malignancies, Carbonic anhydrase IX (CA-IX) is regarded as an attractive diagnostic and therapeutic biomarker for targeting hypoxia. Various classes of antigen recognition molecules targeting CA-IX include small molecule inhibitors, antibody mimetics, peptides and monoclonal antibodies, and these have been radiolabeled for imaging and therapeutic applications. For example, a chimeric monoclonal antibody, cG250 has been labeled with radionuclides (124I, 111In, 89Zr, 131I, 90Y, and 177Lu) and which is the most intensively studied CA-IX radiopharmaceutical [2]. In breast cancer, HER-2 is the most commonly amplified oncogene and it plays major role in tumor induction, growth and progression, and it is regarded as a target for of chemotherapy in breast cancer patients [3]. In the case of inflammatory diseases, macrophages which are the important cellular component having phagocytic nature, abundance and disease homing properties and many imaging agents can be incorporated for the purpose of detection, quantification and in vivo localization of labeled macrophages [4]. EphA5 is receptor expressed on the surface human non-small lung tumor cells [5] and prostate-specific membrane antigen (PSMA) is over-expressed in the epithelium of prostate cancer making it as a suitable target for cancer imaging and therapy [6].
2. **An imaging agent**: enables visualization of the target. It involves use of methods that permit non-invasive visualization with the help of various modalities to identify anatomic, biochemical and functional pathology which hold much promise for disease diagnosis, disease progression monitoring, tracking therapeutic response and all these can intern enhance the knowledge about physiology and pathophysiology. Ideally, the molecular imaging component of a theranostic system would provide critical diagnostic information for the presence and anatomic location of cellular targets for which a therapeutic agent is intended. It makes use of the molecular interaction between the imaging probes and the particular targets at the area of interest [7]. Molecular imaging modalities include magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission-computed tomography (SPECT), ultrasound (US), computed tomography (CT) and optical imaging (quantum dots, Ramen and bioluminescence). Among various molecular imaging modalities, radionuclide imaging technique is the most sensitive one which could provide target-specific information as well as function, pathway activities and cell migration in the intact organism.

   For noninvasively identify estrogen receptor–positive lesions by PET, 18F-labeled estradiol is used [8]. 2-[F-18] fluoro-2-deoxy-D-glucose ([F-18] FDG) PET is ued to monitor the decline of tumor metabolism resulting from the therapeutic use of cytostatic drug Gleevec [9]. The fluorescein isothiocyanate (FITC)-labeled folic acid is used for fluorescence imaging-guided surgery of ovarian cancer [10]. Due to the thyroid selective nature of iodine, radio labeled iodine, ^{131}I is used for the clinical treatment of thyrotoxicosis (hyperthyroidism) and some types of thyroid cancer.

3. **A therapeutic drug**: for treatment at the target site. In the case of cancer treatment, therapeutic strategies like chemotherapy, gene therapy, hyperthermia and radiation combined with diagnostic tools or probes like contrasts agents involved in MRI, contrast agents based on nuclear imaging techniques like PET using ^{18}F and SPECT using iodine-123, iodine-131 or technetium-99 m; fluorescent markers like organic dyes and inorganic quantum dots [11]. Theranostic approaches using monoclonal antibodies (mAbs) are also used for cancer therapy and are particularly interesting because antibodies are designed against specific targets on the tumor cell membrane, immune cells and targets in the tumor microenvironment. Also, these drugs can be radiolabeled easily, and imaging techniques, such as PET and SPECT, provide information on the whole-body distribution of radiolabeled mAbs and antibody-related therapeutics. The best examples for mAbs are anti–human epidermal growth factor receptor 2 (HER2) antibody trastuzumab used for treating breast cancer [12] and the anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody ipilimumab used for treating melanoma [13]. Radioiodine can be used for relatively specific targeting of the thyroid gland for imaging and treatment purpose.
4. **A linker**: which serves to connect the two entities (theranostic agent and binding molecule on target cell). Linkers are used for the attachment of targeting moieties to theranostic agent (usually it is nanoparticle). Nanoparticles may be conjugated to small molecules, peptides and antibodies, using a variety of linkers. The most common chemistry behind linker depends on the reaction between amine-modified nanoparticles and sulfhydryl-containing biomolecules, and for this, cysteine residues are usually present or may be introduced into proteins and peptides.

In the case of cleavable linkers, cleavage of the conjugate can be mediated by either acidic environment or protease activity. Among the cleavable linkers, disulfide bonds are particularly attractive, because these bonds are stable in most blood pools and can be cleaved by cellular thiols, including thioredoxin (Trx) and glutathione (GSH), which are generally present in increased levels in tumors. When fluorophores are inked with disulfide bonds, shifts in the emission maxima or changes in emission intensity are clearly seen upon cleavage as the result of disturbances to internal charge transfer (ICT) processes, and this further allows easy and effective imaging [14]. Thioketal linker can be cleaved by reactive oxygen species [15]. Iodoacetate linkers provide stable linkages between nanoparticles and functional moieties (Fig. 1).

3 Hybrid Nanoparticles (HNPs)

The dramatic developments in the field of nanotechnology have resulted in the design and fabrication of novel materials for biomedical applications. The ability of therapeutic particles in nanodimension to freely circulate in the blood stream,

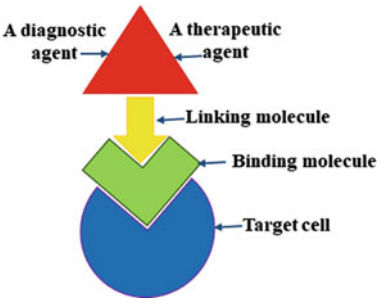

Fig. 1 Basic components in a theranostic system

circumvent blood-cell barriers, escape immune system, and effectiveness to targeted site encouraged to find immense opportunities in clinical and diagnostic medicine. Nanodrugs ensure safer delivery which prevents the drawbacks associated with systemic administration such as uncontrollable distribution, side effects, immune reactions, rapid decomposition and shorter half-life. The nanodelivery system usually exploits nucleic acids, proteins or vectors to the external surface of the particle which are specific toward therapeutic targets. In addition, the anchoring of fluorescent molecules or active complexes for magnetic resonance imaging (MRI) enables to perform optical monitoring.

There are mainly two classes of nanoparticles, organic and nonorganic. Organic ones are mainly lipid or polymeric in nature and possess distinct advantages such as better bioavailability and low toxicity, low immunologic reactivity, ability to be functionalized with ligands and the capacity to load agents with various solubility [16]. As far as nonorganic ones are concerned, they possess superior electric and thermal conductivity and provide a high capacity for encapsulation of chemical agents. Hybrid nanoparticles are obtained by assembling both organic and nonorganic nanoparticle into one single hybrid nanosystem. It allows visualization of affected region and at the same time helps to treat target site through the direct physical tissue destruction or delivering active compounds to the target site.

Coating of HNPs helps to avoid their recognition by immune system, resulting in longer circulation half-life and thereby helping them to reach the targeted sites [17] and also helps in stabilization of particles against aggregation caused by electric charge and other factors such as interfacial tension and attaching ligands with specific affinity toward receptors of targeted cells. Coating also makes it more focused in action [18, 19], like enhanced biodistribution, bioavailability and cell targeting. This designing and fabrication of hybrid nanosystems can be subclassified onto two, either incorporating active compounds on the surface of HNPs or encapsulation it inside the nanocarrier. Attaching of active agent, mainly by conjugating few groups: carboxyl (COOH), amino (NH_2), sulfhydryl (SH) and biotin on HNPs' surface, would be useful for imaging function or for the delivery of external stimuli-responsive systems. Encapsulation method offers a high loading capacity and is safer for delivery of highly reactive or toxic compounds that require a special protection and is achieved by entrapping into matrix (protein, polymer or

lipid) by electrostatic interaction or by direct incorporation during the polymerization, adsorption to mesoporous structure and p-p stacking (Table 1).

4 Synthesis, Characterization and Biological Responses of Hybrid Nanoparticles (HNPs)

The increasing demand for multifunctional HNPs has created a great interest among medical scientists and engineers to develop promising approaches for the design of novel and biologically compatible nanomaterials. A combination of modern nanoplatforms with high performance imaging as well as simultaneous therapeutics is an emerging application in this field. In the last decades, several 'bottom-up' and 'top-down' synthesis approaches have been adopted which led to the development of several clinically relevant HNPs. However, designing and formulation of HNPs with all desired characteristics is challenge and the designed HNPs lacks the positive attributes of individual monomer component in the hybrid. For attaining better characteristic features, the synthetic approach needs to be optimized. This section provides a brief overview of various approaches adopted for the synthesis of HNPs.

5 General Principles

Depending on application, HNPs are being synthesized either by chemical or by physical methods. Based on the parent chemicals used for the synthesis, the physiochemical properties of HNPs vary which in turn allow to acquire different structural, electronic, optical and magnetic properties as well as biological responses. The properties of such nanohybrids influenced by the structural arrangement and concentration of the individual nanocomponents [29]. Also, HNPs display distinct properties depending on the versatile manufacturing approaches employed. However, poor selectivity and low yield of the candidate hybrid during synthesis process is an everlasting challenge in nanoengineering. The engineered nanoparticles need to be tunable in size with a metal component (in general) and their surface plasmon resonance bands are desired to be in visible and near infrared [30].

6 Physical Methods

Physical methods for HNP synthesis mostly rely on the energy transfer of materials. Upon irradiation by ionizing or non-ionizing radiation, the metal surface triggers the reduction reactions leading to the nucleation of metallic particles in nanoscale.

Table 1 Different types of HNPs and their salient features

Sl No.	Types	Salient features
1	Liposomal hybrid NPs	• Fabricated from phospholipids • Closely resemble biological. membranes and they are biocompatible • Able to encapsulate hydrophilic substances in their core and to bind hydrophobic substances to the lipid bilayer [20] • For the delivery of vaccines, drugs, genetic material, radioisotopes and magnetic NPs
2	Micellar hybrid NPs	• Relatively small in size (5–50 nm); hence, they are able to efficiently penetrate cancer tissues with an even distribution • Capable of encapsulating hydrophobic or amphiphilic substances in its • When hydrophilic part of micelles are exposed to aqueous environment, it orients to the aqueous region, leading to stabilization of the colloidal assembly [21]
3	Polymeric hybrid NPs	• A class of NPs-containing polymers as organic component with structural functions • Inorganic component is used for specific functionality (catalytic activity, imaging, luminescence and magnetism) and also enhance mechanical and thermal properties of the polymer [22]
4	Viral hybrid NPs	• Provide a better selectivity and efficient transfection • For delivering nucleic acids for therapeutic purposes • Different types of viruses have been utilized as NPs (Tobacco Mosaic Virus, Potato Virus X), spherical, Cowpea Chlorotic Mottle Virus), and Cowpea Mosaic Virus) [23] • Combination of viral NPs with polymers enhances interfacial activity and reduces degradation rate • Polymers can be attached to viral NPs through covalent and noncovalent interactions
5	Silica-based hybrid NPs	• Having low toxicity, nanoscale dimensions, proven biocompatibility, high surface area, capacity of encapsulation and combination with various materials and excellent optical characteristics • Used for drug delivery, gene transfection, PDT [24], cell imaging, biosensor systems and enzyme immobilization and delivery, fluorescent imaging and MRI [25]
6	Gold-based hybrid NPs	• They are good contrast agents for imaging applications such as optical coherence tomography computed tomography, two-photon-induced photoluminescence and photoacoustic imaging (due to their ability to scatter light) • Preferential accumulation in their biological targets by functionalising with diverse molecules • Widely used for cancer diagnostics and therapy [26] • Different gold-based hybrid NPs include Gold/polymer hybrid NPs, Gold/Fe NPs and Gold/SiO_2 NPs

(continued)

Table 1 (continued)

Sl No.	Types	Salient features
7	Radioactive hybrid NPs	• Utilized for labeling for effective tracking and diagnostics purposes • Used for therapeutic applications to eliminate cancer cells by means of radioactive particles that emit α or β radiation • Also applicable for imaging and diagnostics of disorders like ischemia, atherosclerosis and intraoperative imaging [27, 28]
8	Carbon nanotube-based hybrid NPs	• Used for photoacoustic, PT imaging and cancer treatment

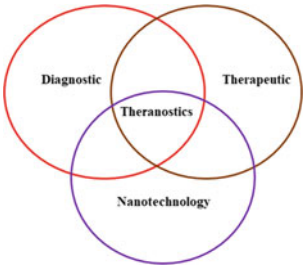

Fig. 2 An overview of theranostic system

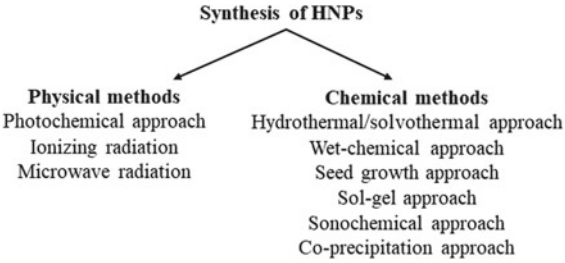

Fig. 3 General methods of HNP synthesis

Principles of photochemistry and crosslinking using ionizing and microwave radiation are the common physical methods employed for HNP synthesis.

7 Photochemical Approach

The photochemical method employs light intensity to control particle size and thus provides a spatiotemporal control of nanoparticle generation. The HNPs generated through this method have been found to be stable for months even without any stabilizing ligands. To cite, McGilvray et al.; photochemically synthesized $\sim$4 nm

diameter monodispersed AgNPs associated with Ferritin [31]. The resulted Ftn-AgNP exhibited superior anti-microbial activity and iron-sequestering abilities which is effective to prevent the growth of human pathogens. Also, aqueous gold nanoparticles are being synthesized using Irgacure-2959 (1-[4-(2-hydroxyethoxy) phenyl]s-2-hydroxy-2-methyl1-propane-1-one). The excitation of I-2959 at 350 nm yields ketyl radicals via Norrish-type-I R-cleavage which act as reducing agents for the reduction of Au^{3+} to Au^{0} forming the AuNPs. This method revealed a simple approach for the synthesis of unprotected aqueous nanoparticles by the reduction of HAuCl4 by controlled illumination [31]. The resulted HNPs exhibited high spatial and temporal resolution. The advantage of this method is the tunability of particle size and shape by choosing the appropriate wavelength of light used for driving the photochemical growth. Such approaches and the resultant HNPs are ideal for light assisted imaging or biosensing applications, however warrants further investigations especially in clinical arena.

8 Ionizing Radiation

The synthesis of HNP using ionizing radiations has been considered to be beneficial over the conventional methods as it generates fully reduced and highly pure nanoparticles which are usually free from by-products or chemical reducing agents [32]. Li et al. [33] synthesized silver and gold nanoparticles from aqueous solution of $AgNO_3$ and $HAuCl_4$ in the presence of 2-propanol and PVP by gamma irradiation method. Similarly, PVP-capped Cu_2CuAlO_2-Al_2O_3 nanoparticles were synthesized by gamma radiation in aqueous solution using varied doses of radiation [34]. The resulting HNPs exhibited superior physiochemical properties suggesting that ionization method exhibits control over particle size and structure. Since this method drives competition between nucleation and growth process, the particle size is influenced by the solvents and stabilizer, the precursor to stabilizer ratio, pH and absorbed dose of radiation which in turn influence the physical and optical properties of the final nanoproducts.

9 Microwave Radiation

Microwave thermally assisted synthesis is comparable to the conventional heating method of HNPs synthesis which requires a reaction temperature of $\sim$100 °C. Horikozhi et al. [35] utilized 2.45-GHz microwave (MW) radiation for the synthesis of silver nanoparticles in aqueous media by reduction of the diamine silver (I) complex, $[Ag(NH_3)_2]^+$, with carboxymethyl cellulose (CMC) in flow reactor system coupled to 1200 W microwave radiation. The silver nanoparticles so formed exhibited a size distribution of 0.7–2.8 nm. Saha et al. [36] synthesized silver nanoparticles in combination with Ocimum leaf extract by microwave irradiation

method in the size range of 5–50 nm. Major advantage of this approach is the short time duration of the whole process when compared to other conventional physical, chemical and biological methods which warrants applications in large-scale synthesis.

10 Chemical Synthesis Methods

The ideal methodology for the preparation of HNPs is bottom-up chemical synthesis, which uses a reducing agent to bind one metal over another metal surface. However, success of this process depends on the choice of reducing agent, purity of components and the methodology of synthesis [37]. The common methods of chemical synthesis are outlined in this section.

11 Hydrothermal/Solvothermal Approach

The solvothermal approach generally applies when the desired particles require more crystalline and lower dissolution characters than those obtained via wet synthesis method. This method proceeds with or without ligands, stabilizers or surfactants. For example, the metal oxide nanoparticles such as Zirconia particles [38], Boehmite (γ-AlO(OH)) [39], $BaTiO_3$ nanoparticles [40] and Yttria stabilized zirconia nanoparticles [41] have been effectively synthesized, by the hydrothermal process. Also, the synthesis of organic–inorganic hybrid materials by exploiting the supercritical hydrothermal properties has been achieved. To cite, by introducing organic materials, modified biomaterials having different amino acid sequences can be engineered which opens immense clinical applications. In addition, alterations in the particle morphology and/or crystal structure can be achieved by changing organic modifiers [42]. By fabricating the nanomaterials using organic solvents or mixed organic-water solvent or non-aqueous systems, a variety of materials such as metals, semiconductors, ceramics and polymers can be scaled up by hydrothermal process.

12 Wet-Chemical Approach

Several bottom-up methods have been routinely used for wet-chemical synthesis which has been considered to be the most promising route for synthesizing high-yield and superior quantity/quality of non-layer structured ultrathin two-dimensional nanomaterials [43]. However, to produce single layered nanomaterials from their corresponding layered bulk crystals, mechanical exfoliation technique is being used. Li and co-workers adopted mechanical exfoliation

technique for the production of mechanically exfoliated single- and multi-layered MoS_2 and WSe_2 nanosheets [44]. Such 2D crystals obtained by this approach exhibited superior quality with larger lateral size. However, low throughput with the native form of the 2D structure limits their biomedical applications. As an alternative approach, liquid exfoliation by direct sonication of layered bulk crystals in solvents or surfactant/polymer solutions has been found as promising approach to produce ultrathin 2D nanomaterials. For example, high-yield production of graphene by liquid-phase exfoliation of graphite [45] and large-scale fabrication of boron nitride nanosheets [44] have been developed with this approach. Considering the efficacy of this method, the non-layered ultrathin 2D HNPs consisting of metals, metal chalcogenides and metal oxides, can be synthesized using wet–chemical method [43]. However, the wet-chemical synthesis of non-layer-structured ultrathin 2D nanomaterials is still in its infant stage. On the one hand, further innovations are warranted in this area with diverse combinations of materials for biomedical applications.

13 Seed-Growth Approach

Seeded-growth has been considered to be an efficient process that replaces the traditional 'nucleation and growth' mechanism for the synthesis of metallic nanoparticles [46]. Seed-growth mechanism generally includes three distinct stages: (1) nucleation; (2) evolution of nuclei into seeds; (3) growth of seeds into nanocrystal of the final microspheres, which is polycrystalline in nature. Ziegler et al. [47] reported a simple seed-growth approach to obtain gold nanoparticles possessing wider dimension range. With this method, by using ascorbic acid as a reducing agent and sodium citrate as stabilizer, they produced particles with uniform spherical shape and narrow distribution of size. Also, Jiang et al. engineered a silver nanoshell on a silica sphere using silver nitrate ($AgNO_3$) and sodium borohydride ($NaBH_4$) with a reducing agent sodium citrate ($Na_3C_6H_5O_7$) [48]. In addition, unique opportunities are available to extrapolate seed-growth chemical method with several techniques such as LASER to engineer larger microspheres [49]. Recently, a laser ablation technique based on 'seeded-growth' mechanism has been reported [49] in which a novel patch-joint football-like AgGe microspheres having a diameter in the range of 1–7 μm with controllable properties were generated. The combination of conventional seed-growth mechanisms with some other versatile techniques inspires to explore novel opportunities such as magnetic resonance imaging.

14 Sol-Gel Approach

The sol–gel process has been considered to be a wet-chemical technique which includes hydrolysis, polycondensation, gelation, aging, drying, densification, and crystallization. The basic chemistry of the sol-gel process relies on hydrolysis and polycondensation reactions [50]. Ueno et al. [51] synthesized Silver (Ag) nanoparticle-loaded strontium titanate ($SrTiO_3$) using sol-gel-hydrothermal method. The resultant Ag-$SrTiO_3$ HNPs acquired a few tens of nanometers and were observed to be distributed without severe agglomeration. A photochromic hybrid spiro-pyran–silica nanoparticles was synthesized via a two-step sol–gel procedure using tetraethoxysilane (TEOS) and methyltriethoxysilane (MTEOS) as silica precursors which exhibited excellent chemical properties and porosity [52]. By sol-gel-hydrothermal method, materials with superior crystalline properties were obtained at low temperature which had the advantage of minimal oxidization and absence of the grain growth of metal particles. These qualities upgrade the sol-gel-hydrothermal method to be an ideal approach for the synthesis of nanoscaled HNPs.

15 Sonochemical Approach

Sonochemical method has been considered to be a convenient one-pot process which has better efficacy than the conventional methods. Ultrasound has been utilized to synthesize metal, metal oxide nanoparticles, and hybrids with desired properties [53]. Teo et al. engineered Janus particles by polymerizing styrene, inorganic tetraethoxysilane and silane coupling agent (3-aminopropyl) trimethoxysilane [54] using sonochemical process. Okistu et al. [55] demonstrated the sonochemical reduction of Au(III) to synthesize Au nanoparticles in aqueous solutions containing 1-propanol exploiting ultrasound frequency. The size and distribution of engineered HNPs were correlated with the rate of Au(III) reduction, which in turn was influenced by the applied frequency [55]. In a similar approach, Cui et al. [56] synthesized graphene oxide wrapped gold nanoparticles (Au NPs) using one-pot sonochemical synthesis and self-assembly, using ethylene glycol as the reducing agent. In general, the ultrasound assisted process is inherently safer single-step process of synthesizing hybrid nanoparticles.

16 Co-precipitation Approach

Co-precipitation is another simple and efficient method for the design of HNPs with better stoichiometric control and higher purity. The method produces particles with wider size distribution in which the average size ranges from submicron to tens of

microns [57]. The physical adsorption of the particles without any chemical interaction is an added advantage for this method which can be confirmed by IR and XRPD analysis [58]. The co-precipitation method was used by Yu et al. to synthesize Fe_3O_4 NPs, in which ferric and ferrous irons (molar ratio 2:1) were coprecipitated to Fe_3O_4 in alkaline solutions at room temperature following hydrothermal conditions. The synthesized HNPs were hydrophilic, which could be easily dispersed in $AgNO_3$ solutions. Rajaeiyan et al. [59] synthesized nanostructured α-alumina powders for catalytic and sensing applications by a combination approach of sol-gel and co-precipitation method which exhibited larger surface area (206.2 m^2/g) than that obtained from sol-gel method (30.72 m^2/g).

The advancements in nanotechnology and medicine have presented several novel synthetic approaches for the design and fabrications for nanobiomaterials for various biomedical applications. However, the theranostic approach by the combination of nanotherapeutics with imaging is an emerging dimension in the field of medicine. The conventional synthetic approaches have introduced ample nanoformulations for the management of several health complications. The dilemma to choose the best approach for syntheses still exists, however largely depends on the outcome properties of HNPs. Appropriate modifications for the synthesis approaches aiming to incorporate ideal imaging probes for theranostic applications are the need of the hour. The following sections throw light to such applications in regard with common health issues.

17 Toxicity, Bioavailability and Mode of Action of HNPs

Several studies have been performed to explore the mode of action of HNPs on in vitro, ex vivo, in silico and in vivo systems. Anti-microbial activity, ROS-induced cytotoxicity, genotoxicity and cell growth promotion are the extensively studied biological properties of HNPs based on their size, shape, dose and concentration. However, a complete knowledge regarding the mechanism of action of nanoparticles is largely unknown [60]. Although HNPs have multimode character, chemical and thermal stabilities of the surface ligands are shown to play an important role in the performance of the HNPs. In general, HNPs act in a living system via three routes, (a) direct uptake (b) indirect activity of HNPs through the production of reactive oxygen species (ROS) and (c) penetration/diffusion through membrane barriers [61]. Metal HNPs exhibited bactericidal and bacteriostatic activity mediated through production of reactive oxygen species, cation release, inactivation of biomolecule, ATP depletion and membrane interaction. Moreover, these NPs are found to have an effect transcriptomics and proteomics of genes [62]. To cite, the administration of silver nanoparticles was to mouse model with burn injury revealed reduced levels of pro-inflammatory cytokines [63]. Shin et al. pointed out the anti-inflammatory potential of hybrid silver nanoparticles was through the downregulation of interferon gamma and tumor necrosis factor alpha [64]. Also, various studies have shown the ability of AgNPs to adhere and penetrate

into *E. coli* cells at sizes much smaller than the original particles, which is mediated via the formation of pits in membrane [65, 66]. In addition, the HNPs act by creating zeta potential electrostatic forces for penetration inside live cells [61]. These qualities made the small sized HNPs to have higher efficiency for anti-microbial properties.

In general, the route of administration of HNPs is an inevitable part in nanomaterial research to understand their toxicity to the biological system. NPs can enter the biological system in an active way (unintentionally) or in a passive way (artificially/intentionally) [67, 68]. Inhalation of NPs naturally in the form of aerosol powders or artificially by instillation into the respiratory tract is considered to be one approach. Warheit et al. [69] tested the toxicity of NPs through oral, intratracheal, oropharyngeal and intrapharyngeal routes in lungs of rats and concluded that the intratracheal instillation as a surrogate route for inhalation. HNPs can also enter the gastrointestinal tract via water, food, cosmetics, drugs, drug delivery devices, the swallowing of inhaled particles or intentional hand to mouth transfer of particles [70, 71]. However, the ingestion can bypass the respiratory tract clearance. Also, the transdermal approach has been found to be plausible as the skin represents a channel for active entry of finer or even large particles [72]. However, alterations in the skin barrier such as wounds, scrapes and/or dermatitis conditions affect the uptake of nanoparticle. On considering the invasive methods, intravenous route is effective in determining toxicology evaluation in animal models. For instance, the intravenously injected gold HNPs were observed to induce oxidative stress in the rat liver cells [73]. Liposome mediated delivery is another innovative approach in the field of nanomaterials [74], which possess advantages such as long circulation, high drug loading efficiency, high stability and biocompatibility.

The advancements in nano-era is focusing to optimize the synthetic approach and reaction conditions to come up with nanoparticles with superior applications in biomedical field. The systemic administration of nanoparticles usually provokes inflammatory response due to the interactions of blood components with NPs. Science highlights comment that NPs with protein 'Passports' can evade immune system by exploiting inherent nature of the immune system to present a specific 'passport' on the cells in the form a protein signature attached on its surface that function to escape the immune system. Dalmoro et al. reported that mucosal damage of NPs has been avoided by using hybrid nanoscale systems composed of liposomes and biodegradable natural polymer [75]. Also, peptide coating derived from the CD47 protein, onto the surface of drug-carrying nanoparticles to escape the macrophages [76]. While considering immune system, there are unique set of challenges such as nonspecific phagocytosis by cells, off-target biodistribution, transport barrier, nonspecific immune-activation, and poor control over intracellular localization need to be addressed [77]. To overcome the immune system, features of fabricated HNPs such as size, shape, charge, ligand density and elasticity to its vascular transport, biodistribution, cellular internalization and immunogenicity need to be considered.

18 Applications of HNPs

The present scenario of nanomedicine emphasizes on tharanostic approaches because of its multimode application. In this regard, HNPs-based drug transport across the biological system seems to be exploited for the theranostic approach. Incorporating both the therapeutic and diagnostic entities in a single nanomolecule enables image-guided interventions and direct monitoring of drug distribution, metabolism and biologic effects in human body. Generally, the imaging agents are considered as functionally versatile and can be translated for clinical utility in most disease conditions. HNPs provide a versatile platform to synthesize the imaging agents with multimodal and multifunctional properties. HNPs facilitate high-sensitivity and high-resolution properties and have the selective property to bind the target tissue for molecular imaging and therapeutic delivery. However, the safety concerns related with HNPs, pharmacokinetic limitations and complexity of human body limit the success achieved in preclinical studies to be translated into clinical arena.

The commonly employed theranostic approaches adopted in various disease conditions are discussed below:

1. **Cardiovascular disease**

Cardiovascular diseases are one of the most prominent causes of mortality worldwide. Since the underlying pathological conditions such as the alterations in endothelia and immune responses remain unpredicted over time, creating the early diagnosis difficult [78]. The routinely used imaging techniques in cardiology mainly detect the changes in the morphology of the affected tissue. Presently, nanotechnology-based theranostic agents have been employed to perform both the diagnostic and therapeutic interventions simultaneously. To cite, Winter et al. [79] reported for the first time that HNPs such as $\alpha_v\beta_3$-integrin targeted paramagnetic nanoparticles loaded with anti-angiogenesis drug fumagillin and administered to hyperlipidemic rabbits for four weeks. The reference group received atorvastatin along with $\alpha_v\beta_3$ targeted fumagillin nanoparticles. Cardiac magnetic resonance (CMR) of angiogenesis demonstrated acute antiangiogenic effects of $\alpha_v\beta_3$-targeted fumagillin nanoparticles combined with atorvastatin, which represents a noteworthy approach to evaluate antiangiogenic treatment and plaque stability. This is one of the successful reports on the prolonged anti-angiogenesis, therapy regimen based on theranostic $\alpha_v\beta_3$-targeted HNPs. In another study, McCarthy et al. [80] developed a novel theranostic strategy to target macrophages. Dextran-coated iron oxide nanoparticles were loaded with near-infrared fluorophores and phototoxic agents to specifically target the activated macrophages to induce apoptosis. In an ApoE KO mouse model, co-localized nanoparticles were imaged by intravital fluorescence microscopy. The adopted HNPs in the study showed massive death of targeted macrophage with least toxicity to the skin.

The widely accepted nanocarrier used as 'theranostic' agents for atherosclerosis are liposomes, owing to its versatile surface characteristics. Hua et al. [81]

developed a perfluoropropane-containing liposomes to target platelets via a peptide (RGDS) derived from the α-chain of fibrinogen. In the liver of healthy rabbits, the thrombolytic drug was visualized using ultrasound imaging. The authors developed a modified ultrasound microbubble carrying thrombolytics which simultaneously targeted the thrombus and locally released encapsulated drug and this approach was efficient in lower dose range. Similarly, Nandwana et al. [82] synthesized HDL-magnetic nanostructures (HDL-MNS) by combining phospholipids and apolipoprotein A1 to the surface of MNS to mimic the properties of natural HDL particles. HDL-MNS exhibited improved cholesterol efflux from macrophages when comparing with natural HDL. The study demonstrated a diagnostic strategy via non-invasive MRI for diagnosing atherosclerotic plaque and an effective cholesterol efflux agent to address the complications of the disease.

Vascular endothelium acts as a barrier and results in off targeted issues or delivery. The transport of HNPs, organ specific delivery, interaction with the endothelial wall and exposure with the inmmune cells may affect the efficacy of the theranaustic agent.

2. **Disorders of musculoskeletal system**

The musculoskeletal complications are increasing, and the main reasons have been identified to be tissue degeneration and inflammation. Although, it well known that bone tissue has inherent repair and regeneration capacity, extensive malformation to bone due to trauma, infection or tumor needs external interventions. This scenario necessitates the need for biologically compromising nanomaterials for transplantation and/or to ameliorate the pathological condition [83]. Theranostic HNPs offer a promising alternative and has growing demand. Kalidoss et al. [84] developed a multimodal calcium phosphates (CaP) drug delivery system with intrinsic antibacterial activity and enhanced contrast for CT/MR imaging modality. Calcium-deficient hydroxyapatite (CDHA) showed an inherent antibacterial activity due to Ag^+ substitution and also showed predominantly burst release of tetracycline antibiotic. CDHA nanocarriers were biocombatible and showed simultaneous T1 and T2 MR contrast. The novel antibiotic loaded CDHA HNPs with antibacterial activity and multimodal image contrast potential are highly suitable for clinical orthopedic applications. Generally, the musculoskeletal system is susceptible to injury due to direct contusion and ligament rupture arising from immoderate exercise. Kim et al. [85] investigated the potential of H_2O_2-triggered bubble-generating PVAX nanoparticles as nanotheranostic agents for musculoskeletal injuries. Generated PVAX nanoparticles administrated through intramuscular and peri-tendinous injection into the lesions of mechanical injury enhanced the ultrasonographic contrast and exhibited superior anti-inflammatory and anti-apoptotic effects. Interestingly, the engineered PVAX nanoparticles are capable of detecting the contusion injury in a H_2O_2-triggered manner, which is their unique feature in ultrasonography. Apart from the extensive research in this field, the extent of muscular injury, effectiveness of the theranostic agent and its compatibility within the biological system are raising concerns which warrants further standardizations.

3. **Cancer**

The heterogenous nature of cancer and anti-cancer drug resistance often limits the potency of cancer therapy. Conventionally, the oligonucleotides carrying nanoparticles are targeted into tumor sites either actively or passively for by protecting the oligos from cleavage by nucleases at the vicinity of target site. Generally, quantum dots, iron oxide nanoparticles and gold nanoparticles tagged with contrast agents such as fluorochromes, radioisotopes and optical and magnetic agents to facilitate the early diagnosis of the tumor and subsequent therapy [86]. However, the quantum dots (QDs)s are mostly designed for therapeutic purposes and less for in vitro imaging. Similarly, Kohler et al. [87] developed a methotrexate (MTX)-modified superparamagnetic iron oxide nanoparticles (SPIONs) for MRI imaging and drug delivery purposes. Also, the modified IONPs in combination with doxorubicin (DOX), an anthracyclene, were used to target lung carcinoma [88]. Ling et al. [89] reported another modified HNP using docetaxel and SPION-loaded nanoparticles for ultrasensitive MRI and prostate cancer therapy.

Multi-model nanoparticles consisting of IONPs provide multiple diagnostic opportunities in the present scenario. Savla et al. [90, 91] developed a pH-responsive QD-mucin 1 aptamer-DOX (QD-MUC1-DOX) conjugate having theranostic to be used as a chemotherapeutic agent for ovarian cancer assisted with imaging. Derfus et al. [92] prepared PEGylated QD core conjugated with siRNA and homing peptides (F3) to the functional groups on the surface of the particle for diagnostic imaging and treatment of metastatic cancer. Melancon et al. [93] reported a novel theranostic strategy using superparamagnetic gold-coated iron oxide nanoshells for targeting head and neck cancer. They developed an efficient drug vector for photo dynamic therapy (PDT) by engineering PEGylated AuNP conjugates with a reversible PDT drug adsorption. Gibson et al. [94] succeeded in developing paclitaxel-functionalized gold nanoparticles (AuNPs) covalently functionalized with paclitaxel. Prabaharan et al. [95] developed doxorubicin (DOX) loaded gold nanoparticle cores for tumor targeting and drug delivery. The AuNPs stabilized with a monolayer of folate-conjugated poly(L-aspartate-doxorubicin)-*b*-poly(ethylene glycol) copolymer (Au-P(LA-DOX)-*b*-PEG-OH/FA) for functioning as tumor-targeted drug delivery carrier by conjugating DOX onto the hydrophobic inner shell by acid-cleavable hydrazone linkage. More recently, RNA interference (RNAi) based molecules that can regulate gene expression are coupled with metal based NPs are used as theranostics for cancer therapy [96]. Synthetically produced RNA oligomers can be targeted to silence a specific oncogene. NPs pairing with RNAi will provide more scope in chemotherapy, photothermal therapy, immunotherapy and radiotherapy.

4. **Wound healing**

Wound healing involves a series of biochemical cascades which in turn largely depends on the immunity, physiological and pathological condition. However, the wounds arising from trauma or burns accounts a major health issue that leads to

morbidity and mortality. For general wound management, a handful of nanomaterials, nanoscaffolds, nanofibers and biomaterials have been used for especially for the topical drug delivery for wound healing. However, theranostic approaches are limited in this area. In addition, the recent therapeutic approaches mainly rely on pH sensors to diagnose early detection of poor healing in a wound. Zhang et al. further extrapolated the idea of pH sensing to a biocompatible pH sensing hydrogel membrane to provide an early diagnostic warning system for early response to poor healing. The hydrogel was intended for the therapeutic delivery of the immunomodulatory viral protein, Serp-1. The limited availability of published reports reveals the infancy of theranostic approaches in wound management, however warrants further research.

5. **Respiratory diseases**

Respiratory disorders commonly affect all age groups globally and are usually treated with corticosteroids. The long-term treatment with the drug and increased prevalence of side effects leads to noncompliance and poor therapeutic outcomes [97]. The past decades have witnessed the evolution of a variety of nanotechnology-based platforms for diagnosis and treatment of lung disease. However, none of these strategies succeeded to establish a promising clinical solution for both acute and chronic respiratory diseases.

Interestingly, the theranostic nanoparticles incorporating semiconductor quantum dots (QDs) have been emerging as a promising strategy in respiratory medicine [98]. QDs, possessing a range of emission spectra (400–2000 nm) in visible and near-IR, have been co-encapsulated with therapeutics in the form of polymeric micellar, or liposomal nanoparticles exhibit greater photostability and function as contrast agents for imaging the respiratory system [99–101]. Kumar et al. [102] encapsulated CdSe QDs and doxorubicin in polymer-lipid hybrid micelles and Bagalkot et al. [103] RNA aptamers, QDs, and doxorubicin for targeting lung cancer. These theranostic HNPs are programed to detect cancer at the single-cell level while simultaneously releasing a therapeutic agent to the site owing to the photothermal ablation potential, the AuNPs are the excellent choice for

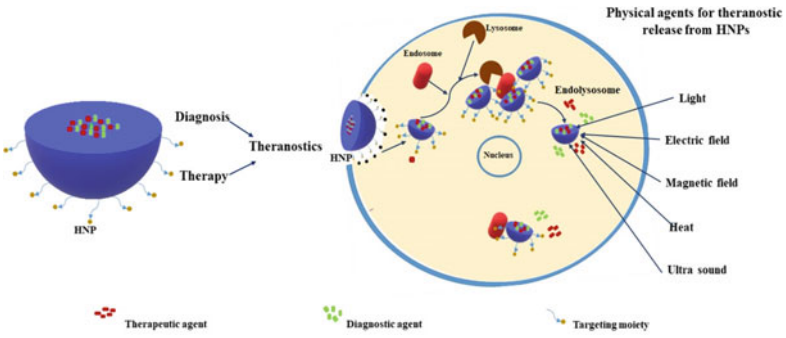

Fig. 4 Mechanism of theranostic HNPs in cancer therapy

photothermally enhanced drug and gene delivery with simultaneous imaging [104]. Yuling Xiao et al. [105] synthesized a multifunctional gold nanorod (GNR)-based platform for targeted DOX delivery and PET imaging of tumors. Those HNPs exhibit pH-sensitive drug release behavior, which maximizes the efficiency of tumor-targeted drug delivery. These theranostic HNPs require the capabilities to overcome biological hurdles due to the complexity of the airway, lung anatomy and physiology [106, 107]. Biological barriers such as nonspecific delivery and poor biodistribution of drugs or contrast agents, drug resistance, non-specificity of treatment and/or monitoring and toxicity issues offer curb for extending the efficacy of these theranostics to clinical arena. The present scenario urges to develop superior theranostics to improve the treatment of chronic respiratory diseases.

6. **Gastrointestinal disorders**

The gastrointestinal tract (GIT) allows easy access for therapeutic and imaging strategies including endoscopy. However, theranostic approaches in GI disturbances or cancer are very limited. Stewart et al. [108] developed a therapeutic capsule endoscopy (TCE) for targeting gastric cancer which possesses immense clinical application. Gastroenteropancreatic neuroendocrine (GEP-NET) tumors are neoplasms with variable clinical expressions [109] and somatostatin analogs labeled with therapeutic beta emitters, such as lutetium-177 or yttrium-90 for radiotherapy have been a better option for patients with unresectable and metastasized NETs. Even though many new targets are being identified in gastrointestinal disorders, the clinical evidences are limited suggesting further research on this avenue.

7. **Renal disorders**

Renal disorders are mainly due to diabetes, high blood pressure or inflammatory conditions which can lead to end-stage renal disease (ESRD), if left untreated [110]. Clinically approved HNP strategies are unavailable for ESRD, however has increasing demand for theranostic approaches [111]. Haick et al. [112] reported a non-invasive ESRD detection in rat model based on a carbon nanotube-based sensor and breath sample analysis. AuNPs coated sensors were designed to extract the volatile organic compounds from breath samples which were further assessed with gas chromatography to distinguish between early and end-stage renal disorders. Interestingly, the renal therapy via specifically targeting of drugs or siRNAs to proximal tubule epithelial cells (PTECs) have been achieved by Gao et al. [110] by siRNA mediated knocking down of target-specific genes in PTECs for knockdown studies and the long lastimg accumulation of siRNA in PTECs bring out the potential of the therapeutical approach. Loss of kidney function due to accumulation of toxins in the blood will create a diagnostic hindrance in renal therapy. No deep routed studies are not yet clinically proved as a theranostic approach in renal therapy.

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Chapter 5
Ceramic-Based Hybrid Nanoparticles in Drug Delivery

Narendra Pal Singh Chauhan

Abstract CaP matrices and scaffolds are recorded to behave as supplies for bone tissue technology development, variables and medicines. Calcium carbonate ($CaCO_3$) nanoparticles demonstrate distinctive benefits of distinct inorganic drug carriers as an optimal biocompatibility and as a delivery system for charging various drug. $CaCO_3$ nanoparticles show a potential dual use in bone substitution and drug carriers for bone disease and defects. Because of the lack of drug molecule specification and solubility, patients have to take high doses of the drugs in order to achieve the desired treatment effects. There are different drug carriers in pharmaceuticals that can supply medicinal drugs at the destination point of the brain to fix these issues. Mesoporous silica nanomaterials are discussed in the next generation of cancer diagnosis and drug and therapeutic gene delivery. Biomaterials based on TiO_2 are defined as related to the development of brain cells, intravascular stents, drug transport devices and biosensor devices. Zirconium dioxide and boron carbide nanoparticles have found an important role for drug and gene delivery in medicine. In this Chapter, different kinds of hybrid ceramic nanoparticles for drug delivery applications are discussed in detail.

Keywords Nanoparticle · Hybrid · Hydroxyapatite · Calcium carbonate · Zirconia · Silica · Drug delivery

1 Introduction

Nanomaterials have distinctive physicochemical characteristics that differ from bulk products of the same structure, such as tiny volume, big ground region to volume percentage, and elevated reactivity. Nanometer-sized materials may have distinctive and beneficial characteristics that are very helpful for various medical purposes, including stomatology, pharmacy, and tissue engineering for implantology. The

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implementation of nanotechnology to medicine, recognized as nanomedicine, issues the use of exactly engineered materials at this length scale to create new therapy and diagnostic modes. Polymer and ceramic nanoparticles have widely been explored as pharmaceutical and medical supplies as a consequence of their regulated and long-term release characteristics, the volume and biocompatibility of subcellular tissues and cells as drug delivery mechanisms. As a matter of fact, they are promising. These characteristics may be used to solve certain constraints of traditional diagnosis and therapy drugs. Currently, raw ceramic materials are being developed for biomedical applications. The use of different synthetic techniques to enhance their physical–chemical characteristics in biological system to decrease their cytotoxicity has been developed in nanoscale ceramics such as hydroxyapatite (HA), calcium chloride ($CaCO_3$), zirconia (ZrO_2), silica (SiO_2) and titanium dioxide (TiO_2). However, the patient (in a multitude of tissues including immune systems) has discovered an adverse reaction to the use of recent ceramic materials. Controlled release of drugs for use in bio-medicine is one of the most utilized fields for ceramic nanoparticles. The dose and quantity are crucial in this field. In addition, the prospective instrument to control the distribution of drugs is some characteristics that give nanoparticles great strength, a large volume of charge, easy inclusion into hydrophobic and hydrophilic structures as well as several modes of administration (injection, inhalation, etc.) [1].

The most frequently used NPs for the construction of nanocarriers are TiO_2 (ceramic nanoparticles (CNs), which develop as drug distribution vehicles, primarily for their tiny volume (<50 nm) and physical-chemical characteristics and include particulate matter produced from calcium phosphate, zirconia. These NPs are not exposed to pH swelling or porosity modifications. CNs can also prevent denaturation caused by pH fluctuations and temperatures in various biomacromolecules, like enzymes, carbohydrates, proteins [2]. These NPs may show magnetism, optical and dielectric characteristics and cannot readily degrade, rendering them beneficial for bone applications [3]. Ceramics with suitable three-dimensional geometry can connect and focus bone morphogenesis proteins into the environment; these can be osteoinductive (functional of osteogenesis) and can be efficient transports of bioactive peptide or bone cell components [4].

In this chapter, I addressed different types of ceramic for possible applications in drug delivery, cancer and also replacement of bone. As bone replacement products, various ceramic substances are provided in the industry. It includes tricalcium phosphate (TCP) or Hydroxyapatite (HA) monophase crystals, biphasic ceramic calcium phosphate, and multiphasic artificial calcium carbon concrete in bioglass.

2 Calcium Phosphate-Based Hybrid Ceramic Nanoparticles

Particulates of CaP, cements and scaffolds have been of considerable concern as carriers for the shipment of medicines. CaP systems with varying stoichiometry, features and dissolve characteristics that render them cellularly appropriate,

including both hydroxyapatite and tricalcium phosphates. They add to their controlled release features by their chemical bone resemblance and consequently biocompatibility, and also by different charge density properties, make them suitable for both drug and growth factor delivery. The nanoparticle magnitude, anatomy, porosity and kinetics of chemical discharge are the most important in particular research fields. Local drug delivery in the treatment of musculoskeletal disorder can deal more efficiently with certain critical problems than structural service. For the treatment of musculoskeletal diseases, CaPs are used as coverings of edible implants, CaP cements, and customized scaffolds.

Bose and Tarafder have highlighted some of the current drug and growth factor delivery approaches and critical issues using CaP particles, coatings, cements, and scaffolds toward orthopedic and dental applications [5]. Characteristics of the carrier, drug/carrier interactions, experimental conditions of drug loading and evaluation of drug delivery are well explained by Parent and coworkers [6].

In the last two decades, the investigation has been carried out of bioactive inorganic materials including bioactive ceramics, bioactive glasses and bioactive glass ceramics [7]. Among these are the main bioactive inorganic materials: (1) calcium phosphate ceramics (CaP) such as hydroxyapatite (HA) ($Ca_{10}(PO_4)_6(OH)_2$) and tricalcium phosphate ($Ca_3(PO_4)_2$), biocompact glass (BG) and b-wollostonite [10], HA/TCP bi-phase ceramic; (4) apatite-wollastonite (A-W) [8–12]. The underside of CaP and BG, after implantation, shapes a biologically effective hydroxyl carbonate apatite coating comparable to bone mineral stage, that offers an excellently interface bonding of ions [13, 14]. BG can be adapted to supply Si ions. BG is also the most important source of exposure to bone restoration applications. In addition, the resorption rate CaP and BG can be adjusted to crystalline HA that lasts years after implantation, whereas the restoration capacity of other calcium phosphates is increased. Additionally, the resorption rate of CaP and BG can be adjusted to crystalline HA that persists for several years after implantation, while the capacity for absorption of other calcium phosphates is increased but reduces the load capacity [15].

Significant health and safety benefits result from the local delivery of drugs. Target drug levels on the bone stage could be reached with this strategy compared to intrinsic pharmaceutical management. The plasma drug level is lowered or destroyed in a local supply and therefore secondary impacts or overall toxicity are avoided [16, 17]. Diffusion through the CaP carrier's pore network and/or rapid biodegradation can take place locally from charged CaP scaffolds according to two primary processes [18–20]. Based on these processes, the service kinetics and the regulation of the released drug involve multiple features of the scaffolds (structure, porosity, specific surface area) as well as the loaded drug.

The CaP family consists of a number of compositions that are characterized by Ca/P ratio and the lower its value the faster the CaP biodegradation. As CaPs provide a powerful biomaterial/bone connection, they have been historically used to improve prothesis osteointegration on steel implants since the 1980s [21]. CaPs have been investigated as cements, granules or scaffolds for bone filling reasons. In bone strengthening or restoration, CaP cements are used and have been produced

since the 1990s. The benefit is that they can be injected in a minimally aggressive way. They then freeze in vitro on the ground, fit flaws with complicated design and provide an ideal connection between implant and bone [22]. A range of forming procedures, such as spum impregnation, heterocarbonification, elevated shear granulation, and 3D printing/speed prototyping, may be used to develop three-dimensional scaffolds, accompanied by a particular thermal treatment to extract the pore shapes and strengthen the scaffold. This allows a highly customized implant for the patient to be designed with custom porous materials [23].

By using the marketable red ginseng extracts, CaP-NPs are synthesized using co-precipitation. Ginseng leaves are a wealthy cause of organic bioactive compounds with a variety of pharmacological capacity [24–26] and are presumed to have been a significant factor in the synthesis method of ginseng products, especially in the capture and stability of synthesized CPG-NPs. Following synthesis, the NPCs of the CPGs and streptomycins are combined with the antibiotic for the creation of CPG-S NPs and both are further identified in terms of morphological and chemical characteristics. By the UV–VIS spectral analysis, the initial detection and nature of synthesized CPG and CPG-S NPs have been determined. The synthesized CPG-NPs are 276 and 280 nm, respectively, with CPG-S NPs. Previous scientists have achieved similar results [27]. The small difference between CPG-S absorbance peaks could be created by a redshift induced by streptomycin conjugation to CPG-NPs [27]. In addition, the FE-SEM–EDS assessment is carried out on the synthetic CPG-S NPs. The SEM image findings revealed a rod-shaped shape with uneven boundaries and it is revealed that the nano-magnitude of each particle with a very tough texture. Martinez et al. have achieved similar results [28].

Two distinct phases of the CP (calcium phosphate) are shown intrinsic antibacterial effects: amorphous CP (ACP) and hydroxyapatite (HAp). The effect is prominent against several common Gram-positive and Gram-negative bacteria and also their multidrug-resistant (MDR) analogues. The ratio of the amorphous and the crystalline phases in HAp was significantly higher than in ACP. The XRD patterns shown in Fig. 1 conclude the monophasic composition of HAp and the mixed-phase composition of DCP (dicalcium phosphate) consisting of its anhydrous form, monetite, dihydrate form, brushite and a small amount of HAp. In the meantime, the ACP showed a broad, diffuse pattern typical of amorphous structures. The SEM and HR-TEM images Hap, ACP and DCP are depicted in Fig. 2.

The optimization of these nanoparticles including Hap, ACP and DCP has shown more intense antibacterial effect to make them therapeutically effective. The selectivity and functionality provide great interest to these nanoparticles for a more powerful antibacterial effect [29, 30]. CP-based nanobiomaterials can be synthesized by simple, effective and environmental benign sol–gel chemistry [31]. This approach is presented in Fig. 3.

The layer of calcium phosphate (CaP) is an efficient technique for the surface functionalization and manufacturing of bioinert material [32]. The LAB method was used for chemical stability and mechanically resistant poly(etherketone) (PEEK) used as an orthopedic and dental implant product. The method of LAB laser-assisted biomimetic was performed by irradiating continuous Nd:YAG beam

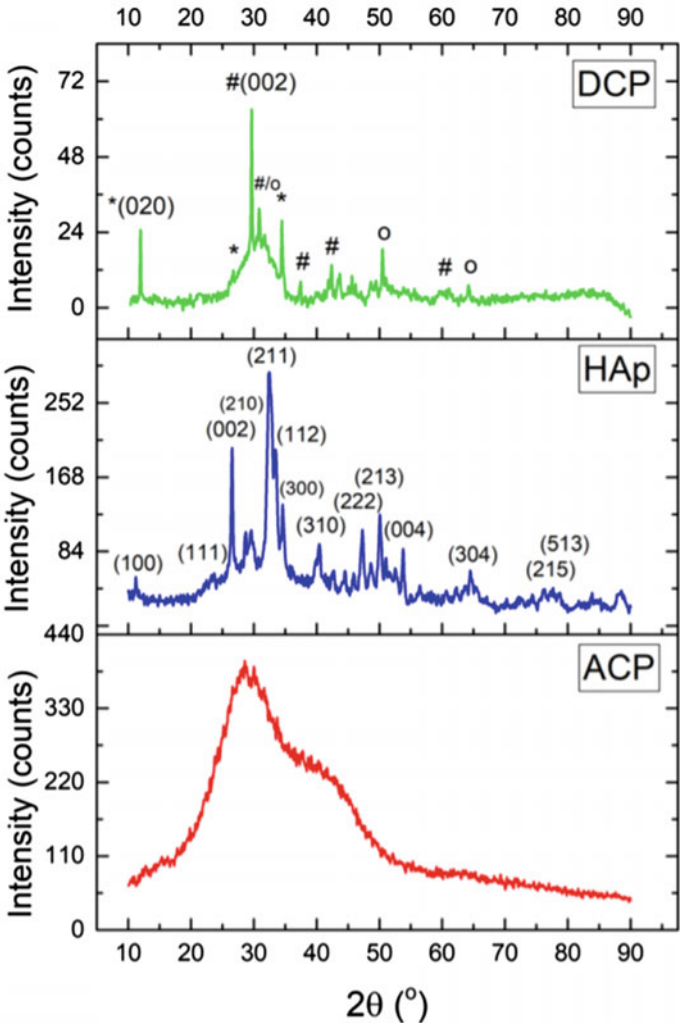

Fig. 1 XRD patterns of amorphous calcium phosphate, hydroxyapatite and dicalcium phosphate [brushite or DCP dehydrate labeled as (*), monetite labeled as (#), Hap labeled as (o)]

(355 nm) on a PEEK poly(etherketone) suspension submerged in a CaP reservoir super-saturated. The application of CaP layer relied on laser fluence, which means the successful formation of CaP on the PEEK layer following the LAB process. Ceramics based on CaP have been commonly used to replace the bone tissue, as they may be connected to, or integrated into, working bone cells (the estate recognized as osteoconductivity) [33, 34], including synthesized hydro Xyapatite and β-tricalcium foam. However, these CaP-based materials may not be used in elevated load-bearing circumstances as they are insufficiently tightly fracted.

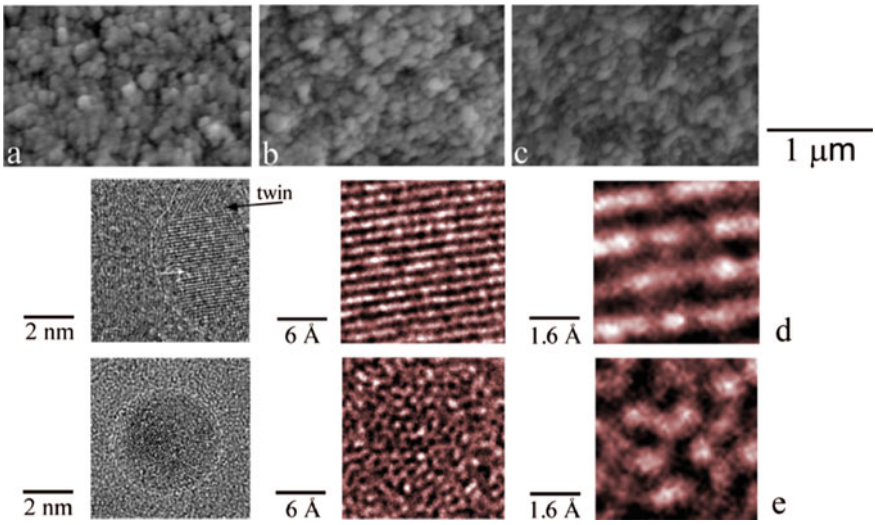

Fig. 2 SEM and HR-TEM images of hydroxyapatite (**a**, **d**), amorphous calcium phosphate (**b**, **e**), and dicalcium phosphate (**c**) nanoparticles. Dashed lines in (**d**, **e**) represent nanoparticular boundaries

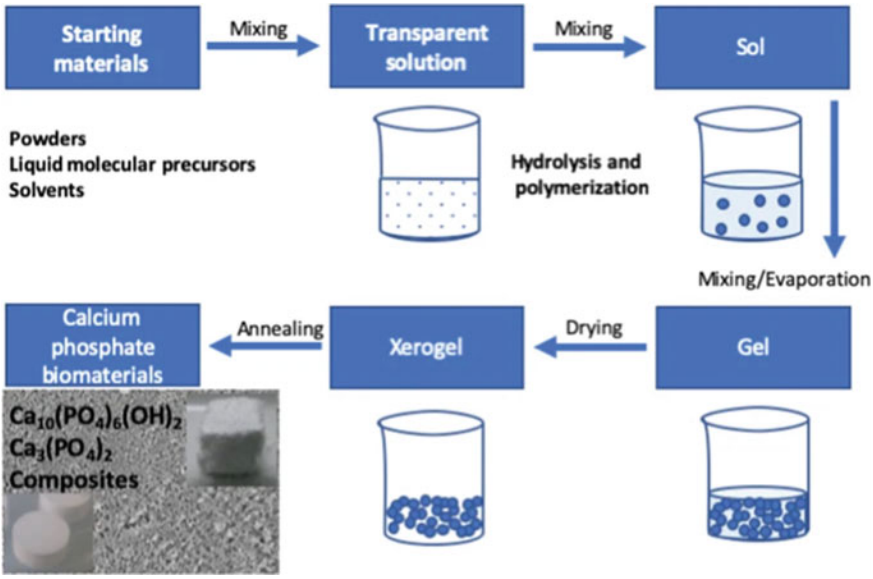

Fig. 3 Calcium phosphate biomaterials synthesized by sol–gel chemistry [31]

Poly(etherquetone) Super-engineered (PEEK), because they show elevated chemical strength and mechanical characteristics suited to body tissue substitution, is common polymeric fabric used for orthopedic and dentistry implants. Concerning the risks of stress protection and allergenic responses, PEEK-based implants are radiological and have few problems. PEEK is intrinsically bioinert, despite its helpful features. As a result, osteoconductive PEEK-based implants are becoming increasingly necessary [35].

PEEK is susceptible to the LAB method for CaP binding. The osteoportic PEEK-based implants can be produced by a helpful instrument. Firstly, the poly (tetrafluoroethylene) layer was attached to one PEEK substrate and then positioned on the base of a glass jar. The jar received the addition of a CP alternative (10 mL), which completely immerses the substrate in it. At 25 °C, the glass bottle was put into a water bath. Using Nd:YAG lasers (30 Hz), the PEEK paper layer was irradiated by pulse ultraviolet (UV) rays (α = 355 nm) [36]. The substratum was separated from the CP fluid and softly rinsed with ultra-pure air after irradiation for different time intervals of up to 30 min. After the LAB phase, the CP fluid was kept intact without causing permanent CaP precipitation. When the laser fluence was fixed at 2 W/cm^2, CaP was developed on the LAB-processed PEEK substructure. For a fixed irradiation period of 30 min, the LAB process was performed at different fluids from 2 to 6 W/cm^2. The PEEK substrates show raw surfaces at all the fluids checked after the LAB procedure. SEM–EDX obviously identified the existence of CaP compounds only on the ground treated with 2 W/cm^2.

The CaP compound's crystalline stage with XRD-thin film measurements is recognized, but due to the detection limit. TEM analyzes for precipitation separated from the PEEK layer processed by LAB. The composition of Ca and P was strengthened by TEM–EDX. The precipitate Ca/P proportion was about 1.4. The CaP precipitation includes hydroxyapatite as a crystalline stage according to its TEM diffraction model. The CaP precipitation did not indicate the octacalcium chloride (OCP)-specific circle. For other precipitates scraped from the same substrate, the same TEM results have been obtained. It may contain calcium-deficient hydroxyapatite and/or other CaP phases, like amorphous CaP and OCP, which are precursors to hydroxyapatite in the judgment of the lower CaP ratio ($\sim$1,4) of the CaP precipitate than stoichiometric hydroxyapatitis (1,67). However, the current analytical circumstances did not reveal their existence.

The system was integrated with a fluidic system that mimics the circulation of the cardiovascular system to discharge a modeled medicine (ibuprofen) from FeHAs according to the frequencies employed. Moreover, intense stimulus of detached Adult Cardiomyocytes and an animal model evaluated the biological consequences of recognized energy stimulus on the cardiovascular structure both in vitro and in vivo. A fascinating strategy is to target the core and adjust the dose of medicine by combining magnetic nanoparticles (NPs) and electronic devices. In order to control drug discharge from biocompatible Supercompatible Fe-Hydroxyapatite NT (FeHAs), Marrella and coworkers have designed an electromagnetic tool using Helmholtz coils to apply low frequency electric stimulations [37]. Gelatin-hydroxyapatite-polylactic acid (PLA) nanocomposites and loaded

with ibuprofen and the amount of drug in the carriers were studied by Nabioura and coworkers. Phosphate buffers (PBS) solution at pH 7.4 and 37 °C have been assessed in drug delivery [38]. Formulation contains nanoparticles (CAPs) and 7-hydroxy-2-dipropyl-aminotetraline (7-OH-DPAT) for the biodegradable calcium phosphate is prepared and it is concluded that the CAP enhances the activity of the delivery system with 7-OH-DPAT which indicates that the CAP is potential for controlled, targeted drug supply for the treatment of ocular diseases [39]. Verron and coworkers have reviewed the calcium phosphate (CaP) biomaterials used as drug delivery systems loaded with various proteins and drugs [40]. Nanostructured hydroxyapatite (nHAp), and its application potentials for controlled drug delivery, drug conjugation, and other biomedical treatments [41]. Schmidt et al. created an approach for aqueous-core calcium phosphates, which incorporates convenience of preparing, reproducibility, volume control, stabilization and average spreadability control, through implementation of the "capped" molecule, carbozyethylphosphoric acid (CEPA) [42]. A template for biomimetic calcium phosphates mineralization is studied as biocompatible and biodegradable polyelectrolyte complex consisting of carboxymethyl cellulose (CMC) and chitosan (CHI). For the production of hybrids in varying organic/inorganic proportion, CMC/CHI/calcium carbonate combinations were made with different levels of simulated body fluid. In the fields of bone tissue technology and medication delivery, combinations developed in that input show excellent opportunities [43]. The hybrid nanoparticles of calcium (ACP) and polylactide-block monomethoxy (polyethyleneglycol) are developed for drug delivery purposes, and Europium-doping is also done to enable ACP porous nanospheres to operate with photoluminescence (PL). In vitro discharge studies demonstrate a smooth, continuous discharge of drugs from simulated body fluid in ibuprofen-loaded Eu^{3+}; ACP porous nanospheres [44].

Calcium phosphate nanoparticles could be used in implantable bioceramic bone graft products for stem cell treatment or enhanced in vitro results Despite the huge medicinal capacity of SiRNA as a therapy approach, unfavorable bio-distribution models and intracellular bioavailability still cause problems. The non-toxic and easy preparation characteristics of calcium phosphate (CaP) co-precipitate are used in in vivo transfection for almost 40 years. The CaP surface load is positively adjusted by surface changes, which are crucial to the enzyme-free siRNA charging and migration of cell DNA. The unique siRNA carrier system will also encourage a siRNA leak from lysosome to produce a continuous delivery of siRNA and a strong efficiency [45].

Porous biphasic calcium phosphate (BCP) granules are being developed to be a drug delivery system for bone regeneration, incorporating drug-releasing poly-(lactic-co-glycolic acid) (PLGA) nanoparticles. Spherical BCP granules are manufactured by the use of a liquid nitrogen technique and a conventional process of emulsion with transparent microchannels and PLGA nanoparticles charged as model medication with dexamethasone (DEX). The DEX-loaded PLGA nanoparticles contain a polyethyleneimine which results in direct, positive edges of the nanoparticles. This can be used in implantable bioceramic bone graft products or enhanced in vitro results for stem cell therapy [46]. mPEG-PE (polyethyleneglycol-

L-α-phosphoethanolamine) is synthesized and applied in the preparation of siRNA delivery nanoparticles consisting of mPEG-PE and calcium phosphate. The stable hybrid nanoparticles of calcium carbonate and mPEG-PE are self-assembled by electrostatic interaction in water. The nanoparticles showed an outstanding serum strength and are able to safeguard siRNA against degradation of ribonuclease. These findings showed that siRNAs can be robust, secure and useful, with mPEG-PE/CaP binary nanoparticles [47].

Nanoparticles with calcium phosphate have a distinctive category of non-viral vectors, which can be used as effective alternate transports of DNA for specific gene delivery. The development and synthesis of ultra-low volume, extremely monodispersed DNA calcium dopped phosphate nanoparticles has been revealed by Roy and colleagues. The inside nanoparticle DNA is protected against the outside DNase and can be used safely for in vitro and in vivo translation of the encapsulated DNA. Furthermore, the surface of these nanoparticles can be appropriately altered by adsorbing a very adhesive Polymer such as polyacrylic acid, which can be used as a coping agent for 1-ethyl-(3-dimethylaminopropyl)-carbodiimide hydrochloride to combine a ligand with carboxylic groups such as p-amino-1-thio-β-galactopyranoside [48].

3 Calcium Carbonate Nanoparticles

Nanomedicinal products are being developed to control the release of drug into the body, to protect medicines against enzymatic or chemical degradation, and to achieve a delivery of organ or tissue. The studies have demonstrated the high pore, biocompatibility, biodegradability, and pH-sensitive characteristics of calcium carbonate ($CaCO_3$) nanoparticles. $CaCO_3$ nanoparticles are one of the greatest applicants in organic drug delivery technologies for these desirable characteristics. Because of its accessibility, small price, safety, biocompatibility, pH sensitivity and rapid degradability, $CaCO_3$ has large biomedical uses. Recently, their use as drug delivery systems for various types of drugs has been of considerable importance. $CaCO_3$ nanoparticles have shown significant possibilities as transports of drug intended at cancer tissues and cells. These nanoparticles may be used to hold cargo for a long time after administration due to slow degradation of the $CaCO_3$ matrices. These nanoparticles may be suitable for dual applications, such as bone replacement and drug release for bone-related diseases like osteomyelitis, as osteoconductivity and bioresorbability [49]. Nanocrystals are synthesized using the spray-drying method, pure and stable calcium carbonate ($CaCO_3$). Vergaro and coworkers used it for the study of the biocompatibility and internalization in HeLa cells as drug vessels [50]. The synthesis and stabilization of nanoparticles of vaterite and its cisplatin encapsulation and the slow minimum of constancy in drug releases at various pH values were reported from Dunuweera and Rajapakse and coworkers [51].

Together with the possibility of functioning with blocking officers the pH-dependent characteristics provide it with the special characteristic to be used for

specific distribution mechanisms for anti-cancer drugs. In addition, because of the slow degradation of the $CaCO_3$ matrices, these nanoparticles can be used for longer periods of time after administration for drug retention in cancer tissue. $CaCO_3$ nanoparticles have been assessed for the development of drug delivery carriers. The present status of $CaCO_3$ nanoparticles as cancer therapeutic product systems, focusing on their specific characteristics, such as pH sensitivity and biodegradability, has a potential role in future safe and effective cancer treatment [52].

Render and coworkers have studied $CaCO_3$ nanoparticles derived from eggshell as well as drug loading capacity. The effect of the nanoparticles on the cell viability is studied in the 3-(4,5-Dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide proliferation assessment with SW-480 (mammalian lung disease) and NIH/3T3 (mouse fibroblasts). The 5-Fluorouracil and Indole-3-Carbinol (I3C) anti-cancer drugs have been filled with $CaCO_3$, as prepared and discharge models have also been investigated [53]. The regulation of fiber (acrylic acid) generates rod-like calcium carbonate (Rod-CC NPs) nanoparticles with required dispersibility of water. The Rod-CC NPs showed beneficial effects on the development of osteoblast cells when cultivated with MC3T3-E1 cells. The observation of alkaline phosphatase activity together with osteocalcin (OCN) and bone sialoprotein (BSP) expression shows that the differentiation of MC3T3-E1, which have a great potential to be used in bone regeneration, could be induced by nanoparticles [54].

Calcium carbonate nanoparticles from cockle shell are promisingly produced by Ghafar and coworkers as efficient carriers for the delivery of the drug and have been produced from cockle, a natural biomaterial with modified surface properties [55]. Nanoparticles derived from Eggshell calcium carbonate ($CaCO_3$) were used in the development of a tablet-like enteric medicines system. Based on a high level down ball milling technique, the $CaCO_3$-nanoparticles have been packed as models with 5-fluorouracil and covered with Eudragit S100 or Eudragit L100, which allow production of stable formulations for the slow-through or regulated discharge of enteric pharmaceuticals [56]. Ciprofloxacin–cockle shells-derived calcium carbonate (aragonite) nanoparticles (C-CSCCAN) are developed by Tijani and coworkers [57]. The different water-solubility of such drugs makes doxorubicin (Dox) and curcumin (Cur) combinations very useful for clinical application. The benefits of PAA and $CaCO_3$ to ensure the discharge of high-impact animal (EE) and pH-sensitive medicinal products on HepG2 cells through a LPCCD [58]. In addition to the CaP component, Zhao and coworkers have developed an easy way to modified nanostructured calcium carbonate ($CaCO_3$) gene delivery systems. In the existence of carbonate and phosphate ions, $CaCO_3$/CaP/DNA nanoparticles are synthesizing Ca^{2+} ion co-precipitation with plasmid DNA. Compared to $CaCO_3$/DNA and CaP/DNA co-precipitates, gene transfection of nanoparticles $CaCO_3$/CaP/DNA could be improved substantially [59]. Calcium phosphate nanoparticles charged with gentamicin sulfate, are revealed by Pan coworkers. The dosage would have an impact on the drug charging and trap effectiveness of gentamicin sulfate [60]. Koroleva and collaborators have noted that doped calcium carbonate-phosphate nanochristalline is an excellent biocompatible substance for the supply of drugs. The results achieved show the potential for bioceramics based

on doped NCC-Calcium carbonate phosphates. This doped NCCC-Phosphate can increase the mechanical strength of the bone tissues [61]. A co-precipitation technique has been used to encode alginate/$CaCO_3$/DNA/DOX-nanoparticle nanoparticles with elevated encapsulation effectiveness, with significant potential for cancer treatment, with doxorubicin hydrochloride (DOX), an antitumor and p53 expression. The alginate/$CaCO_3$/DNA/DOX nanoparticles' in vivo cell inhibition impact was tested by a HeLa MTT assay. A elevated cell inhibition frequency was observed for the alginate/$CaCO_3$/DNA/DOX nanoparticles, which indicated that alginate/DDNA/DOX/alginate nanoparticles could efficiently mediate transfection of the gene and bring the drug to the cells [62].

The primary drawback of nanoparticles of amorphous calcium carbonate (ACC) is their aqueous volatility. A nanoreactor of ACC–doxorubicin (DOX) @silica was recommended for medication shipment for use in tumor treatment to increase their stabilization in physiological environments while maintaining their pH-responsiveness. In exactly the toxic microenvironment of human bacteria, DOX is released by ACC–DOX@silica nanoreactor to produce effective tissue mortality, thus demonstrating its strong capacity for an attractive chemotherapeutic nanosystem for cancer treatment [63].

By taking advantage of the tumor chronic target capacity and the drug loading property of CC, hyaluron-CC well-formed nanoparticles are developed to be a drug delivery system targeted at colorectal cancer of a decent drug load, which is beneficial for colorectal chemotherapy. A hybrid drug delivery System consisting of hyaluronan and calcium carbonate (CC). Bai and colleagues have developed nanoparticles of hyaluron-CC smaller than 100 nm for the construction of hyalurons-CC/Adr to be supplied by the wide-range anti-cancer drug adriamycin (Adr). There is evidence of greater anti-cancers behavior for hyaluron-CC/Adr nanoparticles than free nanoparticles of Adr or CC/Adr that show a minimal capacity for toxic side effects and preferable capacity for cancer suppression [64]. Koo and its coworkers have reported an intracellular model of transport centered on the apoptotic calcium carbonate-loaded protein ($CaCO_3$) [65]. $CaCO_3$ MNPs (Cyt c MNPs) produced from apoptosis-inducing cytochromium c (Cyt c MNP) are produced in situ with $CaCO_3$ mineralized copolymer powder in the absence of Cyt c. $CaCO_3$ polymorphic vaterite with a total hydrodynamical diameter of 360.5 nm and 60% of Cyt c charging effectiveness were found in the resultant Cyt c MNPs. Cyt c MNPs are stabilized in physiological pH (pH 7.4) and effectively prohibited the release of Cyt c. Cyt c release is facilitation for the supply of cell-impermeable therapeutic protection in cancer therapy at intracellular endosomal pH (pH 5.0).

Som and colleagues have created techniques for synthesizing the un-doped monodisperse vaterite of nano-$CaCO_3$. This research defines the strategy to preparing nano$CaCO_3$ over a broad spectrum of particle size, a formula that stabilizes the nanomaterials in water-based alternatives and an acidic cancer atmosphere for possible therapy advantages by pH-sensitive nano-platform [66]. Silver-based hybrid tissue nanoparticles (nAgs) integrated into microparticles of calcium phosphate (μ-$CaCO_3$) that serve as suppliers for continuous releases. In the presence of poly(sodium4-styrene sulfonate) the current material structure was

focused on the co-precipitation of $CaCO_3$ and nAg. The parts of coats and fabrics which protect different parts against colonization of microorganisms may also be used as such microparticles [67]. Kiranda et al. have made nanoparticles (Au-CS$CaCO_3$NPs) for biomedical applications, the conjugate gold cockle shell-derived calcium carbonate [68].

4 Silica-Based Hybrid Nanoparticles

Mesoporous silica is known as a promising candidate to overcome problems and produce controllable and sustainable effects. Mesoporous silica nanoparticles (MSNs) are used as delivery reagents in specific since silica has favorable chemical properties, heat stability and biocompatibility. The distinctive mesoporous silica composition makes it possible to load drugs efficiently and to discharge them monitored at the destination location. The advantages of the use of mesoporous materials in drug delivery are the large area and volume of pore. These properties allow materials to take in large quantities of payload molecules, protect against premature degradation and encourage a controlled and rapid release [69]. A good control over morphology, particle size, uniform and dispersion is growing for the use of mesoporous silica nanoparticles (MSNs) in catalysts, adsorption, polymer filling, optical devices, bio-imaging, drug supply and biomedical applications [70]. The sol–gel process is an extremely versatile method used in the silica NP synthesis, providing many chemicals such as high homogeneity and purity, as well as full pH processing. ORMOSIL NPs or mesoporous NPs are generated through the introduction of organic function units or surfactants in the sol–gel process [71].

Depending on additives used to preparing MSN, the properties of mesope, including pore size, high drug loading and porosity and surface characteristics, can be altered. The active surface enables a change of surface properties functional and the link between therapeutic molecules. It is commonly used in the areas of diagnostics, destination medicines, bio-sensing and cellular use [72]. The biomedical application of mesoporous silica nanoparticles (MSN), as effective drug distributors, can be easily adapted for the reasons of medication charging, regulated discharge, distribution and multi-functionalization, because of their composition, morphology, magnitude and surface characteristics. The in vitro biosafety and drug effectiveness of MSN-based nanodistributors, which include biocompliability, cytotoxicity, tissue compatibility and bone alignment, as well as pharmacokinetics and their opportunities for clinical implementation, are also increasingly highlighted [73]. Hydrated silica particles with high molecular compounds like tyraminylinulins (mol wt 5.0 kD), FITC-desktroins (mol wt 20.0 kD) and horses radish peroxidases (mol wt 40 kD) were prepared and characterized in a novel, injectable and sprayable nanometer size [74]. The MSN is prepared as a structural shaping agent between the kinetic drug and mesoporous size releases and a special surface area of MSNs through the hydrolysis and condensation of tetraethyl orthosilicate (TEOS) with cetyltrimethylammonium bromide (CTAB) [75]. Hollow mesoporous silica

(HMSN), mixed with sodium phosphomolybdate, has synthesized as a non-toxical option to the use of chromates and embedded in a polyelectrolyte coating (PDDA) that is opposite loaded and the release capability and corrosion safety were investigated at distinct pH levels [76].

PMMA/PS silica polymer composites are manufactured using sol–gel technology. The SEM images demonstrate the apatite development of silica fillers in PMMA:PS [77]. The SEM showed that Si enhances membrane bioactivity, and PS played a key role in bioactivity as was observed. It was observed that the PMMA and PS composites had a high degree of bioactivity, while the PMMA or PS compound had a lower bioactivity. Compared to two other composites, the bioactivity of composites with more PS was less bioactive. Composites prepared for use as bone-cement have been checked for the effectiveness of its kinetics for drug release, because these may serve as a multifunction for bone growth by active drug release. Cytotoxicity tests have been conducted to assess the bioconsistency of manufactured orthopedic composite membranes.

Polymer mesoporous silica nanoparticles (MSNs), due to their high drug load, biocompatibility, and high pharmacokinetics, are gaining popularity as supply vehicles. The MSN produced by Moodley and Singh has been functionalized to produce monodispersal NPs with a wide area of 710.36 m^2/g, high pores volume, 9.8 nm diameter and favorable size zeta potential, allowing for stable uptake and increased uptake of 5-FU5-fluorouracil (5-FU). This study was carried out using biocompatible polymers, chitosan and poly(ethyleneglycol) [78]. Liu and Xu have reviewed both the factors affecting protein loading into MSN and general strategies for targeted and controlled protein release using MSN [79]. The 25 kD of polyethyleneimine (PEI) functionalized silicon-nanoparticles (MSNs) were widely used for the delivery of genes [80].

Dye doped silica NPs highly mesoporous fluorescein that can contain a drug payload were synthesized with ease and are characterized by the scan of electron microscopes and the transmitting electron microscope as well as photoluminescence spectroscopy. The findings showed that these silica NPs show outstanding characteristics, including big pore volume, a small size and powerful fluorescent characteristics. The Silica NPs acquired were further used as drug supplies to explore the characteristics of in vivo releasing of drug use as a separate drug model, doxorubicin (DOX) [81]. A significant emerging method of disease treatment is the drug targeting of Silica-Gold core carriers containing antibiotic drug particles. Stober's technique was used for synthesizing silica key particle and with amine communities. The silica-gold key nanoshell vessels were packed with antibiotic Gentamycin, and the substance discharge curve has been explained [82].

5 Titania-Based Ceramic Nanoparticles

Titanium and its alloys have a uniquely strong and biocompatible combination that allows them to be used for medical applications. The rough topography of titanium implants and free energy enhance osteoblast adhesion, growth and subsequent

development of bones. In addition, the adhesion of various cell lines to titanium implant surfaces is influenced by titanium's surface features, specifically the topograms, the distribution of charges and chemical substances [83]. Titania nanotube applications (TNT) are known for their outstanding characteristics and easier preparing method for localized implants. Its biocompatibility is important for the clinical implementation of TNT implants, and regulated drug release may also be caused by temperature, color, magnetic radiofrequency, and ultrasonic stimulus. In addition, numerous instances including the dentistry, orthopedic implants and cardiovascular stents have shown TNT implants for medical therapy. One major advantage of using TiO_2 nanotubes in cell interactions is the fact that TiO_2 morphology is correlated with mesenchymal cell adhesion, expansion, growth and differentiation leading to cell death and apoptose.

Sustainable interest as bio-medical materials and the application of nanomedicine are gained through titanium dioxide nanotube array (TNA). Different tissue mechanisms such as tissue adhesion, growth, reproduction and distinction could be modulated by the characteristics of TNA nanostructures. In order to reveal monolayers of pulmonary epithelial proteins for 7 days, Medina-Reyes et al. have produced TiO_2 nanofibers, and the results are angiogenesis, fibrosis, EMT, genomic disturbance and cisplatin susceptibility. Also, tumors created from embedded TiO_2 nanofibers cells are favorable for the same indicators and, moreover, dedifferentiation and remarkably high erythrocytes and cisplatin sensitivity losses suggest that the nanofibers of TiO_2 are enhanced in lung epithelial cells by the specific cell phénotype [84]. Titanium nanocarrier nanoparticles have been synthesized by grafting folic acid (FA) onto PEGylated titanium dioxide nanoparticles for targeted delivery of the anti-cancer medication, the paclitaxel [85].

Photodynamic therapy (PDT) as a noninvasive treatment strategy with high specificity is a promising method for the treatment of cancer. In this study, a CD44 and N-cadherin dual targeting drug delivery system in combination with mesoporous titanium dioxide nanoparticle (MTN)-based PDT has been successfully constructed for overcoming drug resistance. Hyaluronic acid (HA) and ADH-1 (a cyclic pentapeptide) were grafted onto the surface of MTN to construct ADH-1-HA-MTN, and doxorubicin (DOX) was selected as a model drug. HA can both trap DOX in the wells of MTN and target CD44-overexpressing tumor cells. ADH-1 blocks the EMT process of tumor cells by selectively inhibiting the function of N-cadherin. Besides, a large number of reactive oxygen species (ROS) were generated by MTN under X-ray irradiation, which could provide a cancer cell killing effect [86]. In order to examine the fundamental molecular mechanisms of caused cell death, Zahir et al. have synthesized silver and TiO_2 nanoparticles using green synthesis from Euphorbia prostrata water leaf seed. The green-synthesized silver NPs may provide promising leads for the development of cost-effective and safer alternative treatment against visceral leishmaniasis [87]. Nanoparticles modified with hyaluronic acid (HA) tumor targeting titanium dioxide (TiO_2) have been created to examine the effectiveness of exploiting TiO_2's pH-responsive drugs discharge properties and HA's capacity to develop tumor targeting (CDDP)

distribution scheme (HA-TiO_2) for prospective oval cancer neo-adjuvant chemotherapy [88].

Ciprofloxacin, amoxicillin and curcumin nanoparticles incorporated within the chitosan/TiO_2 nanoparticles and drug release have been investigated by Venkatasubbu and coworkers [89]. The influence of TiO_2 nanoparticles on chromosomal defects and dehydrogenase action in the lactate and carbon carbonate nanoanatase on nanotechnological structure in various doses was explored by Rad and coworkers [90]. It is noted that the interaction of titanium dioxide nanoparticles with 1,2-dipalmitoyl-sn-glycero3-phosphocholine (DPPC) vesicles and the binding of TiO_2 nanoparticles with the Zwitterionic DPPC vesicles have created a more favorable effect on the surface [91]. Zhang and colleagues have reported the interplay between fluorescently marked oligonucleotides and TiO_2 nanoparticles in the detoxification and delivery of therapeutic materials. The fluorescence quenching is accompanied by DNA Adsorption and the double strand DNA has been shown to be reduced quenched so that DNA is detected by TiO_2 nanoparticles [92]. Hybrid drug-loaded TiO_2/polymer amphiphilic nanoparticles of fine-controlled size using a simple and reproducible sol–gel process consisting of the formation of titanium (IV)/acetone oxo-organic complex followed by mixing with amphiphilic poly (ethylene oxide)-b-poly(propylene oxide) block copolymer for use in sonodynamic and drug release therapy [93]. Yu and colleagues recorded the toxicological function of TiO_2-NP in cell organelles and noted that TiO_2-NP caused endoplasmic reticulum (ER) stress in cells and interrupted the endoplasmic reticulum structures (MAMs) associated with mitochondria and calcium ion equilibrium, thus improving autophagy [94]. TiO_2-NP particle shape and size using TEM (Fig. 4a), TiO_2-NP-treated cells viability with respect to concentration and time (Fig. 4b), CLSM images showed that the fluorescence intensity is linear function of treatment time and concentration (Fig. 4c) and FACS (Fig. 4d) data.

6 Zirconia Oxide-Based Hybrid Nanoparticles

Zirconia oxide nanoparticles (ZrO_2NPs) are considered to be one of the benign bioceramic metal compounds that have been commonly used in many biomedical fields, dental implants, skull joint substitutes, medicine delivery and numerous manufacturing devices. Zirconium dioxide nanoparticles with a monoclinically mixed framework are produced using zirconium (IV) acetate hydroxide as a metal precursor, polyvinylpyrrolidone as a capping medium and deionized water using a thermal treatment technique [95]. zirconium phosphate (ZP) nanoparticles have been reported as nanocarrier for curcumin as antitumor drug [96]. Nano-ZrO_2 has antiproliferative impacts at levels of >250 μg/mL by decreasing the system of tissue protection against oxidative pressure [97]. Nanospheres with variable Ti to Zr ratios of titanium zirconium (TiZr) are synthesized using sol–gel chemistry followed by solvothermal treatment. The mesoporous TiZr oxide nanospheres also showed hydrolytic stability, as evidenced by the 21-day retention of the integrity of

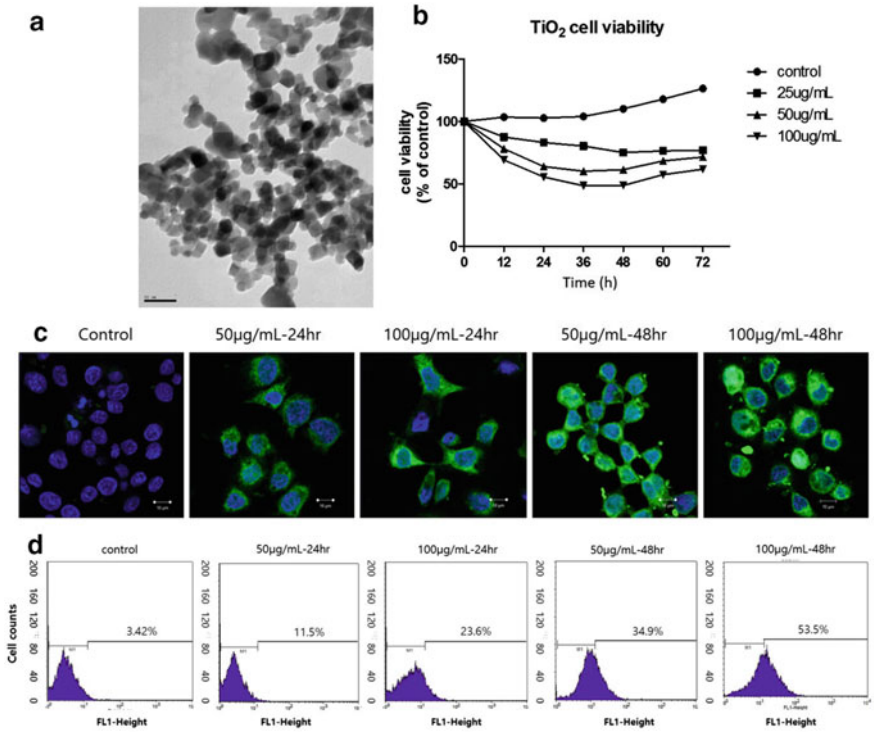

Fig. 4 Characterization of titanium dioxide nanoparticles and identification in mammalian bronchial epithelial cells of reactive oxygen species (ROS). **a** TEM image **b** viability and proliferation of cells for 72 h. **c** H2-DCFDA (2,7-dichlorodihydrofluorescein diacetate) staining **d** FACS (fluorescence-activated cell sorting analysis) [94]

mesostructures in PBS phosphate buffered saline (PBS) after drug release [98]. Due to its high porous structure, hollow mesoporous zirconia nanocapsules (hm-ZrO_2) with a hollow core/porous shell structure are shown to be effective drug vehicles such as doxorubicin (DOX) [99]. Al-Fahdawi and coworkers have determined their cytotoxicity characteristics against cancer cell lines by iron-manganese-doped sulfated zirconia nanoparticles [100].

7 Boron Carbide-Based Nanoparticles

Nanoparticles of B_4C (Boron Carbide) show an extraordinary hardness among the ceramic materials. In several high-performance uses, boron-carbide nanoparticles are therefore an acceptable material [101, 102]. Boron carbide nanoparticles are smaller than 100 nm and can be with the multi-wall carbon nanotube at 1200 °C at 2.5 h in vacuum from thermal decomposition of magnesium diboride boron reaction.

8 Conclusion

Due to their ability to integrate and conserve, to supply the active substance locally regulated over moment and to gradually degrade and replace newly formed bone, CaPs are regarded to be appropriate drug carriers. $CaCO_3$ ions are considered to be an appropriate drug supplier by the accessibility, small costs, safety, biocompatibility, pH-sensitive characteristics, osteoconductivity and rapid biodegradability. MSNs are exceptionally effective and scientists consider them to be substances that can be used to significantly alter cancer therapy, cell delivery and medicine service due to their clear, optically versatile characteristics, usable layer volume, low-toxicity profile and excellent drug charging skills. Nanostructured products based on titanium dioxide (TiO_2) play a significant role in tissue regeneration and diagnosis. ZrO_2 NPs may be helpful for biomedical applications, particularly for potential bone repair and replacement.

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Chapter 6
Biomaterials for Anticancer Drugs

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Abstract Biomaterials for anticancer drug are an important and essential topic in twenty-first-century medicine, because this type of new materials overcomes the drawbacks of current chemotherapy technique and greatly improve the quality of life of the patients. The major issue that has faced in the past and current scenario is the less or non-bioavailability and biodegradability of drug delivery even though they have high therapeutic efficacy. To address this problem, recently most of the researchers were focused to develop nanotechnology to solve the problems in drug delivery. This may provide a better solution and thus changes the way we make drug and the way we take drug. Therefore, in this chapter, we have discussed cancer, oral chemotherapy and different biomaterials for anticancer drug and their advantage over conventional anticancer drugs. This chapter will be a remarkable one for understanding the usage of different type of biomaterials for the enhancement of bioavailability of anticancer drug delivery system.

Keywords Biomaterial · Anticancer drugs · Bioavailability · Nanotechnology

1 Introduction

1.1 Cancer

Cancer is one of the major health issues and second leading death disease in worldwide. It is a broad term and illustrated the disease results in uncontrolled growth and divisions of cells. The number of patients diagnosed with cancer has been increasing each year. Nowadays, a lot of novel studies happened for the earlier

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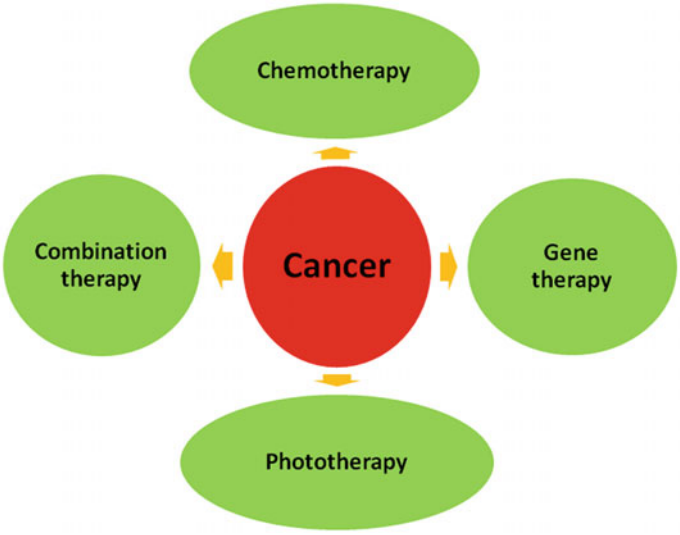


Fig. 1 Cancer therapeutics technique

and easy recognition of the disease and its current stages. Recently most of them focused on the development of new therapies with decreased side effects and increased efficacy. Biomaterials and nanotechnology have attained much more attention in cancer treatment by reducing side effects and excellent efficiency. This new technology has been applied in biomedical applications, especially in cancer diagnosis and treatments because of its biocompatibility and less side effects. Targeted drug delivery, chemotherapy, tumour imaging, photodynamic therapy and other uses were included in this novel field. Therefore, the studies and applications of biomaterials for anticancer drugs are a challenging and useful area for developing safer medicines with increased treatment efficacy [1–5]. Figure 1 revealed the different types of cancer therapeutics.

2 Oral Chemotherapy

Oral chemotherapy is an important and useful technique in current century medicine, because it is used to avoid the side effects of chemotherapy and improve the quality of life of the patients. This type of technique is also used to reduce the huge medical expenses and helpful for the patients to take medicines in home. This oral chemotherapy is beneficial for cancer patients in their last stage, because they were too weak to withstand harsh medical treatment. Unfortunately, most anticancer drugs (e.g. paclitaxel) are not orally bioavailable. That is they are not absorbable in the gastrointestinal (GI) tract. The paclitaxel was found to be bioavailability is less

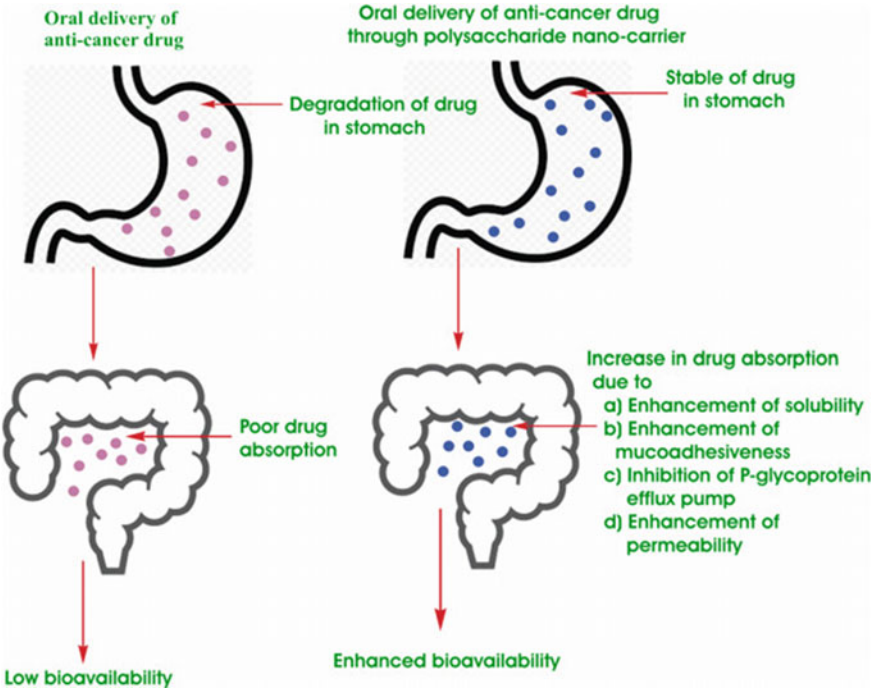


Fig. 2 Enhancement of drug absorption through polysaccharide nanocarriers

than 1% [6–9]. Therefore, most attention is focused on biomaterial included nanotechnology for anticancer drugs. Figure 2 showed the oral delivery of anticancer drug adsorption through nanocarriers and without nanocarrier. This figure illustrated the enhanced bioavailability of anticancer drug because of biomaterial carriers [10].

3 Biomaterial for Anticancer Drugs

Nanomedicine is the fast-growing and innovative field of nanotechnology to solve problems in medicine and it is also acts as a ideal solution for oral chemotherapy. The most widely used strategies in pharmaceutical nanotechnology for controlled and sustained and targeted drug delivery across the various physiological drug barriers for oral chemotherapy are nanoemulsions, prodrugs, dendrimers, liposomes, micelles, solid lipid nanoparticles and nanoparticles of biodegradable polymers [11–23].

3.1 Prodrugs

Prodrug strategies are mainly used to enhance the drug permeability, solubility and stability as well as tissue specificity for improving oral bioavailability of the parent drug [24, 25]. Capecitabine (Xeloda®), which is the first clinically successful prodrug for oral chemotherapy has a bioavailability of approximately 100% with a Cmax of 3.9 mg/L, Tmax of 1.5–2 h, and an area-under-the-curve (AUC) of 5.96 mg h/L. Another good example for oral chemotherapy prodrug is pracinostat and is a histone deacetylase inhibitor and having antineoplastic activity. These types of histone inhibitors behave as an emerging class of therapeutic drugs that enhances tumour cell cytostasis, differentiation and apoptosis in various hematologic and solid malignancies [26–29]. Figure 3 represents the targeting of paclitaxel (PTX) prodrugs to mitochondria for more effective activation by SO generated in mitochondria [30].

3.2 Nanoemulsions

To provide the oral bioavailability of poor water soluble system, nanoemulsions and self-emulsified drug delivery systems (SEDDS) have achieved much more attention. A system consists of two immiscible liquids in which one liquid is dispersed as droplets within the other liquid and formed a heterogeneous non-equilibric system called nanoemulsions [31]. By using improved drug solubilisation and protection against physicochemical and enzymatic degradation mechanisms, nanoemulsions have improved the oral bioavailability of poor water soluble drugs. A new class of supersaturable formulations based on SEDDS formulations (S-SEDDS) was emerged to the risk of surfactant side effects and achieve

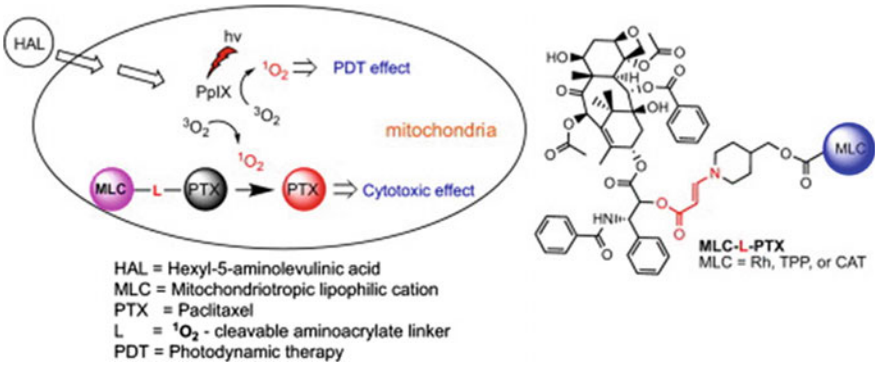


Fig. 3 Mitochondriotropic PTX prodrugs for a light-activatable combination of PDT and site-specific chemotherapy

rapid absorption of lipophilic drugs [32, 33]. Gao et al. have developed a typical SEDDS mixed with hydroxypropylmethyl cellulose for the oral delivery of paclitaxel and it showed a 4-fold higher bioavailability of the anticancer drug that when formulated as Taxol®. Several studies were reported for the formulations of nanoemulsions to enhance the bioavailability of oral anticancer drugs like BLM-SNEDDS, 9-Nitrocamptothecin (9-NC), colchicines formulations, etc. [34–36]. All studies were confirmed that nanoemulsions are behave as a promising and beneficial bio-oral anticancer drugs for the safe and effective delivery of poor oral bioavailability drugs with potential for application to human therapy. Figure 4 gives more idea about the droplet formation in water in oil (W/O) and oil in water (O/W) nanoemulsions and its formation mechanism and drug delivery applications [37].

3.3 *Dendrimers*

Dendrimers are monodispersed and hyperbranched three-dimensional artificial new materials having tree-like structure. These are used as an effective tool for drug delivery applications. Dendrimers are commonly 10–20 nm in size and sit in between sizes of polymeric nanospheres and liposomes. It follows two potential mechanisms; the first one, the dendrimer alters the barrier function of the intestinal epithelium, and thereby, it acts as a permeability enhancer of a co-administered drug and in the second one dendrimer-drug complex itself be moved across the intestinal epithelium. Through this way, polymers have been achieved more attention to potential delivery systems and which act as cross cell barriers at sufficient rates by both transcellular and paracellular pathways. Polyamidoamine dendrimers are used as a potential oral drug carrier and which permeate across intestinal epithelial barriers. Doxorubicin, naproxen, propranolol and terfenadine are good examples and have been applied to be enhanced in Caco 2 cells by associated with PAMAM dendrimers. However, studies have shown some

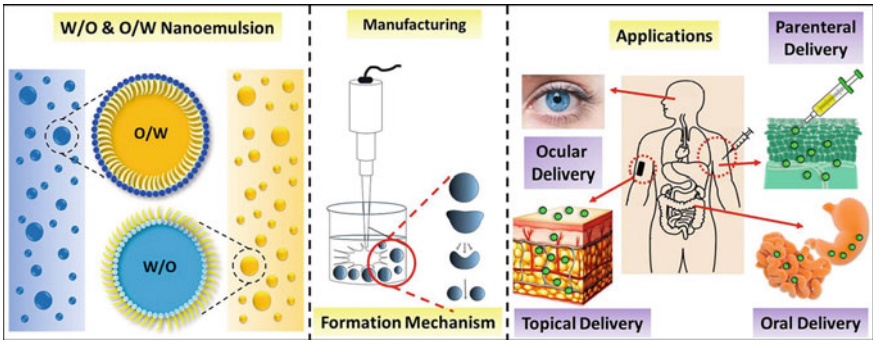


Fig. 4 Droplet distribution of water in oil and oil in water nanoemulsions and its destabilisation mechanisms and drug delivery applications

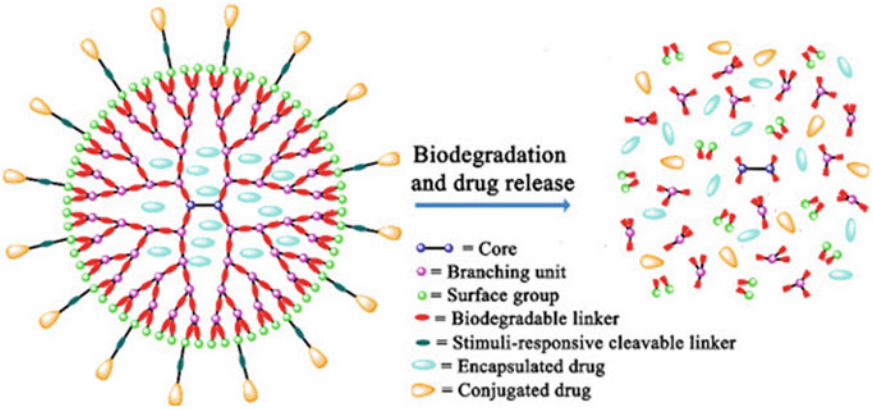


Fig. 5 Biodegradable drug delivery of dendrimers

drawbacks by using dendrimers for drug delivery because there is no direct evidence of dendrimer permeability after oral administration was reported [38–46]. Figure 5 showed an image of biodegradable drug delivery of dendrimers [47].

3.4 Micelles

Micelle is formed by the aggregation of surfactant molecules dispersed in a liquid colloid. Self-assemblies of amphiphilic macromolecules play a major role for the formation of polymeric micelles and which act as vehicles for the oral delivery of poorly water soluble drugs. It enhances the solubility and oral bioavailability of drugs. Polymeric micelles as carriers for paclitaxel (PTX) have been achieved better and remarkable results in the bioavailability of drug delivery. More studies were reported in the bioavailability of drug delivery by using polymeric micelles like micellar shell-forming poly(ethylene glycol) (PEG) block and a core-forming poly(2-(4-vinylbenzyloxy)-N,N-diethylnicotinamide) (P(VBODENA)) block, N-deoxycholic acid-N, O-hydroxyethyl chitosan (DHC)-based micellar system of paclitaxel (PTX), radiolabeled monomethylether poly(ethyleneglycol)750–poly (caprolactone-co-trimethylene carbonate) (mmePEG750P(CL-co-TMC)) micelles, etc. In short, polymeric micelles for oral drug delivery are still a novel, innovative and new system, and also few reports were reported in this area. However, we have sure about that these polymeric micelles would be a good entity for the efficient administration of anticancer drugs [48–53]. Figure 6 showed the formation of polymer micelles and its in vivo and in vitro dug delivery application scheme [54].

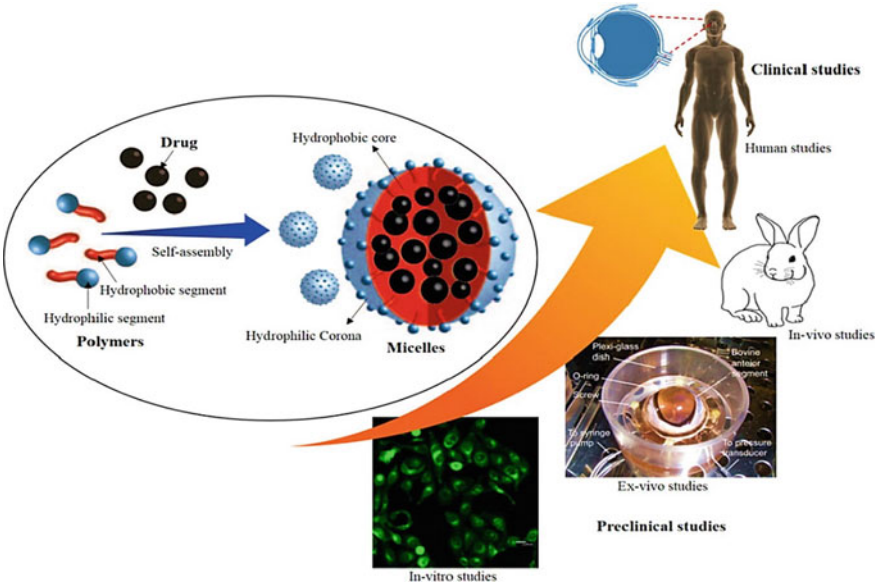


Fig. 6 Polymeric micelles used for the bioavailability of ocular drug delivery system

3.5 *Liposomes*

Closed spherical vesicles consisting of a lipid bilayer that encapsulates an aqueous phase in which drugs can be stored are called liposomes. But at the present, orally administered liposomes for cancer chemotherapy are very rare. Few studies have been reported in the area of liposomal drug delivery for cancer treatment. Ryan et al. reported the toxicities of combined liposomal doxorubicin (Doxil) and topotecan and also to determine a regimen for future phase II testing in ovarian cancer. Moutardier et al. encapsulated various anticancer drugs such as 5-fluorouracil (5-FU) and methotrexate (MTX) into polymeric particles (liposomes with polymeric cores (LSP)) and reported a slight increase of their bioavailability by the oral route. Sun et al. have been reported the bioavailability of TFu-loaded liposomes was higher than the suspension after oral administration and also the absolute bioavailability of TFu suspension and TFu-loaded liposomes was 39.23 and 78.05%, respectively [55–57]. The following Fig. 7 revealed the liposomal drug delivery of anticancer chemotherapeutics for the treatment of glioblastoma [58].

3.6 *Solid Lipid Nanoparticles*

In the current century, lipophilic drugs through selective lymphatic uptake have been chosen as a very attractive candidate as carriers for oral drug delivery systems

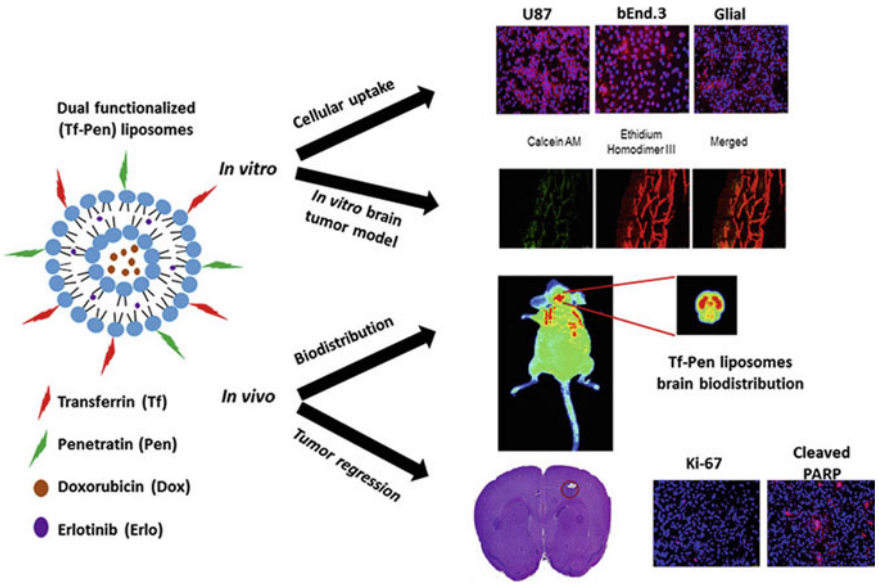


Fig. 7 Dual functionalised liposomes for efficient co-delivery of anticancer chemotherapeutics

because of their biocompatibility, physiochemical diversity and ability to enhance oral bioavailability of poorly water soluble properties. Solid lipid nanoparticles are originated from lipids and are behave as solid at room temperature. This solid lipid nanoparticle is a safe and effective alternative for conventional polymeric nanoparticles. For the enhancement of oral absorption of Tfu, Liu et al. developed and evaluated the potential novel lipid-based drug delivery system based on N3-O-toluyl-fluorouracil (TFu) loaded cationic solid lipid nanoparticles (TFu-SLNs). Another type cationic TFu-SLNs were used to enhance the GI absorption of TFu by oral administration and improve about 2-fold of relative bioavailability comparing to TFu suspensions [59–61]. Figure 8 represents the advantage and structure of solid lipid nanoparticles for drug delivery system [62].

3.7 Nanoparticles of Biodegradable Polymers

Nowadays polymeric nanoparticles have achieved significant therapeutic potential for cancer treatment through oral drug delivery system. Promotion of drug permeability across the mucosal membrane will be an adequate strategy for oral chemotherapy and is promised through the usage of biodegradable polymeric nanoparticles. Another important advantage of these types of polymeric nanoparticles is the controlled and sustained release of drugs. These biodegradable nanoparticles have been widely used in nanoparticle-based drug delivery systems

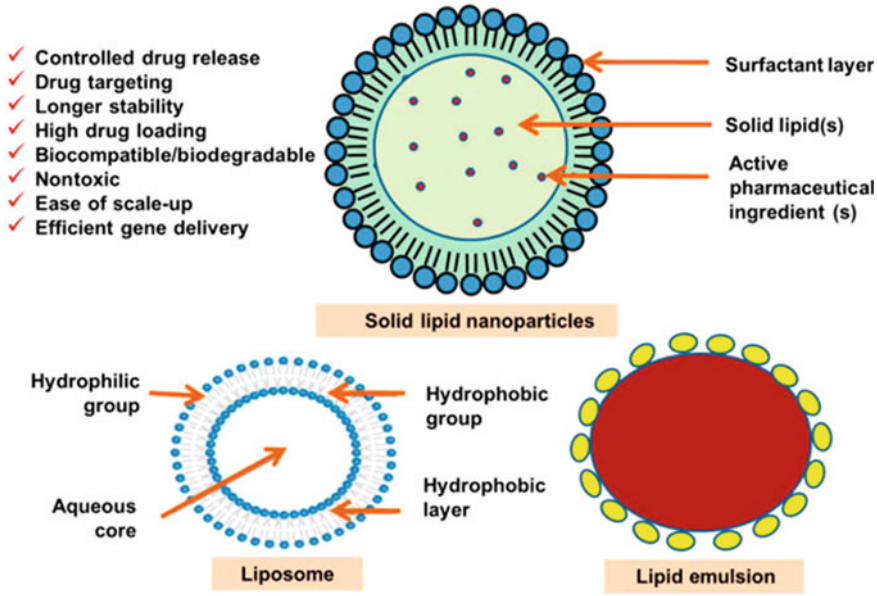


Fig. 8 Solid lipid nanoparticles for drug delivery system

for oral chemotherapy. The most important advantage of these type of biodegradable polymeric nanoparticles is which can be easily eliminated from the body after fulfilling their task as a drug carrier. In the initial stage, researchers have been used polymeric nanoparticles-based poly (lactic acid) (PLA), poly (lactic-co-glycolic acid) (PLGA), poly (caprolactone) (PCL), etc. But it faced some problems such as non-friendly approach to hydrophilic drugs like peptide, proteins, slow drug release because of high mechanical strength and hard to conjugating targeting ligands. Later this problem was solved by using two different methods: one is to coat the nanoparticles by using hydrophilic polymer such as PEG, Chitosan and TPGS and the other is to use the hydrophilic element incorporated copolymers in the hydrophobic chains of the polymers. For example, incorporation of hydrophilic TPGS into hydrophobic chains of PLA to form PLA-TPGS strategy is a novel and good example for biodegradable drug delivery. Therefore, nanoparticles of poly (lactide)/vitamin E TPGS (PLA-TPGS) are used for controlled and sustained release of paclitaxel and docetaxel. More researchers were evaluated the feasibility and efficiency of polymeric nanoparticles to increase the oral bioavailability of anticancer drugs. It was also reported that oral bioavailability of paclitaxel in nanoparticles is 70% for PTX-NP2, 40% for PTX-NP6 and 16% for PTX-NP10. Cyclodextrins are another important one and the combination of cyclodextrin-poly (anhydride) nanoparticles was about 80%, and therefore, we can say that combination of bioadhesive and inhibitory properties of these nanoparticles lead bioavailability and biodegradability of anticancer drug [11, 12, 17, 18, 63–70].

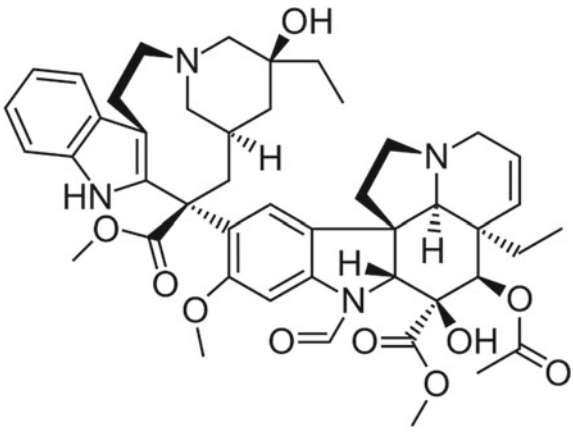
4 Natural Products as Anticancer Drugs

The biological diversity of the marine environment is immeasurable and therefore is an extraordinary resource for the discovery of new anticancer drugs. Cancer is the most severe worldwide health problem during this era. It is a serious disease characterised by uncontrolled continuous cell multiplication within the body, which results in the formation of malignant tumours, which has the potential to be metastatic. There is a great and steady demand for treatments to cure and prevent this life-threatening disease. Scientific research community is drawing their interest towards naturally derived anticancerous compounds/anticancer drugs since they are easily available, and lower side effects compared to the existing cancer therapies such as radiotherapy, chemotherapy and chemical drugs. The natural antiseptic properties of plants make suitable them for the treatment of various diseases. Many plant species are already being used to cure or prevent cancer (Fig. 9). The most common example is the *Catharanthus roseus* and *Podophyllum peltatum* [71–73].

Vinyl alkaloids are a subset of drugs obtained from the Madagascar periwinkle plant. Figure 10 represents the structure of vinyl alkaloid. They are naturally

Fig. 9 Images of *Catharanthus roseus* and *Podophyllum peltatum*

Fig. 10 Structure of vinyl alkaloid



extracted from the pink periwinkle plant, *C. roseus* G. Don and have hypoglycemic as well as cytotoxic effects. Currently, they are used to treat high blood pressure and diabetics they are also important for being cancer fighters. The mechanisms behind the cytotoxicity of vinyl alkaloid is their interactions with tubulin and disruption of microtubule function, particularly of microtubules comprising the mitotic spindle apparatus, directly causing metaphase arrest. There are four major vinyl alkaloids in clinical use: VBL, VRL, VCR and VDS. VCR, VBL and VRL have been approved for use [74–77].

4.1 Curcumin-Based Materials for Drug Delivery

Curcumin(1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also called diferuloylmethane, is an important polyphenol obtained from the rhizome of Curcumin and other *Curcuma* spp. Because of its excellent antimicrobial, anti-cancer, antifungal, antimutagenic and anti-inflammetry properties, they are widely used as a medicinal material from ancient time onwards (Fig. 11).

Curcumin loaded nanoparticles are considered as more efficient antimicrobial agent than the Curcumin itself. However, the destabilisation in excessive heat and poor water solubility are the main limitations of Curcumin. Samrot et al. reported the synthesis of Curcumin loaded chitsan for drug delivery [78, 79]. Curcumin is highly unstable in acidic pH of the stomach and degraded at alkaline pH before reaching the blood and other constituents might be metabolised by the liver. Nanocarriers applying to curcumin will carry optimum amount of the drug to their

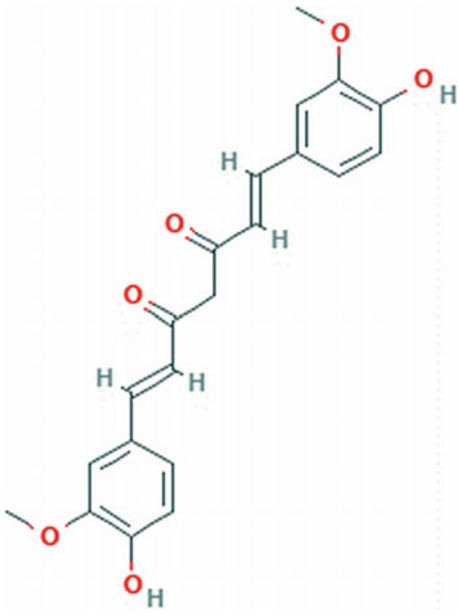


Fig. 11 Structure of curcumin

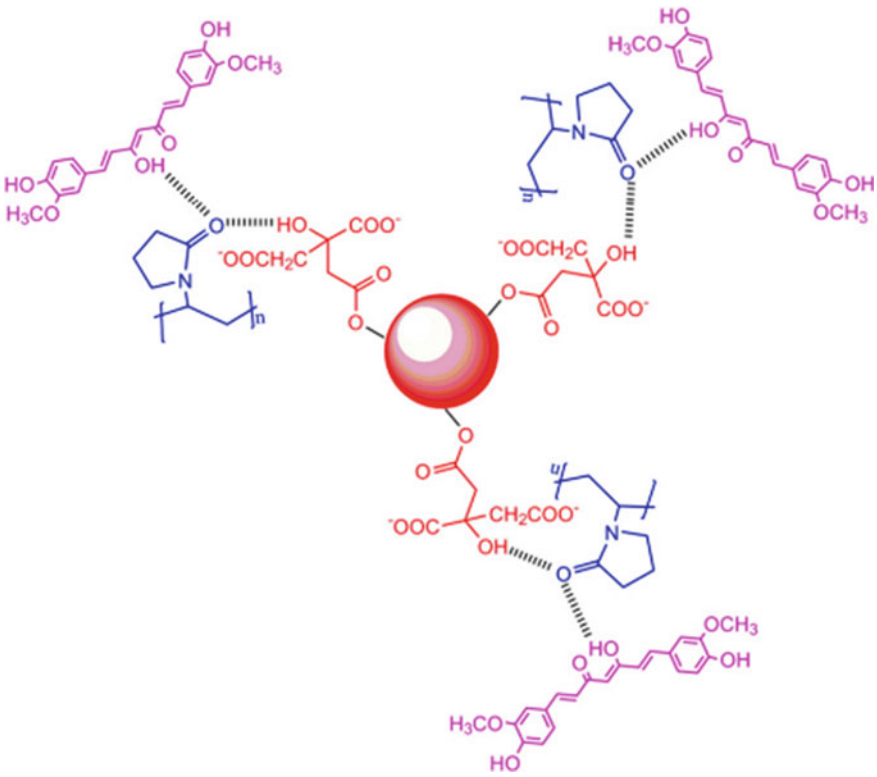


Fig. 12 Possible conjugation with polyvinyl pyrrolidone with curcumin and gold nanoparticles

site of action bypassing all the barriers such as acidic pH of stomach, liver metabolism and increase the prolonged circulation of the drug into the blood due to their small size.

Gold nanoparticles (AuNPs) are used extensively in various biomedical fields as biosensors, drug delivery, and immunoassays, etc. gold nanoparticles are easy to synthesis, higher surface area and biocompatibility, so they can also be considered as a good candidate for drug delivery applications.

Gangwar et al. reported the bioavailability of curcumin with PVP capped gold nanoparticles; they have found that the conjugation shows increased bioavailability. Figure 12 shows the possible conjugation with polyvinyl pyrrolidone with curcumin and gold nanoparticles. The morphology of the prepared conjugate was core-shell structure with gold nanoparticle as core surrounded by curcumin conjugated PVP as shell. PVP enhances the hydrophilicity to the curcumin molecules required for its bioavailability [80]. In short, there are lot of studies were going on different biomaterials for anticancer drug delivery with enhanced bioavailability and biodegradability. These all research will be a promising one for future medicinal development and through this way better cancer treatment.

5 Conclusion

Drug design and drug formulation are a great challenge in cancer treatment, because the conventional chemotherapy technique faced more drawbacks. Pharmaceutical nanotechnologies based on biomaterials have played a major role in cancer nanotechnology or nanomedicine and drug delivery. This is achieved by formulating the drugs in the various nanocarriers, which include prodrugs, nanoemulsions, dendrimers, micelles, liposomes, solid lipid nanoparticles and nanoparticles of biodegradable polymers. These newer materials as drugs help the slow and sustained release of drugs and enhance the bioavailability and biodegradability of drugs. Thus, "chemotherapy at home" can be realised soon, and also patient life would be extended for long period with the enhancement of bioavailability of drugs up to 95%.

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Chapter 7
Quantum Dots in Drug Delivery

Durgadas Cherukaraveedu

Abstract The QDs based drug delivery systems offer enormous opportunities in future for the theranostic approaches and will be important NPs systems for nanomedicine. Despite their extraordinary features for biomedical applications, more studies have to be completed for a clinically applicable DDS. The major concerns currently facing are the large scale synthesis of monodisperse, stable colloids with no long-term cytotoxicity and genotoxicity (Hanada et al. in Int J Mol Sci 14:1323–1334, 2013 [1]; Tu et al. in ACS Med Chem Lett 2:285–288, 2011 [2]). The interdisciplinary merge of various disciplines will certainly can impart strong developments in the QDs based nanomedicine (Erogbogbo et al. in ACS Nano 2:873–878, [3]). More synthesis, evaluation standards need to be proposed for a universally acceptable synthesis, characterization protocols to unify various researchers' skills in the area. The bright future of nanomedicine can definitely address the unmet clinical concerns in cancer drug delivery by exploring the brightly emitting quantum dots.

1 Introduction

The concept of using chemicals as drugs against diseases have begun in the early 1990s and the term chemotherapy gained much attention thereafter [4]. Nanomedicine is the new interdisciplinary area which includes various disciplines of science and bioengineering techniques. This discipline uses the targeted nanoparticle systems mostly for cancer therapy. This area primarily focuses on the development of nanoparticles(less than 100 nm) which can be from biocompatible metals, metal oxides, polymers, and also from biomolecules [5]. The nanoparticle-based sensing and imaging have made tremendous contribution in the

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area of nanomedicine which was difficult to achieve by the conventional techniques and materials available. The nanoparticle-based imaging systems have entered the sophisticated clinical imaging systems like Magnetic Resonance Imaging (MRI).

Positron Emission Tomography (PET), Computed Tomography (CT), Single Photon Emission Computed Tomography (SPECT). There are excellent reviews available about the application of these materials in various fields of nanomedicine [5–9].

This chapter is mostly dedicated for the discussion of the developments and future of the fluorescent semiconductor nanocrystals also called Quantum Dots (QDs) for cancer drug delivery applications. An overview about the structure and synthesis are given to provide a basic understanding about the QDs. This chapter also discusses the highly promising noble metal quantum dots, emerging carbon and graphene QDs. As we are moving forwards with the bioengineered QDs for drug delivery applications, it would be interesting to see a brief description about the physical characteristics of these materials which defines them as QDs.

The QDs are the most interesting classes of the nanoparticles due to their photostability, good quantum yields and stability against various engineering manipulations for the desired applications [10, 11]. The early uses of the QDs were reported during the late 1990s and early 2000s with the ground breaking approaches of the engineering of fluorescent QDs as cellular imaging probes [12–19]. This foundation of the QDs application as biological imaging probes encouraged the researchers to explore the QDs as cargo vehicles for cancer drug delivery and diagnostic probes, which in the later periods referred to as 'theranostics' [20–22].

The semiconductor materials possess characteristic electrical and optical properties when compared to metals-conductors and insulators. When the size of metals were reduced to nanosize regimes it was observed that the metals can behave as semiconductor with substantial changes in their electrical and optical characteristics [23]. The QDs are composed of metal clusters with semiconductor features and with enhanced optical and electrical properties.

As the size of the materials brigs down to nanosize the electric band gaps change and this directly influences the charge transfer band gaps (Fig. 1). The semiconductor properties are largely classified based on the Fermi levels exist in each of these materials. In a simple explanation, the QDs follows the elementary quantum mechanics principles called 'particle in a box' and are referred to as the materials with electrons are in "quantum confinements". The readers are further recommended to refer the book/articles [24–26] for the detailed understanding of the physical definitions for QDs.

The nanotechnology-based cancer drug delivery gained much attention as it could provide substantial improvements in the conventional drug delivery challenges [27]. In the conventional drug delivery systems, the drugs are being delivered as non-specific and require high dose due to poor bioavailability. Moreover, the low specificity and high dosage creates side effects on the patients and the therapy becomes expensive in case of monoclonal antibody-based therapeutics [8, 28]. There were various approaches followed for the QDs based drug delivery systems; bioconjugation, loading drugs in the liposomes, polymer shells bearing

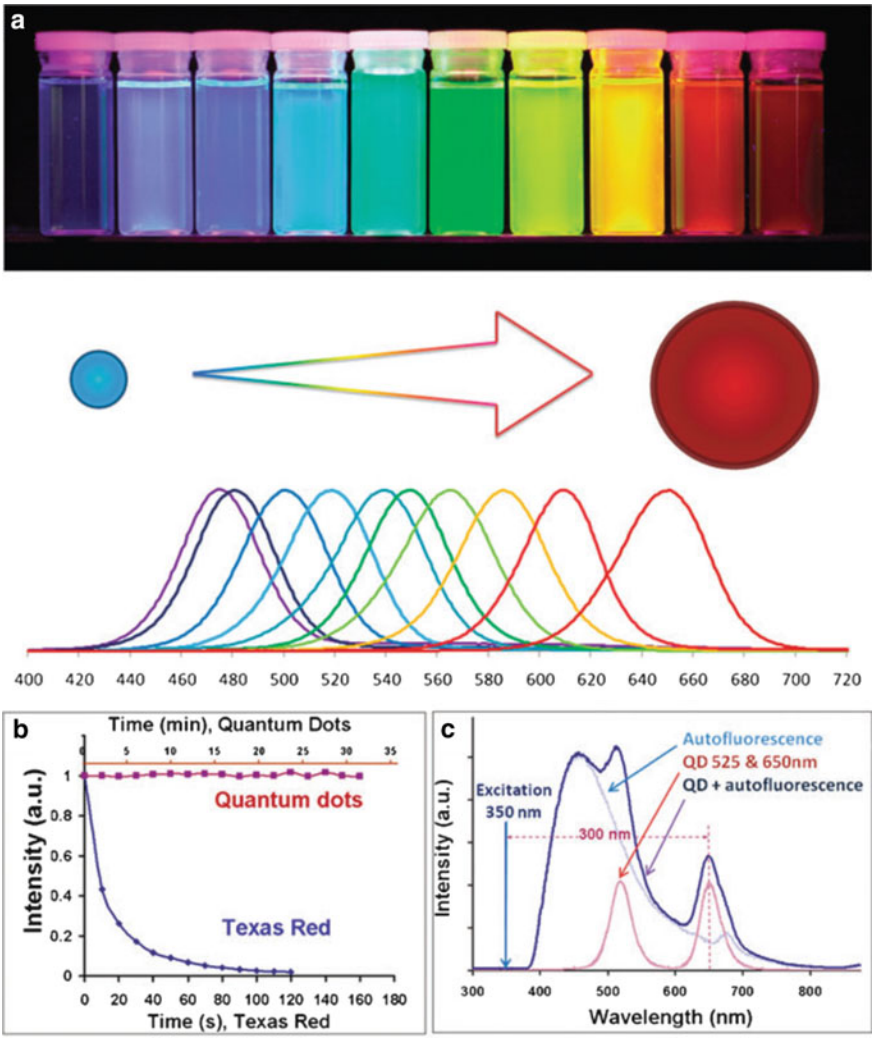


Fig. 1 Photo-physical properties of QD probes. The size tunable and tunable fluorescence emission from QDs **a** the photostability of QDs studied against an organic fluorophore, **b** the ability of QDs to avoid tissue autofluorescence, **c** makes them unique for biomedical imaging and therapeutic applications. Requires permission from Elsevier., Curr. Opin. Biotechnol., 2005, 16, 63–72

QDs and multifunctionalised nanoparticle systems. Before going in the details of QDs based drug delivery systems (DDS) it may be interesting to see the brief discussion on various QDs and approaches for their biofunctionalization.

As defined above the QDs are semiconductor fluorescent nanocrystals in the size of 2–10 nm atomic clusters composed of 200–1000 atoms which are usually

composed of heavy metals like cadmium (Cd), zinc (Zn), copper (Cu), indium (In), selenium (Se), tellurium (Te) or their combinations and oxides. The earliest known QDs were based on zinc sulphides (ZnS), zincoxides (ZnO), cadmium sulphides (CdS), cadmium selenide (CdSe) and copper selenide (CuSe). The new classes of quantum dots from carbon origin, carbon dots, and grapheme dots are also potential candidates for biomedical applications. Though many of these materials are not directly biocompatible materials for in vivo applications, an appropriately bio-engineered QDs can effectively deliver drugs in the desired site of action as bio-conjugated QDs device [29]. The various approaches for QDs engineering for cellular delivery, active cell targeting, passive tumor drug delivery, and future perspectives are discussed below. The noble metal based fluorescent clusters (gold-Au and silver-Ag) are also an attractive QDs that can also contribute more biocompatible QD like properties for biomedical applications [30–32].

2 An Overview About the Structure and Synthesis of QDs

As explained above, the QDs generally are heavy metals, their combinations or oxides which are at the size of less than 10 nm resulting the phenomenon referred as 'quantum confinements' [33]. Mostly they are from the group II–VI, IV–VI, and III–V(e.g., cadmium, zinc, and selenide, Indium, etc.). The quantum confinements are responsible for the bright photoluminescence properties. The core quantum dots optical properties may get affected by the surface defects or by electronic interactions with the surroundings [34]. To minimize and improve the qualities of the QDs the core may be further coated with another semiconducting layer [35, 36]. So based on core/shell structure there are two types of quantum dots called type I and type II. The well-studied and explored (CdSe)ZnS core-shell quantum dots are termed as type 1 QDs as here the bandgap of the core (CdSe) will be smaller than the shell(ZnS). In type II, the core will have higher band gap than the shell. For example, the CdTe/CdSe core/shell quantums dots are called type II and gained attention for biomedical imaging applications [37].

There are various physical and chemical methods followed for the synthesis and functionalization of the QDs. The detailed explanation is on the synthesis are beyond the scope of this chapter and the readers are advised to refer the articles and reviews dedicated for the synthesis and functionalization of QDs [34, 36, 38–40]. In most chemical methods the decomposition of precursor compounds were performed in high boiling solvents in presence of surface passivating/coordinating agents like tri-*n*-octylphos-phine oxide (TOPO). Additionally doping is another method to create wonderful luminescent materials for various applications [41]. Here a metal or more metals were doped with the QDs during the synthesis or after the synthesis using appropriate chemical methods [42]. The doping method can generate new materials with desired optical and physical properties [34, 42–45]. In most cases, there will be a strong coordinating organic ligand molecule as monolayer on the surface of the QDs.

Another class of QDs are generated from the noble metals (gold, silver, and platinum). They are referred to as noble metal quantum dots and are synthesized from gold or silver [32, 46]. The noble metals showed excellent photoluminescent properties when they were brought down to sub-nano size clusters formed by very few atomic clusters [30, 47]. The highly fluorescent clusters were synthesized by various chemical approaches and generally termed as noble metal quantum clusters [48–50]. These quantum clusters were highly biocompatible and were widely been explored for biosensing and imaging applications [51–53].

3 QDs Bioengineering Strategies

Though these surface passivation agent offers high stability for the semiconductor QDs, they are not dispersible in aqueous media. These colloids were then phase transferred to aqueous system for biomedical applications by various amphiphilic structures (liposomes, peptides, aminoacids, or some thiol containing bifunctional molecules). The details of the bioengineering of the QDs are followed here. There are various chemistries followed in the QDs engineering for biomedical applications. As these QDs are generally heavy metals, their oxide or combinations of metals, lacks poor water dispensability and high cellular toxicity [54]. In order to solve these issues, researchers followed modifying the surface of these systems without compromising the desired properties of the QDs. The most followed strategy is surface modification by hydrophilic coatings or exchanging the water-insoluble stabilizing agents of QDs with lipids, thiol ligands and water-soluble polymers like polyethylene glycols (PEGs) [10, 12–15, 18, 20, 55, 56].

General biofunctionalisation strategies are explained in Fig. 2. These methods enabled the large-scale synthesis and water dispersion of QDs for biomedical application and for bioconjugations. Two examples for such modifications are discussed below (Fig. 3 and Scheme 1).

Figure 4 shows the applications of appropriately functionalized QDs in the in vivo tumor imaging application in a tumor-bearing mice. The autofluorescence from the tissues are well resolved with the highly fluorescent and functionalized QDs emission. The cancer cell uptake was imaged with the antibody (PSMA) functionalized QDs.

4 Engineered QDs in Cancer Targeted Drug Delivery Applications

The small size, ability of engineered for multifunctionality, and photostability makes the QDs an attractive nanoparticle system for cancer drug delivery and simultaneous imaging. An example for such active targeted delivery is

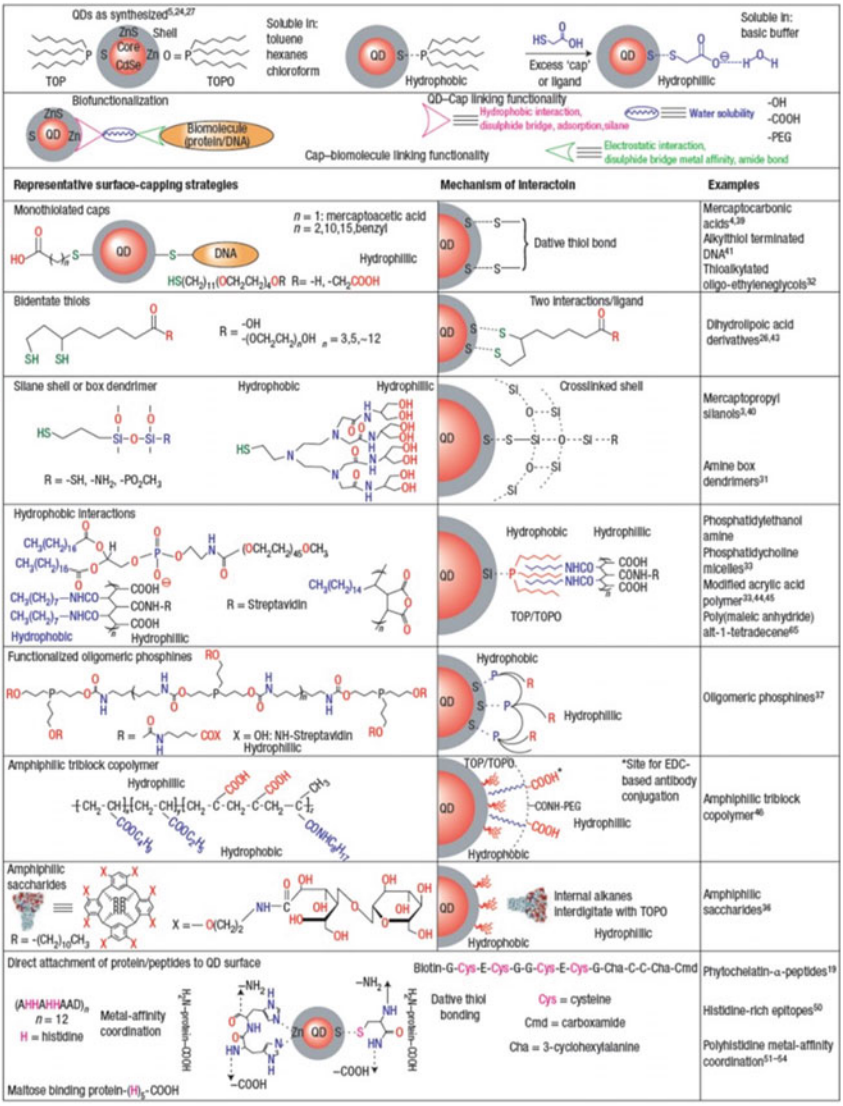


Fig. 2 The surface capping strategies, biofunctionalization, and water solubilization strategies are provided here. Most ligands were bifunctional molecules with thiol as one of the functional group which replaces the organic ligands TOP/TOPO from the surface of the QDs. *Nature Materials* volume 4, pages 435–446 (2005). Requires the copyright permission

demonstrated through the aptamer conjugated QDs with anticancer drug doxorubicin-loaded systems which enabled a FRET-based sensing of the intracellular drug delivery [20].

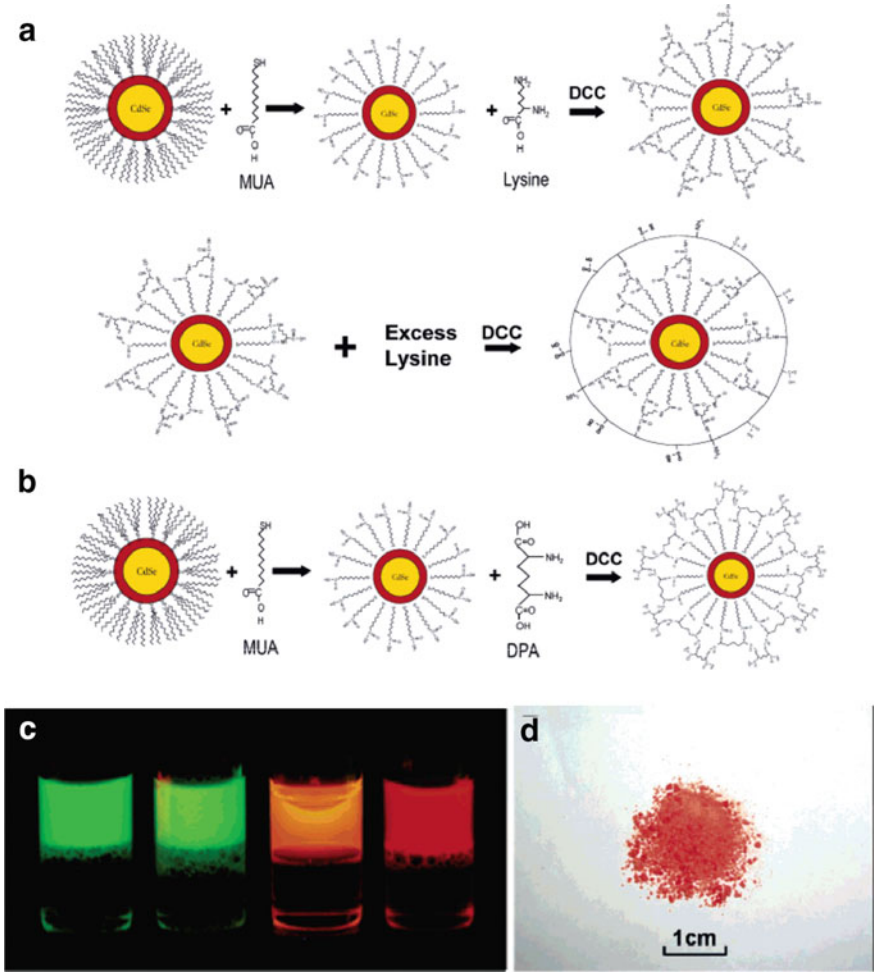
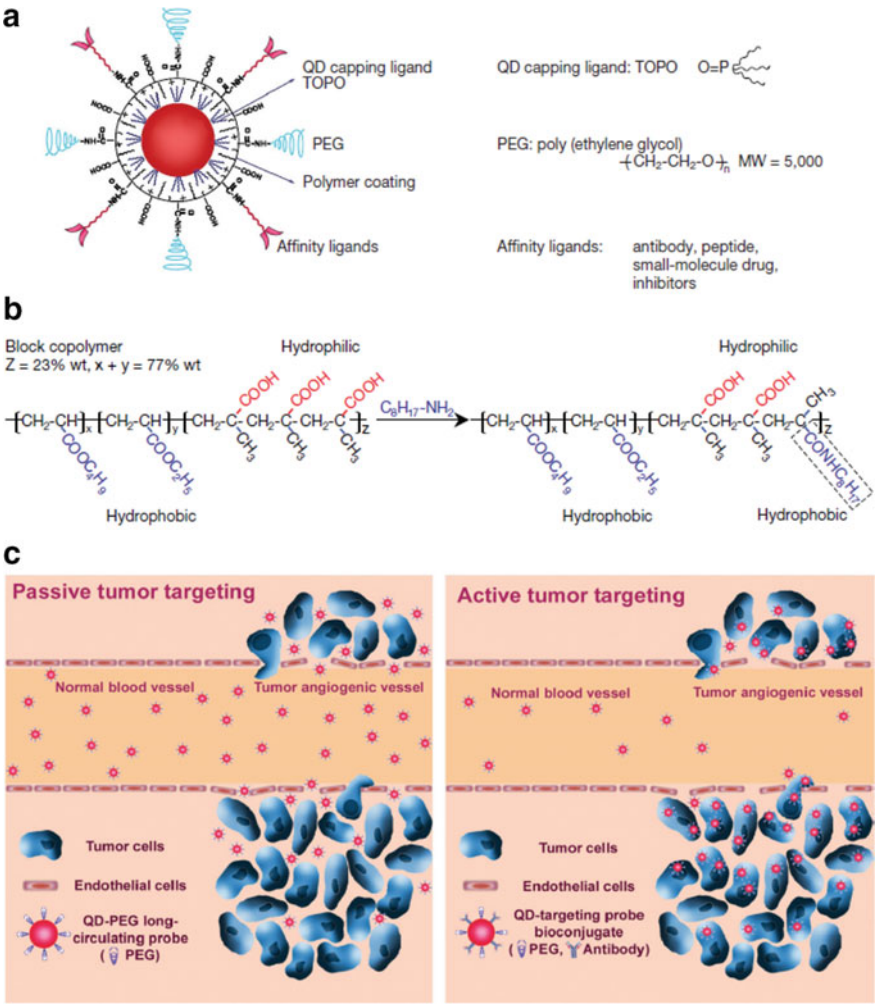


Fig. 3 The exchange of the ligands on the surface of the CdSe/ZnS core/shell QDs prepared having varying size and tunable fluorescence emission. The hydrophobic ligands on the QDs were exchanged to hydrophilic thiolligands by treating with mercaptoundecanoic acids (MUA) and then further cross linking with aminoacid lysine through the carbodiimide chemistry (**a** and **b**). Vials containing The LM-QDs are soluble in the water layer (top) after surface modification and cross-linking (**c**). This enabled the synthesis of large amount of LM-QDs (**d**). Reprinted with permission from (https://doi.org/10.1021/cm051393) Copyright (2006) American Chemical Society

In this study, the CdSe/ZnS core/shell quantum dots (QD490) were functionalized with A10-PSMA parameters (Fig. 5). This parameter has a binding site for the anti-cancer drug doxorubicin through its special sequences. Upon intercalation of the drug to the A10 PSMA both the fluorescence of the drug and the QDs quenches. As the QDs-Apta conjugate reaches a specific targeted cell delivery



Scheme 1 The scheme showing the preparation of water-soluble QDs (CdSe/Zns core/shell) from hydrophobic ligands coated QDs through a hydrophilic polymer ligand (**a** and **b**) which enabled the QDs for active and passive tumor targeting as illustrate (**c**). Requires copyright permission from Nature (Nature Biotechnology volume 22, pages 969–976 (2004)

through the aptamer sequences the drug releases in the cells, the fluorescence turns on by FRET and enabled the cellular delivery by fluorescence imaging.

Another example for the FRET-based anti-cancer drug delivery of the doxorubiscin with QDS-490 were shown by exploring the targeted delivery of the QDS conjugates by mucin-1 aptamer [57].

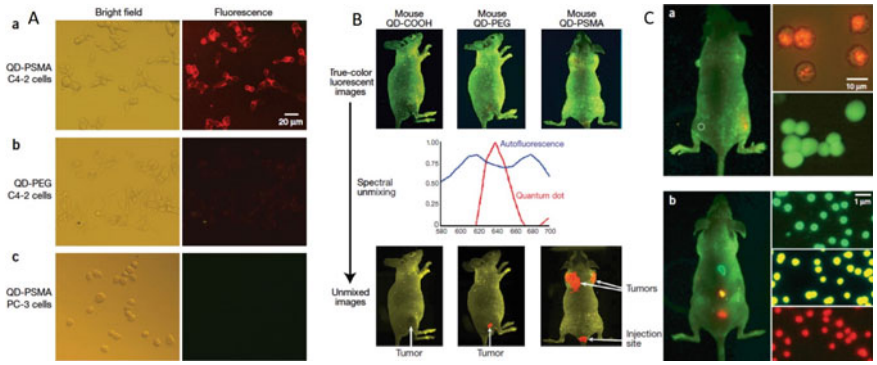


Fig. 4 Adapted from Nature Biotechnology. The QDs prepared by the above exchange method were further explored for antigen conjugated specific cell staining (A). The C4-2 cells were specifically imaged with prostate specific monoclonal antigen (PSMA) conjugated QDS against the control cells (b, no PSMA conjugation) and against PSMA lacking cells (c, PC-3 cells). These QDS were also used for tumor-specific imaging in vivo (B) and the microbeads of these QDs used for invivo multicolor imaging (C) in mice bearing tumor models. Requires copyright permission from Nature (Nature Biotechnology volume 22, pages 969–976 (2004)

The drugs were conjugated to the multifunctional QDs via a pH-sensitive hydrazone chemical linkage as shown in Fig. 6. The cell studies and further animal studies were used to demonstrate the efficacy of the system.

A polysaccharide-based nanogels with multifunctional optical imaging, targeting, and drug delivery were reported using the insitu formed CdSe QDs in a hydroxypropylcellulose (HPC)-poly(acrlicacid) (PAA) polymer network [58]. This gel enabled simultaneous imaging and high loading of an anti-cancer drug. The –OH groups of the HPC sequesters the cadmium ions and later forms fluorescent QDs of cdSe inside the gel. A model anti-cancer drug TMZ was loaded on the gel and were delivered to cells for cytotoxicity. The TMZ was tightly loaded due to the hydrogen bond formation between the –COOH and –OH groups of the polysaccharide gels with the amide bonds of the drug TMZ. A different approach were also reported for the anti-cancer drug delivery by exploring the biodegradable saccharide chitosan and biocompatible quantum dots ZnO [59]. The ZnO was generated by a hydrolysis method and was encapsulated in the chitosan. The ZnO provides both biocompatibility compared to the CdSe and CdSe/ZnS QDs and is an environmentally friendly QDs for the biomedical applications. The chitosan was modified with folic acid via carbodiimide chemistry and was then used for the encapsulation of the ZnO QDs via electrostatic interactions. The drug Dox was then loaded on the gel which showed nearly 75% loading. These prepared Qds-chitosan gels were then tested for the drug release profiles at various pH values (7.4 and 5.3). The ZnO QDs with blue emission encapsulated in biodegradable polymer system with Dox loaded showed initial rapid release followed by a controlled release pattern.

The active targeting with other than aptamers were reported using cell targeting ligand-like folic acids. The folate receptor-based drug delivery also gained much

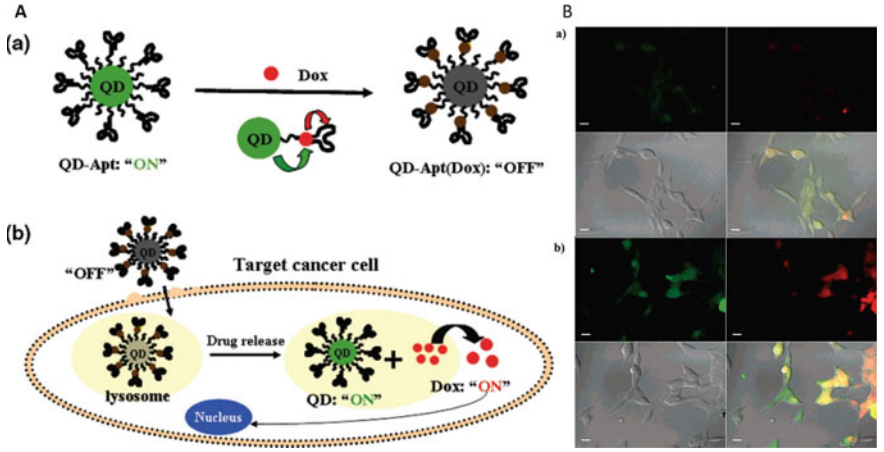


Fig. 5 Schematic representation of the QDs-Aptamer-Dox system for the FRET enabled sensing of the drug delivery (**A**). The aptamer A10 makes the QDs to selectively and specifically targets the PSMA expressing cancer cells. The confocal images of the cells treated with the QDs-Aptamer-Dox systems (**B**). The PSMA expressing LNCaP cells were treated with the conjugates are imaged after oh (**a**) and 1.5 h (**b**). The Dox is red and QDs are green. The lower right images are the merged images of the cells. Reprinted with permission from (https://doi.org/10.1021/nl071546n) Copyright (2007) American Chemical Society

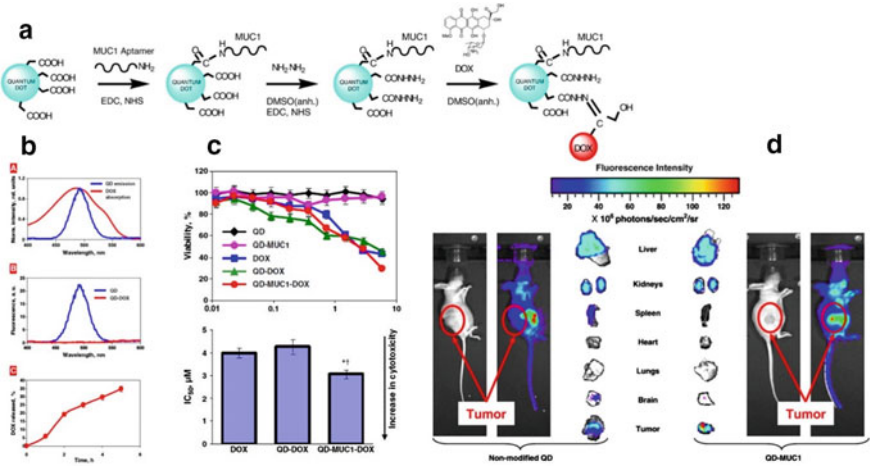


Fig. 6 **Adapted from Elsevier**. The schematic representation of the preparation of acid-sensitive drug conjugates on QDS modified with cell-specific aptamer mucin-1 (**a**). The FRET response of the QDs system tested after the Dox conjugation via hydrazine linkage (**b**). The cytotoxicity response of the cells before and after treating with the conjugates were tested in A2780/AD human ovarian cancer cells (**c**). The conjugates showed comparable toxicity with the free drug. The developed QDs-Dox-mucin-1 conjugates were then tested on an ovarian cancer model of mice (A2780/AD cells) (**d**). The images were taken after 24 h of injection. The intensity of the QDs fluorescence is mapped in organs removed the mice. The blue is lowest intensity and red is with highest intensity. Requires copyright permission from Elsevier https://doi.org/10.1016/j.jconrel.2011.02.015

attention due to the easiness of the method for preparing the conjugates with folic acid [60, 61]. The folate receptors were used in the cell-targeted delivery by blending a co-polymer of poly (lactide) with vitamin E, PLA-TPGS-COOH with PLA-TPGS. The PLA-TPGS-COOH were then conjugated to folic acid and the commercially available organic QDs were extracted by the PLA-TPGS. These systems were then appropriately characterized by surface analysis techniques and physicochemical properties were recorded. The QDS conjugates were then tested for cytotoxicity in cancer cell line MCF-7 and in normal cell line NIH 3T3. This study showed the possibilities of a folate targeted polymer blend containing QDS were able to deliver to cancer cells via targeted method [62].

In another approach, the ZnS QDs were doped with manganese were explored as folate conjugated targeted drug delivery systems. Here the carboxymethyl chitosan stabilized QDs with folic acid conjugation were loaded with anticancer drug 5-fluorouracil were prepared. These QDs drug delivery systems had a size of 130–150 nm and were used to study the drug delivery and simultaneous imaging in MCF-7, breast cancer cell lines [63]. A highly fluorescent ZnO QDs were reported for the simultaneous imaging and cancer drug delivery in cells. These QDs were prepared in non-aqueous method and later made water soluble by ligand exchange method. Thus prepared ZnO QDs were used as delivery plus traceable cargo to deliver anticancer drug doxorubicin. The QDs were initially functionalized with folic acid for cell targeting by carbodiimide chemistry and the drug doxorubicin was loaded based on the metal(Zn) drug coordination complex formation. Thus prepared systems were unstable in mildly acidic conditions like cancer cells. This enables the targeted drug delivery and imaging of the cells. A further advance win the ZnO-based acid-sensitive drug delivery system reported recently by using Poly (ethylene) glycol stabilized ZnO QDs with hyaluronic acid conjugation to target the CD44 a glycoprotein over expressing cancer cells. Here also the drug doxorubicin were loaded based on the metal-drug complexation, which were less stable under acidic conditions. These acid-sensitive QDS-drug conjugates were able to target the A549 cancer cells which overexpress the CD44 [64].

The targeted drug delivery by QDs is still an active and continuously progressing research topic in drug delivery systems. The nanoparticle toxicity is a big concern when we think about their application for nanomedicine. Other than the CdSe, ZnS or InP-based QDs the CuSe based QDs are also potential materials for biomedical applications. The anti-cancer drug delivery with CuSe/ZnS/silica (CSS) core/shell/shell QDs and their invitro biocompatibility by cytotoxicity and blood compatibility was also reported [65].

The CSS were synthesized and functionalized with amino terminal silica shell for bioconjugations. The anti-cancer drug methotrexate was conjugated to the CSS and were delivered to cancer cell lines (HepG2 and C 6 glioma cancer cells) Fig. 7.

A very recent study explored the conjugation of the carboxy terminated commercially available CdSe/ZnS QDs with tyrosine kinase inhibitor drug Erlotinib hydrochloride via an ester bond. These QD-drug conjugates were tested for their cytotoxicity by drug release by the esterase enzyme. The studies were performed in non-small cell lung cancer (NSCLC). The cadmium release toxicity was also used

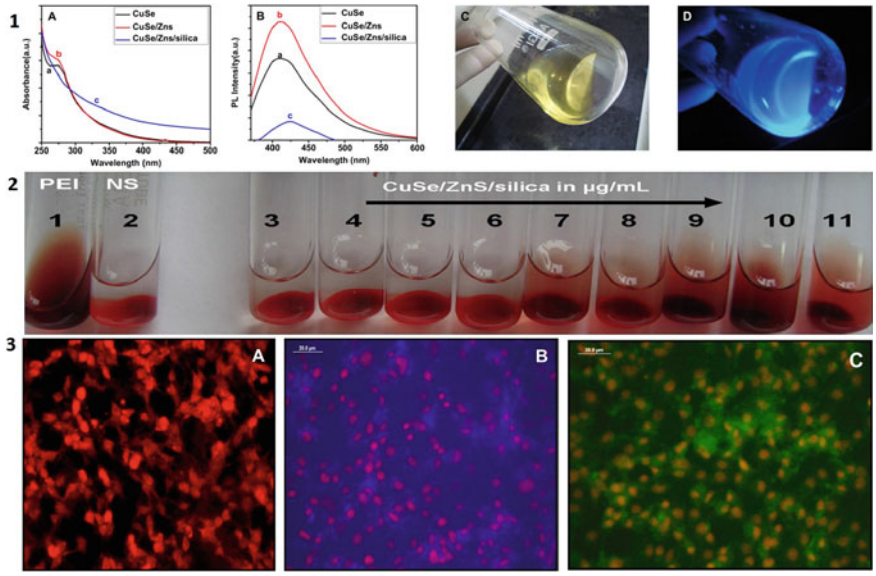


Fig. 7 The biocompatibility studies and drug delivery with CuSe/Zns/silica CSS. The panel 1 shows the spectroscopic analysis (1**A** and 1**B**) of the CSS and their visual images under ambient (1C) and UV excitation (1D). The panel 2 shows the blood compatibility studies by red blood cell lysis caused by varying concentrations of CSS against positive control (PEI) and negative control (Normal saline). The panel 3 shows the cell delivery of methotrexate conjugated CSS, the nuclie imaging (3**A**—red, PI staining), QDS fluorescence (blue-3**B**) and the methotrexate fluorescence (green-3**C**) Adapted from Biomaterials 33 (2012) 6420e6429, requires copyright permission

to measure the efficacy of the QDs and the drug release were further studied in tumor spheroids generated from the NSCLC cell lines (A549) [66].

The QDs were also able to work as 'theranostics' as described above due to their inherent high fluorescence property in cells and tissues. These are highly photostable and can be tuned without the interference from the autofluorescence from tissues. The QD-hybrids were also able to work as multiimaging probes when used together with other contrast agents. In one such example, the micellar encapsulated QDs with magnetic nanoparticles (MNPs) were able to use as fluorescent probe and magnetic resonance imaging (MRI) contrast agents. The MNPs and the QDS were simultaneous encapsulated in a PEG modified lipid to form a micellar hybrid system.

This multihybrid nanoparticle (MHN) probe were tested for the simultaneous fluorescence imaging and MRI imaging in cancer cells MDA-MB-435 tumors by conjugating the MHN with a peptide(F3) which targets the cell surface of endothelial cells in tumor blood vessels and to cancer tissues, Fig. 8. The MHN-F3 probe were later explored as simultaneous MRI imaging and NIR fluorescence imaging of an in vivo mouse model bearing the MNA-MB-435 tumor. These MHN were also able to deliver the drug Dox to cancer cells [67].

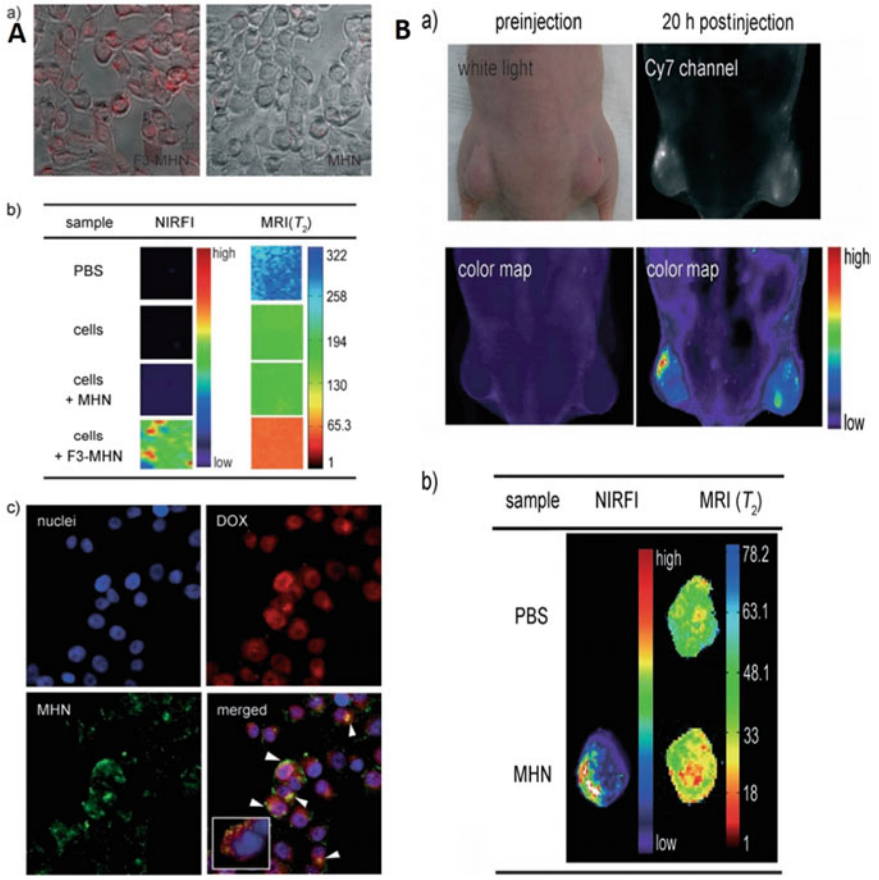


Fig. 8 Cell targeting studies with MHN (**A**). **a** Intracellular delivery of F3-conjugated micellar hybridnanoparticles (F3-MHNs) into MDA-MB-435 human carcinoma cells. The F3-MHN particles and the MHN control particles appear red in the images. After incubation for 2 h with the cells, the F3-MHN particles were strongly associated with the cells, whereas the control MHN nanoparticles without the F3 ligand did not penetrate. **Multimodal imaging invivo by MHN (B)**. **a** NIR fluorescence images showing the passive accumulation of MHNs containing QDs (emission at 800 nm, MHN(800)) in a mouse with MDA-MB-435 tumors. The mouse was imaged preinjection and 20 h postinjection (injection dose: 10 mg/kg). **b** Imagetable describing the results of multimodal imaging (by MRI and NIR fluorescence) of the tumor harvested from the mouse in (**a**). PBS: a control in which a mouse with a tumor was injected with phosphate buffered saline; NIRFI: near-infrared fluorescence image; MRI(T2): T2 values from T2-weighted MRI Adapted image: Angew. Chem. Int. Ed. 2008, 47, 7284–72

The QDs based DDS offers greater opportunities to design and develop multi-functional theranostic systems. In other way, the QDs offer a platform to prepare a system which can act as a both therapeutic delivery system and a diagnostic agent (Theranostic). A few examples of such systems are explained here. A QD encapsulated liposome were developed for simultaneous fluorescence imaging and drug

delivery system by incorporating a PEG-coated QD inside lipid vesicle [68]. This multifunctional system was further tested for the efficacy in the 3D cell spheroids of cancer cells and in animal imaging. Another liposome-encapsulated theranostic system were also developed for the co delivery of an anti-cancer drug docetaxel and QDs [69]. This system was tested for targeted and non-targeted delivery approaches and was found to be an efficient theranostic system for the cancer imaging and anticancer drug delivery. The readers are recommended to see the review on QDs to understand the general basics of the QDs developments towards the imaging and drug delivery systems [70]. The concept of bringing various nanoparticle properties under one hybrid system to create a delivery system gained much attention since 2000s. Researchers tried to combine the well characterized nanoparticles like carbon nanotubes (CNTs), QDs, and super paramagnetic iron oxide nanoparticles (SPION) in one system for magnetically guided multiimaging drug delivery systems [71].

The hybrid DDS designed by encapsulation of SPIONs (poly (sodium 4-styrenesulfonate) coated-PSS) the hollow cavities of CNTs and the exterior were coated with silica coated Qds and transferrin(Tfr) receptor for targeted drug delivery to cancer cells. As these hybrid DDS is magnetically active, the delivery of encapsulated (the silica shells provide efficient encapsulation of drug) anticancer drug doxorubicin was effectively directed to HeLa cells (Fig. 9).

Recently an efficient theranostic was developed by incorporating the magnetic nanoparticles and QDs in a polymeric vesicle [72].

Here the researchers successfully fabricated a hybrid system by co encapsulating the SPIONs, manganese dopped Zns QDs (Mn:ZnS) and an anti-cancer drug bisulfan into the poly(lactic-*co*-glycolic acid) (PLGA) vesicles. This multifunctional theranostic offers fluorescence imaging possibilities by the QDs and T2-weighted image by magnetic resonance imaging (MRI) and delivers the anti-cancer drug into the cancer tissues (Fig. 10).

The noble metal Qds also gained attention in the imaging and therapy. A multifunctional NIR emitting Au cluster based doxorubicin delivery and imaging were reported for S180 tumor-bearing mice [73]. Later the gold clusters were further conjugated to cyclic RGD (cRGD) as a targeted drug delivery systems to tumor tissues [74]. Recently the gold clusters were functionalized with cyclic RGD (cRGD) were used for radiotherapy in cancer [75].

As the inorganic heavy metal semiconductor-based and noble metal based QDs as multifunctional DDS systems are progressing, there is a parallel approach by the exploration of carbon-based QDs (graphene QDs-GQDs and carbon dots-C-dots) are also gaining much attention in recent years due to their low toxicity compared to the metal based QDs [76, 77]. Also, the silicon QDs based imaging and DDS are also an attractive approach for the QDs based DDS [1, 2, 78, 79]. The silicon QDs were excellent fluorescent labels and biocompatible systems for future drug delivery applications based on QDs [3].

In an approach to develop multifunctional theranostic DDS based on GQDs, the GQDs were capped with a magnetic mesoprous silica nanoparticles and the anti-cancer drug doxorubicin was tested for the external nonharmful Near Infrared

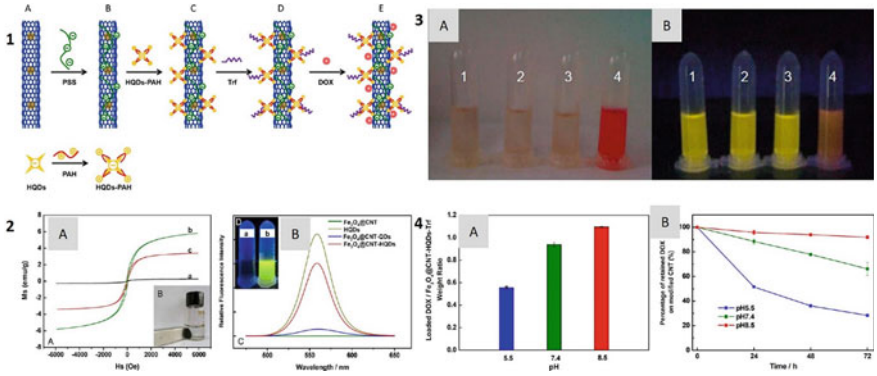


Fig. 9 The schematic representation of the hydridnanosystem preparation (1) (**A**) Fe3O4@CNT; (**B**) PSS-coated Fe3O4@CNT; (**C**) Fe3O4@CNT-HQDs; (**D**) Fe3O4@CNT-HQDs-Trf; (**E**) DOX-Fe3O4@CNT-HQDs-Trf. The magnetic and fluorescence properties of the hybrid magnetic systems (2). The hysteresis properties of the system (**A**) Magnetic hysteresis curves of **a** CNTs, **b** Fe3O4@CNT, and **c** Fe3O4@CNT-HQDs. (**B**) Fe3O4@CNT-HQDs dispersed in water with a magnetic field and their corresponding fluorescences properties (**B**) were studied. The particle stability studied under different conditions (3). Digital photographs for the dispersion status of Fe3O4@CNT-HQDs in (1) NaCl, (2) PBS, (3) BSA, and (4) DMEM (10% serum-containing medium) for 4 h incubation at 37 °C ((3C) ambient condition, (3**D**) UV irradiation). The pH-dependent loading (4**A**) and release (4**B**) of DOX with Fe3O4@CNT-HQDs-Trf as drug carrier

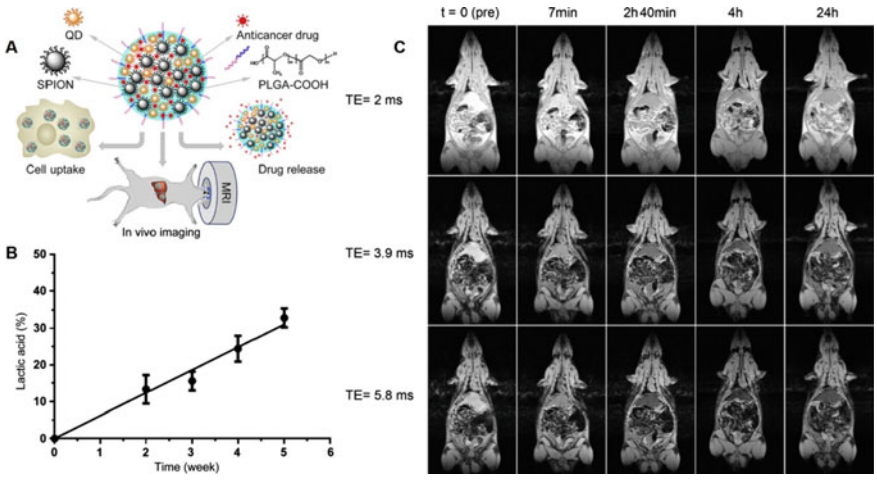


Fig. 10 The schematic representation of the developed theranostic system (**A**) by Ye et al. [72]. The invitro drug release (bisulfan) showed that 70–80% of bisulfan was release over the five hours at biological pH(7.4) from the total 89% entrapped in the polymer vesicle (B). The hybrid drug delivery system also explored for the MRI imaging in mice models through T2-weighted image at various time points after an intravenous injection (**B**) Copyright Biomaterials 35 (2014) 3885–3894

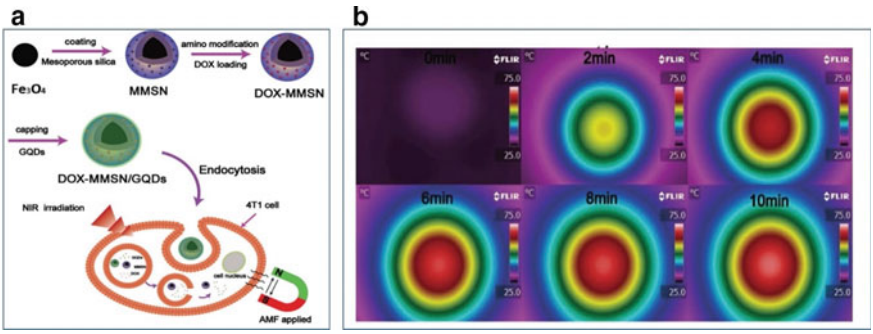


Fig. 11 The Schematic representation of the preparation of GQDs based theranosticanti-cancer DDS (**A**). The infrared thermal images of the GQDs system developed (**B**). The thermal images mapping of a 10 mg mL^{-1} sample with 808 nm laser irradiation are shown here. Adapted image from Small-https://doi.org/10.1002/smll.201602225 copyright required

(NIR) irradiation. This NIR irradiation can also cause the hyperthermia effect on cancer cells tested (breast cancer cells-4T1cells). The GQDs systems were able to release the anticancer drug Dox in acidic conditions in cancer cells and were studied for their pH-dependent drug release and the effect of NIR irradiation on cytotoxicity with and without irradiation in cancer cells were reported (Fig. 11).

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Chapter 8
Nanotechnology and Its Implication in Antiviral Drug Delivery

K. S. Joshy, S. Snigdha, and Sabu Thomas

Abstract HIV/AIDS has been major source of concern all over the world for past few decades. The current treatment regimes include the use of antiviral drugs belonging to the classes of nucleoside analogue reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The use of highly active antiretroviral therapy (HAART) using multiple drugs has raised the life expectancy of HIV-infected patients. However, the HIV infections is yet to be targeted in anatomical reservoirs, such as the brain, testes, gut, liver, kidney, and secondary lymphoid tissue. Potential nanocarriers have been studied and analysed thoroughly to overcome the hurdles in the delivery of antiretroviral drugs for HIV prevention and therapy. This review provides an insight into the life cycle and infection of HIV and various nanoparticulate delivery vehicles used for antiretroviral drugs. Biocompatible polymeric nanoparticles, liposomes and hybrid nanosystems have been thoroughly discussed. Such nanostructured materials hold great promise for the future of HIV treatment and can be expected to improve the quality of life of HIV victims.

Keywords Lipids · Lipid–polymer hybrid nanoparticles · Nanotechnology · HIV/AIDS · Drug delivery

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1 Introduction

The human immunodeficiency virus (HIV) is the causative agent of HIV infection which acts against the infection-resisting CD4 cells of the immune system. The major areas of localization of these viruses are the central nervous system, macrophages and lymphoid tissues. The severe loss of CD4 cells makes the body incapable of fighting infections. The person infected by HIV is left untreated; the viruses can slowly destroys immune system and lead to acquired immuno deficiency syndrome (AIDS) which is the most advanced stage of the HIV infection. HIV is commonly transmitted through sexual contact, direct blood contact and from mother to baby. The discovery of the human immunodeficiency virus (HIV) in 1983 accounted for the set of symptoms currently known as AIDS. HIV/AIDS has turned into a global epidemic claiming the lives of millions of adults annually [53, 54]. Figure 1 shows the major areas of infection of HIV.

According to reports published in 2015 by the UN, India has the third highest number of people living with HIV in the world with 2.1 million in Indians accounting for about four out of 10 people infected with the deadly virus in the Asia —Pacific region. About 36.7 million people are reported to be living with HIV infections globally, of these 1.8 million are children below the age of 15. Approximately, 2.1 million individuals have been newly infected by the deadly virus. The use of medicines for treating HIV infection is called antiretroviral therapy (ART). ART involves a daily HIV regimen which is a combination of HIV medication. ART prevents HIV from multiplying and reduces the viral load in the

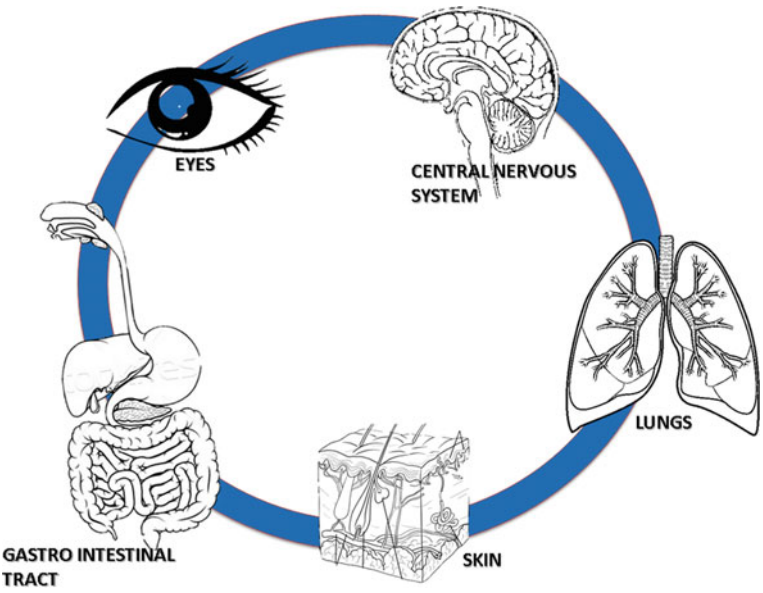

Fig. 1 Schematic representation shows the major areas of infection of HIV

body. This safeguards the immune system and prevents HIV infection from advancing to AIDS. Though ART is incapable of curing HIV infection, it can aid infected people to live longer and healthier lives. A world-wide statistics showing the number of people living with HIV infection is shown in Fig. 2.

Inspite of continued advancement in the modes of treatment and prevention HIV/AIDS, it still remains as an important and unsolved problem for the human race. This pandemic continues to be a major economic and social burden. The absence of a complete cure or curative agents for stopping HIV infection emphasizes the need for seeking out new approaches for HIV/AIDS treatment and prevention [114]. Global overview of HIV infection is shown in Fig. 3.

1.1 The Virus

Infection by the HIV, a lentivirus belonging to the family retroviridae, leads to AIDS in primates. The virus is composed of membrane derived from the host, a nucleocapsid and genetic material in the form of RNA containing three structural genes. The dimension of the virus measures around 100–150 nm. The three genes present in the virus code for group-specific antigens (gag gene), essential viral enzymes such as reverse transcriptase, integrase and protease (pol gene), and for the glycoproteins expressed on the outer viral membrane, namely gp120 and gp41 (env

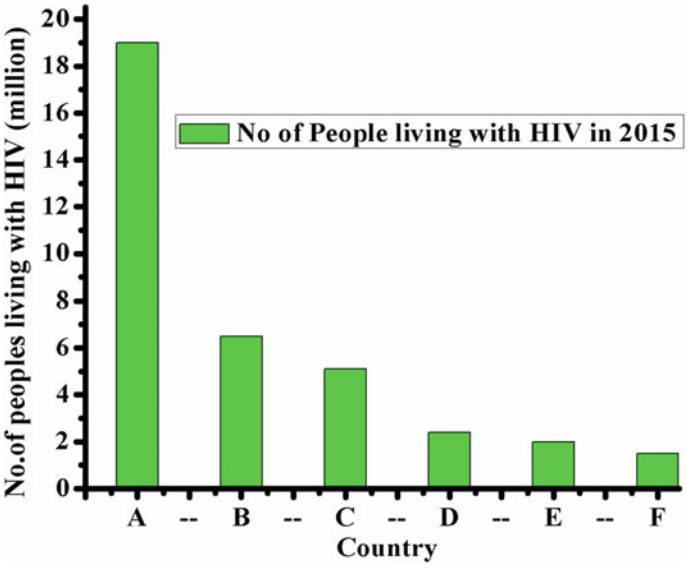

Fig. 2 Statistics showing the number of people living with HIV infection in different countries. (A: Eastern and Southern Africa, B: Western and Central Africa, C: Asia and Pacific, D: Europe and N. America, E: Latin America and Caribbean, F: East Europe and central Asia)

Fig. 3 Global overview of HIV/AIDS infection

gene). The glycoproteins gp120 and gp41 aid in recognizing the CD4 receptor and the CCR5 or CXCR4 co-receptors on the host cell membrane, and for virus/ cell fusion, respectively. Transcription errors of these genes result in high polymorphism which leads to mutation, thereby increasing the difficulty in developing and targeting drug against this virus. HIV-I and HIV-2 are the two different types of this virus known to cause infection and disease. The HIV-1 virus is more common, effective, infectious and is responsible for the majority of HIV infections in the world. HIV-2 is has demonstrated slower progression to immunodeficiency, and its transmission is less efficient compared to HIV-1 which explains its lower prevalence when compared to HIV-1 [107]. A schematic representation of the structure of virus is shown in Fig. 4.

1.2 Life Cycle of HIV

HIV mainly infects the cells of the immune system. The virus exhibits a great affinity for the cells expressing CD4 receptors. The life cycle of HIV consists of the following steps.

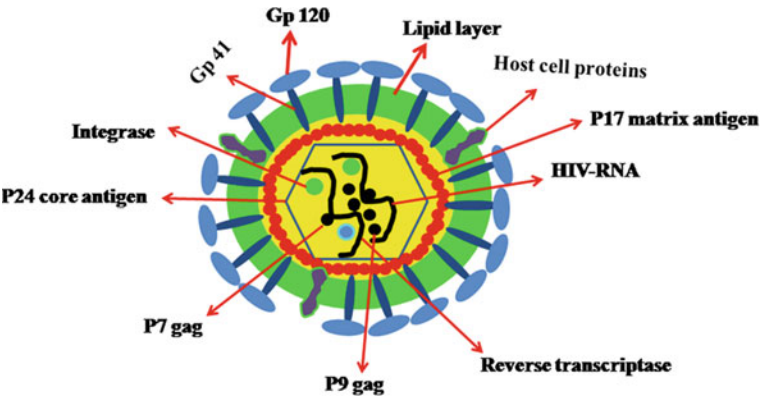

Fig. 4 Detailed structure of HIV

1.2.1 Binding and Fusion

HIV begins its lifecycle by binding to CD4 receptor and co-receptors found on the CD4+ T-lymphocyte. The virus then fuses with the host cell and releases its genetic material (ssRNA) into the host cell.

1.2.2 Reverse Transcription

The reverse transcriptase enzyme converts the RNA to DNA within the host cell.

1.2.3 Integration

The DNA thus produced enters the host nucleus and gets integrated into the host genome. This integrated viral DNA is called a provirus, and it remains inactive for several years.

1.2.4 Replication

The provirus then utilises the host machinery to transcribe mRNA which then codes for the HIV proteins. The RNA is transcribed into long chain proteins.

1.2.5 Assembly

The viral proteins and the viral RNA move towards the cell surface. They are then assembled into immature non-infective viral particles.

1.2.6 Budding

The non-infective viruses then push itself out of the host cell. The HIV then releases the protease enzyme which then cleaves the long chain proteins into shorter ones; these proteins then associate together to form the infectious virus. Copies of HIV genetic material are present among the strands of messenger RNA. These form new HIV particles, which are then released from the T-helper cell. These are then ready to infect other cells and begin the process all over again [77]. A schematic representation of the different steps involved in the life cycle of HIV is shown in Fig. 5.

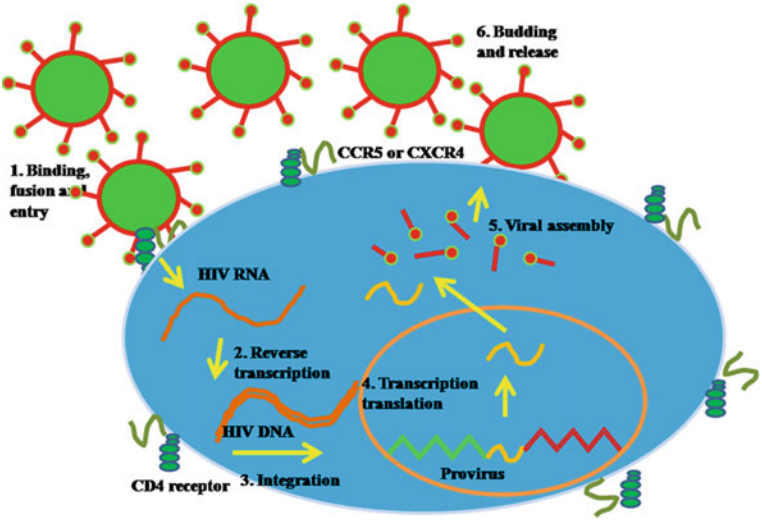

Fig. 5 Life cycle of HIV

1.3 HIV Transmission

The most common means of HIV transmission is by vaginal or anal sexual intercourse [90]. Vaginal sexual intercourse has been attributed to viral penetration of the vaginal and cervical mucosa. Upon sexual intercourse, HIV gets transmitted as free virions or associated with macrophages, which are the primary carrier of HIV in semen and vaginal discharges. Rectal viral transmission is also very common. The simple columnar epithelial lining makes the rectum and terminal colon easy for transmission of HIV infection [22]. Other significant means of HIV spread is by transfusion of contaminated blood products, sharing of contaminated needles among intravenous drug users, and transmission from mother-to-child during pregnancy, labour or breastfeeding [92].

1.4 HIV Pathogenesis

The virus invades the new host and undergoes local amplification at the mucosal site. The infected cells then migrate to the regional lymph nodes where the virus undergoes some mild amplification in the native T cells. From the regional lymph nodes, the infection quickly spreads via the T cells to the lymphoid organs, especially the gut-associated lymphoid tissues (GALT), spleen and bone marrow. This leads to a burst in the viral load (acute infection) [91]. The gastrointestinal tract is severely affected by the HIV during the early acute stages of infection leading to a

severe loss of CD4+ and CD8+ T cells [10, 46]. The acute infection lays the foundation for the establishment of chronic and persistent infection by HIV, which despite vigorous immune response in the early stages is never completely eliminated from the body [27].

1.4.1 HIV/Host Cell Interaction

CD4 expressing human cells are the primary targets for the HIV. CD4 is a cell surface protein expressed by macrophages, T cells and dendritic cells (DCs) [47]. The life cycle of HIV-1 is complex and affected by several viral and host factors. Interaction of gp120 (envelope glycoprotein) of HIV with the cell-surface receptor on CD4+ cells is required for the attachment of HIV envelope with the target cell membrane. Once the interaction is established, gp120 undergoes a conformational change that aids its binding to either of the two chemokine co-receptor molecules designated as CXCR4 or CCR5 [79]. Viruses (R5) that prefer CCR5-expressing cell tropism are responsible for most HIV new infections [23]. After fusion with the cell, the viral core consisting of RNA, reverse transcriptase and integrase are released into the cell cytoplasm. The core then undergoes disassembly, and the RNA is used as template for producing DNA by the viral reverse transcriptase. The DNA then moves into host nucleus and gets integrated into it by the action of the enzyme integrase. At this point, the infection becomes irreversible, as the cell is now capable of producing virions [79, 113]. The host cell interaction is schematically represented in Fig. 6.

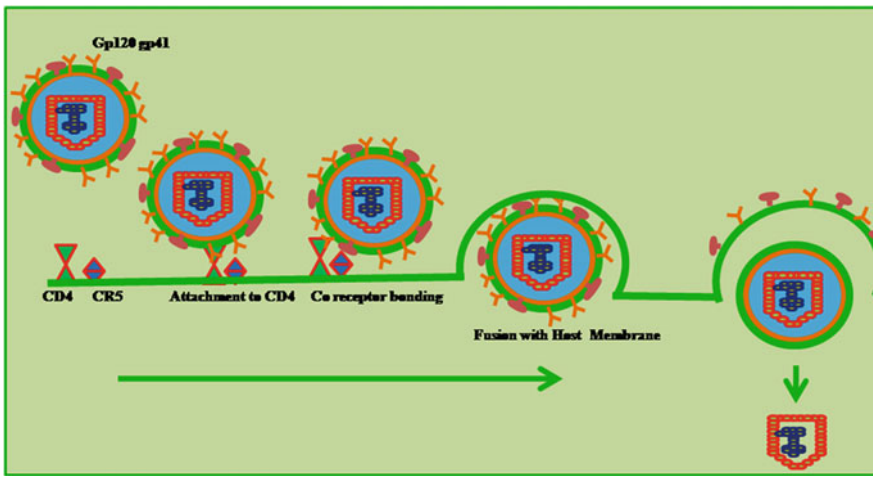

Fig. 6 HIV/host cell interactions

1.5 The Complexity of HIV/AIDS

HIV infection is associated with very high viral load in the host if left untreated; it leads to the depletion of CD4+ cells, leaving behind a defective immune system. The virus is capable of maintaining reservoirs and protecting itself from the effect of drugs. The viral reservoir then releases progeny into the circulation as long as the patient lives. This makes it one of the most challenging and life-threatening diseases in the world. The anatomical and cellular reservoirs within the tissues provide a safe haven for the virus. Anatomical reservoirs are tissues that are inaccessible to antiviral drugs; such regions include the central nervous system, retina and testes. The cells which possess the efflux proteins such as P-glycoprotein, the virus may remain latent and hence escape the action of antiviral drugs. The extracellular virions present on the surface of dendritic cells remain infectious in spite of being bound by many antibodies. They are not susceptible to retroviral drugs as they have not infected any cell. The virions can remain in this form for several months. Dendritic cells within lymphoid tissue trap a large number of extracellular virions on their surface, thereby shielding the virus from antiretroviral drugs. The monocytes/macrophages that are found in brain, pulmonary alveoli, spleen and lymph nodes have relatively long life span and the low cytopathic effects of the HIV makes them a persistent reservoir of HIV in spite of the presence of highly active antiretroviral therapy [123]. Such stable and persistent reservoirs make it difficult to eradicate HIV from the body even in the presence of antiretroviral drugs. These drugs in free form have poor local bioavailability and low residence time in these reservoirs when administered systemically [65]. Thus, it is of utmost importance to develop new drugs and/or drug delivery systems.

1.6 Detection of HIV

The HIV infection is commonly detected by the antibody screening test (immunoassay). The body starts producing these antibodies 2–12 weeks after getting infected by HIV. The current diagnostic strategies make use of blood, oral fluids or urine to detect the antibodies to the virus. Various serological tests such as enzyme-linked immune sorbent assay (ELISA), rapid HIV test and HIV antibody confirmation test 118 are used for diagnosing HIV/AIDS. Several tests have been developed which can detect the antibody or the antigen. All detection tests should be confirmed with western blot or HIV viral load test.

The U.S Center for Disease Control and Prevention (CDC) defines the signs or symptoms of AIDS. People are diagnosed with AIDS when they show certain symptoms, such as

- CD4+ T cell count less than 200 per cubic mm of blood compared with about 1,000 CD4+ T cells (healthy people).
- CD4+ T cells count less than 14% of all lymphocytes.

Recommendations of CDC include testing of CD4+ T cell count for every three to six months in all HIV-infected persons, though the need may vary from patient to patient [91, 95].

1.7 HIV/AIDS Current Therapeutic Strategies

The HIV infection is a worldwide health challenge. A cure for HIV/AIDS has been elusive to research for almost 30 years. Early treatments focused on antiretroviral drugs that were effective only to a certain degree. The first drug, zidovudine, was approved by the US FDA in 1987, and till date, about 25 have been approved and available in fixed dose combinations and generic formulations in resource-limited settings (to date, only zidovudine didanosine is available as true generics in the USA) [8, 51, 132]. The antiretroviral drugs (ARV) are divided into six classes according to their effect on the HIV life cycle: fusion/entry inhibitors, integrase inhibitors, protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside analogue reverse transcriptase inhibitors (NRTIs) and multidrug combination products. Tables 1, 2 and 3 show the list of different classes of drugs approved by US FDA [131].

The emergence of antiretroviral therapy has greatly contributed to the increased life expectancy and quality of life of patients. In the 1990s, a good breakthrough was observed in the knowledge about the disease, advancement in therapeutic resources, increase in life expectancy and epidemiologic profile. The mid-1990s saw the advancement of pharmacology studies and the arrival of protease inhibitor antiretrovirals that gave rise to an anti-HIV agents known as highly active antiretroviral therapy (HAART) [43, 109] where a combination of three or more different classes of drugs are administered simultaneously. The use of the HAART regimen was reported to have been successful in boosting the life expectancy and quality of life of the patients. Despite the success of HAART, latently infected cells can escape the viral immune response and persist for long periods of time [3]. In addition, the HAART could exhibit side effects such as fatigue, nausea, sickness, diarrhoea and lipodystrophy. These symptoms contributed to patients not adhering to the treatment regimen which led to increased blood viral load, a decline in CD4 + T cells, decreased tolerance to anti-HIV drugs, increased opportunistic infections, economic loss and ultimately failure of the treatment [43]. The antiretroviral drugs are exposed to extensive metabolism and the harsh environment of the gastrointestinal tract which result in inadequate oral absorption as well as low bioavailability. The half-life for most anti-HIV drugs is short, which calls for frequent drug administration, which might be difficult for the patient to comply with. Moreover, certain antiviral drugs exhibit poor solubility, low absorption and limited bioavailability. Another limitation of the current HAART regimen is its inefficiency to eradicate HIV from various anatomical reservoirs (e.g. central nervous system (CNS) and gastrointestinal tract) and intracellular sites (e.g. macrophages, hepatocytes, dendritic cells and langerhans cells) [101, 112]. High concentrations of the

Table 1 US FDA-approved nucleotide reverse transcriptase inhibitors (NRTIs)

Antiviral drug	Oral adult dose/frequency	Half-life (h)	Bioavailability (%)	Solubility (mg/mL)
Abacavir (ABC)	300 mg/twice daily 600 mg/once daily	1–1.5	83	77
Didanosine (ddI)	200 mg/twice daily 400 mg/once daily	1.3–1.5	21–43	27.3
Emtricitabine (FTC)	200 mg/once daily	10	93	112
Lamivudine (3TC)	150 mg/twice daily 300 mg/once daily	3–7	82–87	70
Stavudine (d4T)	30–40 mg/twice daily	0.9–1.6	80–86	83
Tenofovir disoproxil fumarate (TDF)	300 mg/once daily	4–8	25–30	13.4
Zalcitabine (ddC)	0.75 mg/every 8 h	1–4	80–88	76.4
Zidovudine (AZT)	200 mg/thrice daily	0.5–3	64	20.1

Table 2 US FDA-approved non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Anti viral drug	Oral adult dose/frequency	Half-life (h)	Bioavailability (%)	Solubility (mg/mL)
Delavirdine (DLV)	400 mg/thrice daily	2–11	60–100	0.2942
Efavirenz (EFV)	600 mg/once daily	52–76	40–45	3–9 μg/mL
Etravirine (TMC125)	200 mg/twice daily	41	Unknown	10 μg/mL
Nevirapine (NVP)	200 mg/once daily	45	90	0.007

drugs are essential for eliminating HIV from these reservoirs in order to achieve the desired therapeutic effect. Such large doses may contribute to severe side effects associated with anti-HIV therapy [48, 101]; currently, new strategies are being worked out to improve and overcome the limitations of existing therapeutic regimen through the design and development of novel drug delivery systems [101, 118]. The absence of complete cure for this malady calls for continued efforts in the quest for innovative approaches for treatment.

Table 3 US FDA-approved protease Inhibitors (PIs)

Anti viral drug	Oral adult dose/ frequency	Half-life (h)	Bioavailability (%)	Solubility (mg/ mL)
Amprenavir (APV)	1200 mg/twice daily	7–10	25–19[a]	4.91e.02 g/L
Atazanavir (ATV)	400 mg/once daily	7	60–68	4.5
Darunavir	600 mg/twice daily 800 mg/once daily	15	37	1.8
Fosamprenavir (FOS-APV)	1400 mg/twice daily	7.7	Not established	0.84
Indinavir (IDV)	800 mg/every 8 h	1.4–2.2	30	2.9
Lopinavir and Ritonavir (LPV/RPV)	400 mg/100 mg/twice daily/800 mg/ 100 mg/once daily	4.4/6.1	No data available	No data available
Nelfinavir (NFV)	1250 mg/twice daily 750 mg/thrice daily	3.5–5	80[a]	6
Ritonavir (RPV)	600 mg/twice daily	3.5	64	3.9
Saquinavir (SQV)	1200 mg/thrice daily	13	4–10	3.8
Tipranavir (TPV)	500 mg/twice daily	5.5–6	30[a]	6.9

[a]Reported in animal studies

1.7.1 Administration Routes

The choice of route of administration depends on the properties of the drug like solubility, bioavailability, accessibility to patient, etc. A delivery route is driven by patient acceptability, access to the site of infection and/or effectiveness in dealing with the specific disease. One of the promising routes for delivering therapeutic compounds is *Nasal delivery.* Inhaled medications have been available for many years for the treatment of various lung diseases. They are widely accepted as being the optimal route of administration of first-line therapy for asthma and chronic obstructive pulmonary diseases. In recent years, the lung has been studied as a possible route of drug administration for the treatment of systemic diseases, such as diabetes mellitus. The advantage of this type administration route is the availability of large surface area for delivery, high permeability of the nasal epithelium, allowing a higher molecular mass cut-off for permeation (i.e. approximately 1000 Da), the rapid drug absorption rate sometimes almost identical to that of intravenous injections, absence of first-pass metabolism and potential for central nervous system delivery [5, 24, 130]. In addition, nasal vaccination has received a lot of attention since the nasal cavity is rich in nasal associated lymphoid tissue (NALT) through which viral infections can be acquired. Intranasal immunization is straightforward (i.e. administration via drops or sprays), and in general, lower doses

are required to elicit comparable antibody titres than by oral or other mucosal route of immunization. Furthermore, intranasal vaccination has proven to be a safe, easy and cost-effective means of controlling viral and bacterial diseases. Finally, regarding both nasal vaccination and nasal delivery of therapeutics, it has been shown that nanoscale drug carriers exhibiting mucoadhesive and permeation enhancing properties have a great potential for improving the delivery through the nasal route [89, 130].

1.7.2 Major Setbacks for Anti-Retroviral Therapy for HIV/AIDS

The current treatment regimens do not completely eradicate the virus as the virus resides in 'cellular reservoirs such as the memory CD4+ T cells and cells of macrophage–monocyte lineage [16]. It has been found that in addition to acting as latent reservoirs, macrophages have also been found to aid in the generation of elusive mutant viral genotypes by serving as the host for viral genetic recombination [30]. The secondary lymphoid tissue, testes, liver, kidney, lungs, gut and the CNS act as anatomical reservoirs for the HIV [75, 81, 104]. The eradication of the virus from such reservoirs is essential to achieve long-term relief for the HIV/AIDS patients. Therefore, there is a great and urgent need to explore new approaches for developing non-toxic, low-dose treatment regimen that provide sustained release and effective eradication of the virus from the reservoirs, thereby eliminating the need for lifelong treatment.

1.8 Nanotechnology in Medicine

Nanotechnology is the engineering of materials and devices, at an incredibly small scale—between 1 and 100 nm. Nanotechnology has exposed incredible applications in healthcare sector. Nanomedicine is the use of nanostructured materials for preventive, therapeutic and diagnostic purposes [125]. It involves a large number of applications from targeted delivery to regenerative medicine including providing interfaces of nanomaterials with living human material and significantly improving conventional practices [13]. Major goals of nanomedicine in drug delivery are improving drug bioavailability and efficacy, achieving control of pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity and as well as overcoming obstacles due to low drug solubility, degradation, fast clearance rates, decreased biological activity and inability to cross-biological barriers such as air–blood barrier and blood–brain barrier. Nanomedicine may also help in achieving non-invasive modes of delivering drugs to various parts of the body. Drug characteristics differ substantially with respect to chemical composition, bioavailability, molecular size, hydrophilicity, optimum concentration range (above or below which the drug may be toxic or non beneficial), etc. Therefore, the design of new drugs can be challenging. The challenges of most conventional drugs include poor

bioavailability, in vivo instability, solubility, intestinal absorption, sustained and targeted delivery to site of action, therapeutic effectiveness, side effects and plasma fluctuations of drugs. However, nanotechnology in drug delivery has been designed to forego such challenges through the development and fabrication of nanostructures at submicron and nanoscale. Polymeric materials are mainly used, and they have multiple advantages [131]. Nanostructured materials have the ability to protect drugs encapsulated within them from harsh environment in the gastrointestinal tract and target the delivery of the drugs to various areas of the body. These materials are also known to facilitate sustained release of drugs, proteins or genes. They are capable of delivering drugs that are hydrophobic; they can bypass the liver, thereby preventing the first-pass metabolism of the incorporated drug. They can also increase oral bioavailability of drugs due to their specialized uptake mechanisms such as absorptive endocytosis and are able to remain in the blood circulation for a longer time. The sustained release feature enables drug delivery in a sustained and continuous manner leading to less plasma fluctuations, thereby minimizing side-effects caused by drugs. Due to their nano-size they, are capable of penetrating into tissues and may be taken up by cells thus achieving efficient delivery of drugs to sites of action. Nanostructures were found to be effectively taken up 15–250 times more than the microparticles in the 1–10 μm range. Polymeric nanoparticles have also been known to effectively penetrate the blood brain barrier for management of various CNS related diseases. Research and development of new drugs are capital and time intensive. Therefore, new drug delivery methods enable pharmaceutical companies to reformulate existing drugs, thereby extend the life of products, enhancing their performance, improve their acceptability by increasing effectiveness, as well as increase safety and patient adherence and ultimately reduce healthcare costs. Nanotechnology is strategic in developing drug delivery systems which can expand drug markets. Nanotechnology can be applied to reformulate existing drugs. Nanotechnology may also enhance the performance of drugs that are unable to pass clinical trial phases. It provides drug carriers, which may aid in efficient treatment and management of chronic diseases such as cancer, HIV/AIDS and diabetes mellitus [124].

1.8.1 Nanotechnology Approaches in HIV/AIDS Management

The existing nanoparticle-based delivery systems have greatly helped to enhance conventional treatment of HIV/AIDS and also in exploiting the progress in therapeutic strategies such as gene therapy, immunotherapy and vaccine development. The nanotechnology-based platforms for systemic delivery of anti-retroviral drugs offer myriads of improvements over the conventional methods. Nanotechnology-based therapeutics for HIV have advantages like sustained release, enhanced half-life, improved drug concentrations at target sites, fewer side effects and targeting concealed HIV in anatomically restricted sites. Nanotechnology-based systems improve treatment by maintaining the circulation of drugs at therapeutic concentrations for longer extent. Nanomaterials have also been shown to have

therapeutic effects of their own and their great surface to volume ratio improves and alters the distribution of hydrophobic and hydrophilic drugs in tissues. Various nanomaterials have been found to inhibit viral replication in vitro, and it is suggested that these effects are based on structural interference with viral assembly [12, 21, 40].

1.9 Nanocarrier-Based Drug Delivery Systems

The drug delivery systems which make use of nanocarriers usually comprise biocompatible and/or biodegradable materials that have components like synthetic proteins, lipids, polymers, inorganic materials, and/or a combination of these materials [106]. It would be desirable for the nanocarrier formulation to be non-toxic, biodegradable, biocompatible, stable and exhibit improved pharmacokinetics and controlled release. Nanoparticles are particulate dispersions of solid particles with a size in the range of 10–100 nm. Nanoparticles are comparable in size to virus or an antibody. Due to this, they are capable of entering into smallest capillaries and thereby avoiding rapid clearance by phagocytes from the blood stream, which prolongs their life in circulation. They have been shown to be successful in penetrating a wide range of organs including the CNS. The nanoparticles have been used for delivery of conventional drugs [78], recombinant proteins, vaccines and nucleotides [1, 85]. They have been extensively used in cancer therapeutics, antimicrobial applications and for delivering vaccines, genes and proteins with excellent targeting efficiency. In nanosized drug delivery systems, drugs may be absorbed onto the particle surface or encapsulated in the core of the particles. The use of nanoparticle (NP)-mediated drug delivery is advantageous due to high surface-area-to-volume ratio which provides platforms for further modification and tunable size. The size of carrier controls the penetration of materials through the endothelium and further perfusion of the materials through tissues. Size of the delivery system is more than 200 nm, and it will be eliminated from circulation by the macrophages. The size ranging from 10 to 200 nm is of particular importance in drug delivery system due to their improved bioavailability. The unique properties of the nanoparticles make them very promising, and a variety of nanostructures have been widely used, most of which are spherical, such as polymeric micelles, liposomes, calcium phosphate, gold, iron oxide, hydrogel nanoparticles and dendrimers. Hydrophobic drugs present a barrier for administration, and to overcome this issue, Dimethylsulphoxide (DMSO), cyclodextrins, etc., are used for solubilising or altering the chemical structure of such drugs. The excess use of cyclodextrin may limit the route of administration. Tablets or capsules that are very large in size are highly impractical. The use of nanoparticles is the best alternative to overcome all the limitations of conventional therapy. Nanoparticles enable the incorporation of both hydrophobic and/or hydrophilic drugs in their matrix [124]. The key parameters that determine the role of various drug carriers are shown in Fig. 7.

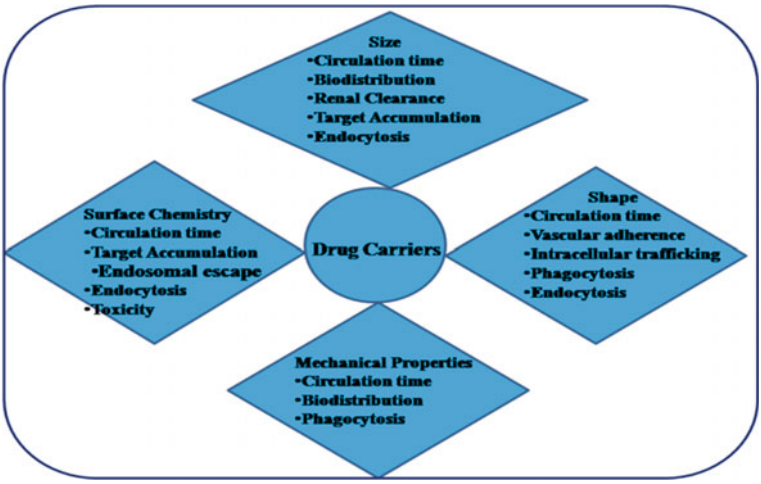

Fig. 7 Key properties that determine the role of drug carriers

The use of nanoparticles in drug delivery enhances the drug activity. An efficient drug delivery system comprises a pharmaceutically active ingredient and an engineered NP of biological (lipids, polymers, etc.) or non-biological (metals) origin [14]. The nanoparticle-mediated drug delivery system could be an engineered nanoparticle or drug itself formulated in the nano-scale and functioning as its own carrier. From an industrial point of view, nanoparticles for pharmaceutical applications are formulated within the size range of 100–250 nm or in the suspended form (nano-emulsions). With an effective drug delivery system, the drug is released in the diseased target site in the body in a controlled manner, which depends on the competent delivery structure of the carrier molecules. This is possible by biodegradable nanoparticles. So, an ideal nanoparticle drug delivery system is one which does not interact with the encapsulated material and does not undergo any chemical change. They possess fast biodegradability, drug delivery and bio-compatibility [34]. It is very challenging to target a drug into the central nervous system by conventional mechanism. It is also due to the blood brain barrier (BBB). Although a life-supporting protective mechanism of the brain, its existence strictly restricts the delivery of most drugs to the brain because they do not cross the BBB in sufficient amounts. Therefore, therapeutic efficiency is diminished because systemic administration of the drug does not lead to an effective concentration in the brain. Pharmaceuticals are not able to cross the blood brain barrier as it is specifically tight at the interface with the brain astrocytes. However, the barrier properties may be compromised intentionally or unintentionally by drug treatment allowing passage of nanoparticles [29]. The delivery of drugs by nano-carrier has been meticulously studied and reviewed. For extended flow, the size of the carrier should be small enough (<150 nm) in order to flee from being captured and subsequently removed by the resident macrophages in the reticuloendothelial system,

such as the liver and spleen [6]. In this regard, materials with diameters between 10 and 150 nm are chiefly useful due to their better bioavailability and their ability to take advantage of the enhanced permeation and retention (EPR) effect [94].

A variety of nanostructured materials have been used for application in drug delivery; some of the commonly used structures include dendrimer, polymeric nanoparticles, nanocrystal, inorganic nanoparticles, metal-based nanoparticles, liposomes, etc. A range of functionalities can be incorporated in these nanoparticles which facilitates drug encapsulation within the nanoparticle complex. The surface chemistry of nanoparticles also allows the conjugation of cell-specific ligands for targeted delivery. Coatings to the surface of nanoparticles have been found to increase circulation time for enhanced bioavailability. The incorporation of specific materials on the surface or in the core of nanoparticle enables the storage of a therapeutic agent until the target site is reached which allows the controlled delivery of therapeutics to the target cells [124]. Site-specific targeting of nanoparticles can be achieved by avoiding clearance by the reticuloendothelial system (RES), utilizing improved retention and permeation effect. Two types of approaches are applied for using nanoparticle as carrier for drug:

- Surface bound: The drug molecules are adsorbed on the surface of nanoparticles.
- Core bound: In this method, the drug particles are encapsulated inside the nanoparticle and carried to the target.

Drugs can either be loaded onto preformed nanoparticle solution or by adding them to the reaction mixture during the fabrication process. Nature of the interaction between the drug molecules and nanoparticles may be chemical or physical adsorption in which the drug adsorbed on to the surface, without any binding or interaction at all. The type of interaction depends on the chemical structure of the drug and the carrier, the conditions of drug loading, etc. [69]. A schematic representation showing different categories of drug carriers is depicted in Fig. 8.

1.9.1 Dendrimers

Dendrimers are highly branched polymers with unique and controlled structure with topologic features that are 2.5–10 nm in size [98]. These hyper-branched polymers have chains extending from a centre, resulting in a nearly perfect three-dimensional geometric pattern. They are characterized by their polyfunctional core, interior layers and multivalent surface. The presence of polyfunctional core allows the attachment of several biological moieties. The small size of their multiple terminal groups, narrow molecular weight distribution and ease of incorporation of therapeutics and targeting moieties make them attractive for drug delivery. They can be synthesized from synthetic or natural sources like amino acids, sugars and nucleotides. A number of dendrimer families have been already reported [15] and among them polyamidoamine (PAMAM) and poly(propylenemine) (PPI) families have been most widely used for biomedical applications. Various drugs can be

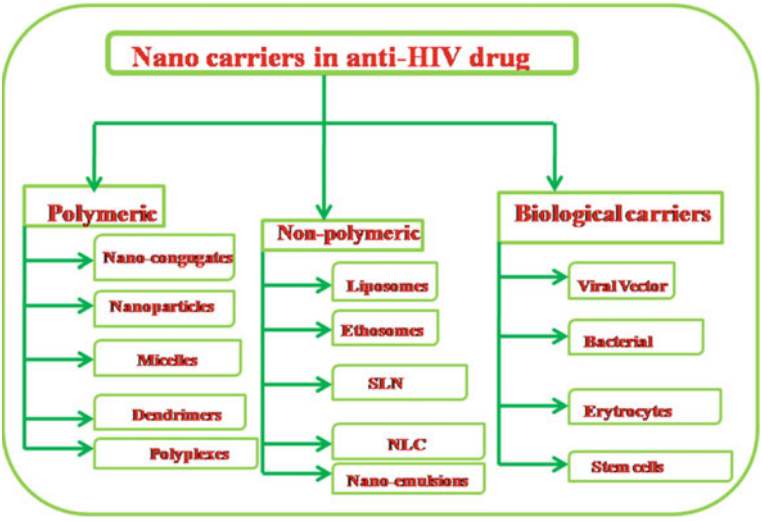

Fig. 8 Schematic representation of various categories of nanoparticulate drug carriers

incorporated into dendrimers either by covalent conjugation or electrostatic adsorption due to the presence of multivalent surfaces. The dendrimers can be loaded with drugs by using the cavities present in their cores through hydrophobic interaction, hydrogen bonding or chemical linkage. Their surface can be fabricated with precise spacing of surface molecules, thereby conjugating the targeting moieties. The unique surfaces of dendrimers may be designed with functional groups in such a way that they resist trans-cellular, epithelial or vascular permeation [127].

1.9.2 Polymeric Nanoparticles

Polymeric nanoparticles are solid, colloidal particles made from macromolecular substances. Their sizes vary from 10 to 1000 nm. Polymeric nanoparticles (NPs) for controlled drug delivery have shown significant therapeutic potential, since drug can be dissolved, entrapped, adsorbed, attached or encapsulated inside the nanoparticles. Nanospheres or nanocapsules are commonly used in drug delivery. Polymeric nanoparticles can protect the drug from degradation (physical stability during storage and in biological fluids), enhance its transport and distribution (through modification of surface with inserted ligands such as antibodies, surfactants, polymers, etc.), allow sustained and controlled release and also improve the plasma half-life of the entrapped drug [4]. Polymeric nanoparticles can be engineered for any application by optimizing properties like particle size and surface charge. Both synthetic and natural polymers can be used for preparing drug delivery vehicles. They include natural polymers, albumin, gelatin, alginate, collagen, chitosan and synthetic polymers like polyesters, their copolymers polyacrylates and polycaprolactones.

1.9.3 Inorganic Nanoparticle

Silica or alumina are two important classes of ceramic nanoparticles for biological applications. Other inorganic nanoparticles with varying size, shape and porosity are metals, metal oxides and metal sulphides. Mesoporous silica nanoparticles in addition possess stable mesoporous structures, large surface areas, tunable pore sizes and volumes and well-defined surface properties which aid in site-specific delivery of drug. Quantum dots, polystyrene, magnetic, ceramic and metallic nanoparticles are other important inorganic nanoparticles that have a central core composed of inorganic materials with fluorescent, magnetic, electronic and optical properties [45, 87].

1.9.4 Metal Based Nanoparticle

Gold nanoparticles (Au NPs) are a suitable platform for development of an efficient delivery vehicle because of the ease of synthesis, functionalization and biocompatibility. Magnetic nanoparticles of 10–20 nm size with a Fe^{2+} and Fe^{3+} core surrounded by dextran or PEG molecules have been used in biomedical field to label biomolecules in bioassays and as contrast agents for MRI, etc. They are also used for active targeting in in vivo or for in vitro diagnostics after surface functionalization [45].

1.9.5 Liposomes

Liposomes are spherical bilayered vesicles composed of natural or synthetic amphiphilic lipid molecules [128, 137]. They have superior biocompatibility as they are basically analogues of biological membranes. The amphiphilic nature of liposomes, their biocompatible and biodegradable composition, their simplicity of surface modification and their unique ability to encapsulate both hydrophilic and hydrophobic therapeutic agents make them excellent vehicle for therapeutic agents. They prevent drugs from degradation, reduce toxicity and side effects and enable site-specific targeting. The aqueous interior of liposome may be used to encapsulate hydrophilic drug and the phospholipid membrane may encapsulate hydrophobic compounds. Liposomes are made from naturally occurring phospholipids, so they are free from unwanted toxic or antigenic reactions. They are coated with biocompatible moieties like polyethylene glycol (PEG) to prolong their circulation time [128]. This type of polymeric coating can also be functionalised in order to provide site for targeting of the liposome to different regions. Phosphatidylcholine and phosphatidyl ethanolamine are two important classes of compounds for liposomal preparation. Passive diffusion or active extrusion is the possible mechanism of liposomal drug delivery. Due to the poor bioavailability, liposomes are easily cleared by the reticuloendothelial system (RES). Different nanocarriers used for the delivery of anti-viral drugs are shown in Fig. 9.

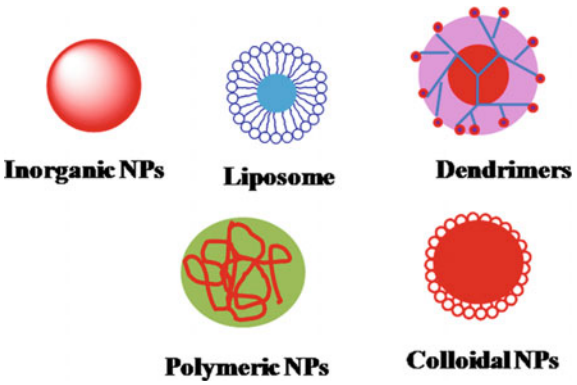

Fig. 9 Nanocarriers for antiviral drug loading

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are nanocrystalline structures made of fatty acids that are solid or semisolid at room temperature. SLNs are a comparatively stable colloidal carrier system in which melted lipid is dispersed in an aqueous surfactant by high-pressure homogenization or micro-emulsification [97]. SLNs can be made from a wide variety of high melting-point lipids using number of methods [97]. Over the years, they have emerged as a variable substitute for liposomes as drug carriers. They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLNs offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interfaces. They are noted for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials. Their hydrophobic core usually entraps the dissolved or entrapped drug [63, 64]. SLNs exhibit certain potential advantages over other polymeric nanoparticles. They have been shown to be taken up by brain and exhibit the least toxicity due to the biodegradable nature of the constituent materials [11]. Their nanoscale dimensions allow them to cross various anatomical barriers and also to bypass the liver. They have high drug entrapment efficiency and render the drug more stable in their lipid matrix and provide a controlled release of the entrapped drug. Their production can be scaled up with excellent reproducibility. SLNs also offer greater drug stability and better control over drug-release kinetics compared to nanoemulsions [86]. They are being promoted for intravenous applications. Surface coating of SLNs with hydrophilic polymers or surfactants, such as poly(ethylene glycol) (PEG), minimizes their uptake in liver cells and results in improved bioavailability. Stearic acid–PEG 2000–has been used for their stearic stabilization, whereas the use of complex lipids (mono-, di-, triglycerides of different chain lengths) results in an increased loading efficiency [93, 105]. The structure of SLN is shown in Fig. 10.

SLNs incorporate the advantages and eliminate the drawbacks of several colloidal lipid carriers. The drug loading capacity of conventional SLN is limited by the solubility of the drug in the lipid matrix, the structure of the lipid matrix and the

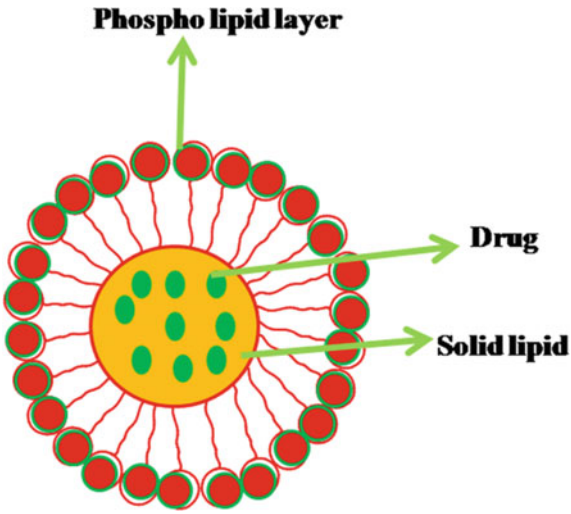

Fig. 10 Scheme depicting a typical solid lipid nanoparticle

polymeric state of the lipid matrix. If the lipid matrix consists of similar molecules (i.e. tristearin or tripalmitin), a perfect crystal with few imperfections is formed. The incorporated drugs are located between fatty acid chains, between the lipid layers and also in crystal imperfections; highly ordered crystal lattice cannot accommodate large amounts of drug. Hence, the use of more complex lipids can be considered desirable for higher drug loading [97].

Nanostructured Lipid Carriers (NLC)

NLC are developed to solve the potential difficulties with SLNs in order to increase the drug loading and prevent drug expulsion. Three models have been proposed for the NLCs in the first model, different lipids (like glycerides) composed of different fatty acids are mixed. The use of spatially different lipids creates larger distances between the fatty acid chains of the glycerides and increases general imperfections in the crystal and thus provides more room for accommodation of drug molecules. High drug loading can be achieved by mixing solid lipids with small amounts of liquid lipids (oils). This model is called imperfect-type NLC. Drugs exhibiting greater solubility in oils compared to solid lipids can be dissolved in the oil, thereby protecting them from the surrounding solid lipids. These types of NLC are called multiple types NLC, and are analogous to w/o/w emulsions since it is an oil-in-solid lipid-in-water dispersion. Drug expulsion is caused by continuous crystallization or transformation of the solid lipids. This can be prevented by the formation of the amorphous-type NLC. Here, the particles are solid, but crystallization upon cooling is avoided by mixing special lipids like hydroxyl octacosanyl, hydroxyl stearate and isopropyl myristate. The NLCs have mainly been investigated in the topical and dermatological formulations [97] in the delivery of clotrimazole [119, 121],

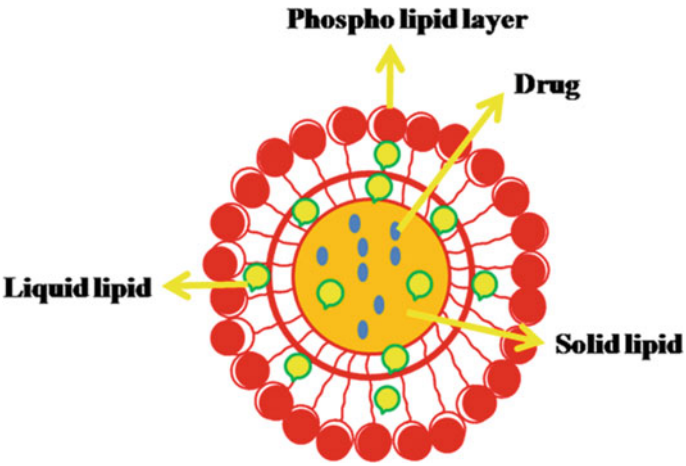

Fig. 11 Nanostructured lipid carriers

ketoconazole [120] and other antifungal imidazoles [119]. The structure of NLC is shown in Fig. 11.

Lipid Drug Conjugates (LDC)

A major drawback of SLNs is the low efficiency in loading hydrophilic drugs due to partitioning effects that occur during the preparation. Only highly potent low-dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix. In order to overcome these limitations, the LDC nanoparticles with high drug loading capacities were developed An insoluble drug-lipid conjugate bulk is first prepared either by salt formation (e.g. with a fatty acid) or by covalent linking (e.g. to ester or ethers). The obtained LDC is then processed with an aqueous surfactant solution (such as Tweens) using high-pressure homogenization (HPH) to obtain a nanoparticle formulation. Such matrices may have applications in brain targeting by hydrophilic drugs in serious infections [115].

Lipid–Polymer Hybrid Nanoparticles

Lipid–polymer hybrid nanoparticles are a new class of core–shell-type hybrid systems that typically consist of a polymeric core, coated with single or multiple layers of lipids that constitute the shell. The successful combination of lipids and polymers opened up new systems with great applications in science, medicine and technology. The LPNs combine the biomimetic properties of lipids and mechanical robustness of the polymeric core to yield a theoretically superior delivery system. They have been extensively used for delivery of both hydrophilic and hydrophobic

drugs. They tend to carry hydrophilic drugs inside the polymer and hydrophobic drugs within the lipid bilayer. In this system, the therapeutics are usually entrapped in the polymer core. The lipid layer confers biocompatibility and the PEG outer layer aids in prolonging circulation time and provides steric stabilization. The liposomal layer minimises the leakage of therapeutics and provides sustained release. Various bioactive molecules such as drugs, genes, proteins, etc., can be entrapped, adsorbed or covalently attached in the hybrid system. The LPNs have the ability to carry moderately hydrophilic drugs with high encapsulation efficiency and loading yields. These NPs can be tuned to achieve desirable sustained drug-release profile and differential targeting of cells. They have been known to have excellent serum stability. These hybrid NPs can also be used as adjuvants for vaccination [88]. The LPNs can be easily synthesised by self-assembly of the components, hence facilitating cost-effective mass production of these delivery systems [103].

1.10 Methods of Preparation of Lipid-Based Drug Delivery Systems

SLNs consist of solid lipid, emulsifier and water/solvent. The lipids used may be triglycerides (tristearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmiticacid) and steroids (cholesterol) and waxes (cetyl palmitate). Various emulsifiers and their combinations (Pluronic F 68, F 127) have been utilised to stabilize lipid dispersion. A combination of emulsifiers may reduce particle agglomeration [19]. The lipid matrix of SLNs is made from physiological lipids which decreases the danger of acute and chronic toxicity, thereby acquiring a clear advantage over other means of drug delivery. The choice of the emulsifier depends mainly on the route of administration.

1.10.1 Homogenization

High shear homogenization technique was initially used for synthesizing solid lipid nanodispersions [122]. Microparticles that can hamper its quality may be present in the dispersion. High-speed homogenization method is used to produce SLN by melt emulsification [2], it is a variant of the high shear homogenization method. Olbrich et al. investigated the influence of different processing parameters, including emulsification time, stirring rate and cooling condition on the particle size and zeta potential. It was found that higher stirring rates did not significantly change the particle size, but slightly improved the polydispersity index [102].

1.10.2 Hot Homogenization

Hot homogenization process utilizes temperatures above the melting point of the lipid and is similar to the homogenization of an emulsion. High-shear mixing device (like silversion-type homogenizer) is used to obtain a pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature). The quality of the pre-emulsion affects the quality of the final product, and it would be desirable to obtain droplets in the size range of a few micrometres. High-pressure homogenization of the pre-emulsion is done above the lipid melting point. Usually, lower particle sizes are obtained at higher processing temperatures because of lowered viscosity of the lipid phase [76]. This might accelerate the drug and carrier degradation. Better products are obtained after passing several times through the high-pressure homogenizer (HPH) (typically 3–5 passes). High-pressure processing always increases the temperature of the sample (approximately 10° at 500 bar) [96]. In most cases, 3–5 homogenization cycles at 500–1500 bar will be sufficient. High kinetic energy of the particles may lead to an increase of the particle size due to particle coalescence.

1.10.3 Cold Homogenization

The cold homogenization of solid lipid is considered to be similar to milling of a suspension at elevated pressure. Effective temperature regulation is needed to ensure the solid state of the lipid during homogenization [96]. Cold homogenization has been developed to overcome temperature-mediated accelerated degradation of the drug and partitioning and hence loss of drug into the aqueous phase during homogenization. Uncertain polymorphic transitions of the lipid due to complexity of the crystallization step of the nanoemulsion lead to several modifications and/or super-cooled melts. The first preparatory step is the same as in the hot homogenization procedure and includes the solubilization or dispersion of the drug in the lipid melt. The drug containing melt is then cooled rapidly using dry ice or liquid nitrogen to promote homogenous drug distribution in the lipid matrix. The drug containing solid lipid is then pulverized using ball/mortar milling. Particle sizes obtained by this process are typically in the range of 50–100 μ. The SLNs are dispersed in a chilled emulsifier solution and chilled processing aids in particle milling by increasing the fragility of the lipid. The dispersion is subjected to high-pressure homogenization at or below room temperature with appropriate temperature control. However, when compared to hot homogenization, cold homogenized samples possess larger particle size and a broader size distribution. Though cold homogenization minimizes the thermal exposure of the drug, it does not eliminate the need for melting of the lipid/drug mixture in the initial step.

1.10.4 Ultrasonication or High-Speed Homogenization

SLN can also be developed by high-speed stirring or sonication. The equipment required for this process is commonly available. Broader particle size distribution ranging in the order of micrometres is a potential drawback of this method. This leads to physical instabilities likes particle growth upon storage. Potential metal contamination is also a major problem in ultrasonication. Studies have been performed by various research groups using a combination of high-speed stirring and ultrasonication performed at high temperature for making a stable formulation [108].

1.10.5 Solvent Emulsification/Evaporation

Nanoparticle dispersions can be produced by precipitation in o/w emulsions. The lipophilic material is dissolved in a water-immiscible organic solvent that is then emulsified in an aqueous phase. Upon evaporation of the organic solvent, nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. Lipid nanoparticles of ~25 nm have been obtained using this method [129]. A schematic representation of the solvent evaporation process for the preparation of nanoparticles is shown in Fig. 12.

1.10.6 Microemulsion

Gasco and co-workers developed SLN preparation techniques based on the dilution of micro-emulsions. They are made by stirring an optically transparent mixture at 65–700 rpm. The mixture is typically composed of a low melting fatty acid (stearic acid), an emulsifier (such as polysorbate 20, polysorbate 60), co-emulsifiers

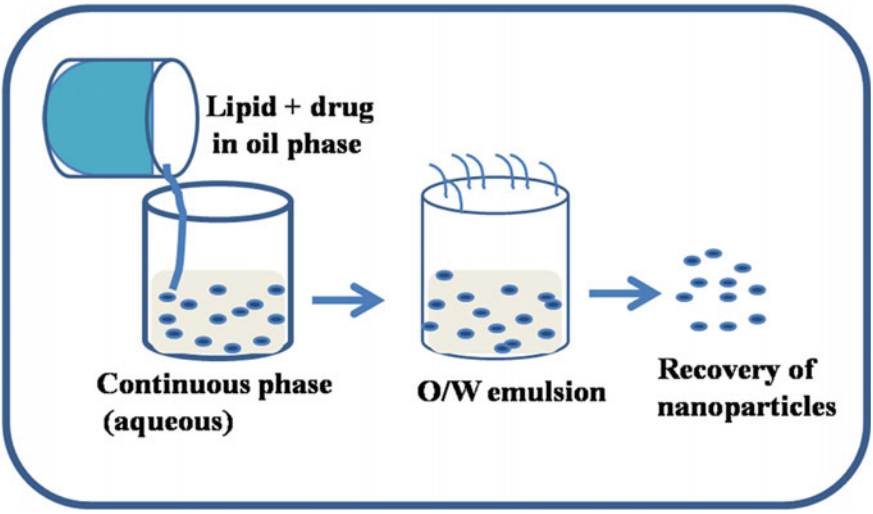

Fig. 12 Solvent emulsification process for nanoparticle preparation

(sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water in the ratio range of 1:25 to 1:50 under stirring. The dilution process is determined by the composition of the microemulsion. According to the literature [42, 111], a droplet structure is already contained in the microemulsion, and therefore, no energy is required to achieve submicron particle size. Polymer nanoparticles are typically produced with solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes are obtained with more lipophilic solvents [25]. The hydrophilic co-solvents of the microemulsion may also play a similar role in the formation of lipid nanoparticles as acetone in the formation of polymer nanoparticles.

1.10.7 Supercritical Fluid Technique

This is a relatively new technique for SLN production and has the advantage of being solvent-less processing technique [136]. There are several variations in this technology platform for preparation of powder and nanoparticle. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) is the good choice as a solvent for this method [44].

1.10.8 Spray Drying Method

It is an alternative procedure to lyophilization to produce a drug powder/product from an aqueous SLN dispersion. It is a cheaper method than lyophilization. This method may cause particle aggregation due to high temperature, shear forces and partial melting of the particle. The use of lipid with melting point >70° is recommended for spray drying [38].

1.10.9 Double Emulsion Method

For the preparation of hydrophilic drug-loaded SLN, a novel method based on solvent emulsification evaporation has been used [25]. Here the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion. The double emulsion process for the preparation of nanoparticles is shown in Fig. 13.

1.11 Synthesis of Polymeric Nanoparticles

Polymeric nanoparticles have proved to be promising carriers for therapeutic agents. They are attractive vehicles for drug delivery as they can be engineered to

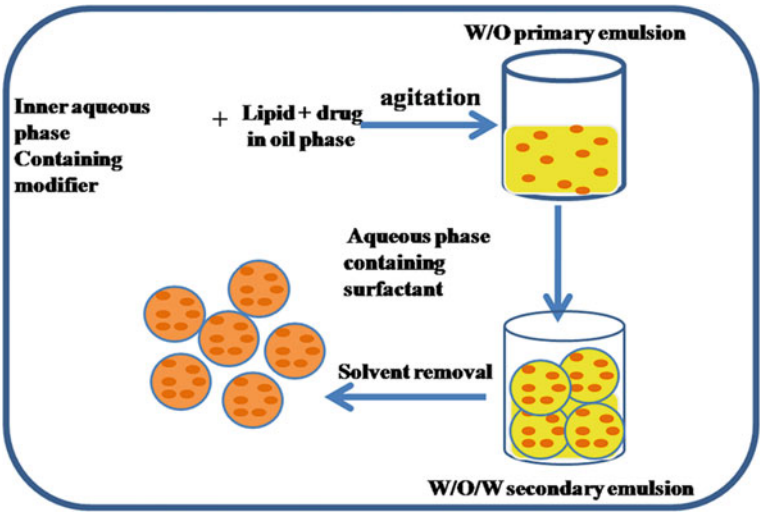

Fig. 13 Double emulsion process for nanoparticle preparation

prevent degradation of the drug, control release profiles and to achieve targeted delivery, thereby lowering the dose-dependent toxicity of the drug. Usually, the chosen polymers are biocompatible and biodegradable.

The most commonly used nanoparticles of polymer are nanospheres and nanocapsules. In nanospheres, the drug is loaded in the matrix, whereas in nanocapsules, the drug is encapsulated within a thin polymer layer. Various methods of preparation are used for synthesis of polymeric nanoparticles and they include.

1.11.1 Nanoprecipitation

It is a single-step method with high reproducibility, and it results in the formation of uniform-size nanoparticles. In this process, the polymer and the drug are dissolved in a water miscible organic solvent. This mixture is then added to an aqueous solution under moderate stirring causing nanoparticles to precipitate instantly due to solvent diffusion into the aqueous matrix. The solvent is then evaporated at reduced pressure, and an aqueous suspension of nanoparticles is thus obtained. Nanocapsules are also prepared using the same method. In addition oil is added to the solution of the polymer in order to form an inner oily cavity to accommodate the drug. A schematic representation of the nanoprecipitation process is shown in Fig. 14.

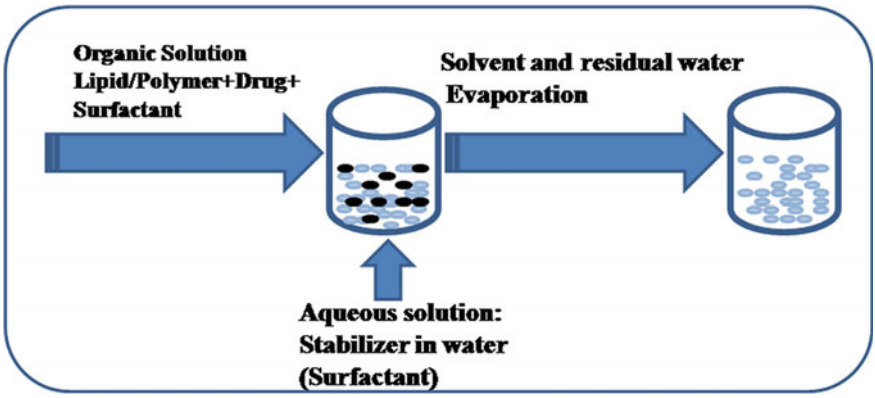

Fig. 14 Schematic representation of nanoprecipitation technique

1.11.2 Salting Out

In this technique, two phases are mixed together to form an oil-in-water emulsion. The oil phase is essentially the polymer solution containing the therapeutic agent in a water miscible solvent. The aqueous phase is a solution or gel containing a colloidal stabilizer and a salting out agent at high concentration which hinders the solvent diffusion. The oil-in-water (o/w) emulsion thus formed is then diluted such that the concentration of the salting-out agent is lowered below a certain threshold value; this enables the organic solvent to rapidly diffuse into the aqueous phase and result in the formation of nanoparticles. Then, the organic solvent is removed by evaporation at reduced pressure. Repeated washing steps are then needed to remove the salting-out agent.

1.11.3 Emulsification Diffusion

In the emulsification diffusion method, a partially water miscible solvent and water are mutually saturated following which the polymer and the therapeutic agent are dissolved in the saturated solvent and the stabilizers are dissolved in water, resulting in the formation of a stable emulsion. In the final step, sufficient amount of water is introduced and the solvent diffuses into the aqueous phase resulting in the formation of nanoparticles.

1.11.4 Emulsification Evaporation

In this technique, the polymer and the therapeutic agent are dissolved in a volatile water-immiscible organic solvent. Then, this mixture is emulsified with an aqueous phase containing a stabilizer resulting in the formation of o/w emulsion.

Ultrasonication or homogenization is carried out to break the emulsion droplets and formation of nanoparticles.

1.11.5 Double Emulsion

There are two main types of double emulsions, they are—water-oil-water (w/o/w) and oil-water-oil (o/w/o). In double emulsions, the droplets of dispersed phase contain smaller components of another dispersed phase; hence they are commonly referred as 'emulsion of emulsions'. They are capable of encapsulating both hydrophobic and hydrophilic molecules either individually or together. Double emulsion solvent evaporation technique is commonly used for preparation of nanoparticulate drug delivery vehicles. In this process, the aqueous phase containing the therapeutic agent is dispersed in an oil phase of the polymer/drug to form the primary emulsion. This primary emulsion is dispersed in outer aqueous phase containing suitable stabilizer to form double emulsion. Evaporation of the organic phase results in the formation of the nanoparticles.

1.12 Synthesis and Fabrication of Lipid–Polymer Hybrid Nanoparticles

Lipid polymer hybrid nanoparticles are usually prepared through two distinct techniques. One technique consists of two-step process wherein the polymer core and lipid shell are separately synthesised and then mixed together to facilitate the formation of hybrid entities. The other technique involves a single-step process in which nano-precipitation and self-assembly method are employed to prepare hybrid nanoparticles.

1.12.1 Two-Step Method

The two-step method is the most commonly used method for the development of lipid–polymer hybrid nanoparticles. Preformed polymeric nanoparticles are mixed with preformed lipid vesicles in the conventional two-step method. In this technique, the lipid vesicles are adsorbed on to the polymeric nanoparticles through electrostatic interactions. They are generally prepared by mixing liposomes and polymeric nanoparticles (PNPs) in which a lipid bilayer or lipid multilayer covers the surface of the polymeric core. The polymer core particles are prepared using any of the several methods available. After preparing the polymeric core nanoparticles, liposomes are prepared by techniques like thin—film hydration and sonication. Mixing of the polymeric nanoparticles and the liposomes followed by vigorous vortexing result in the fusion of liposomes with the polymeric core. The mechanism

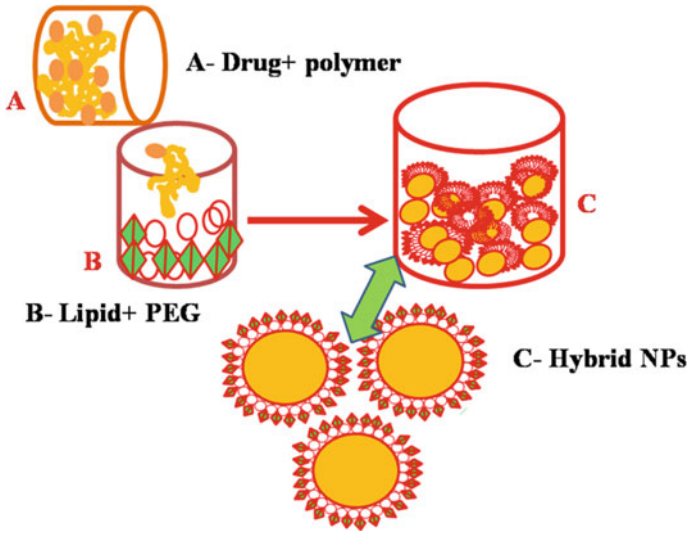

Fig. 15 Schematic representation of the preparation of LPN via two-step method

behind the fusion of the liposomes and the polymeric core particles may be due to an electrostatic interaction between the polymer core and the liposomes. It is important therefore to choose polymer and lipid systems that are compatible with this method [80]. Core–shell nanoparticles find applications in various areas due to their improved physical and chemical properties. Numerous synthesis procedures have been employed for the manufacture of core–shell nanoparticles. LPNs generally forms core–shell structure which exhibit high structural integrity, stability during storage, controlled release capability attributed to the polymer core, high biocompatibility and bioavailability owing to the lipid and lipid–PEG layers [20, 138]. Large-scale production of LPNs can be carried out using soft lithography particle moulding [37] and by continuous nanoprecipitation in a microchannel. A schematic representation of the process is shown in Fig. 15.

1.12.2 One-Step Method

One-step synthesis involves preparation of lipid–polymer hybrid nanoparticles with a lipid monolayer shell (Fig. 16). This technique involves dissolving free polymers and hydrophobic drugs in a water miscible organic solvent, and the lipid or lipid-PEG conjugates are introduced into an aqueous solution. The solubilization of phospholipids in the aqueous solution is facilitated by adding a small amount of water miscible organic solvent to the aqueous solution. The polymer solution is then added drop wise to the lipid-aqueous dispersion. Upon mixing, the organic solvent diffuses into the aqueous solution, leaving polymer to precipitate into

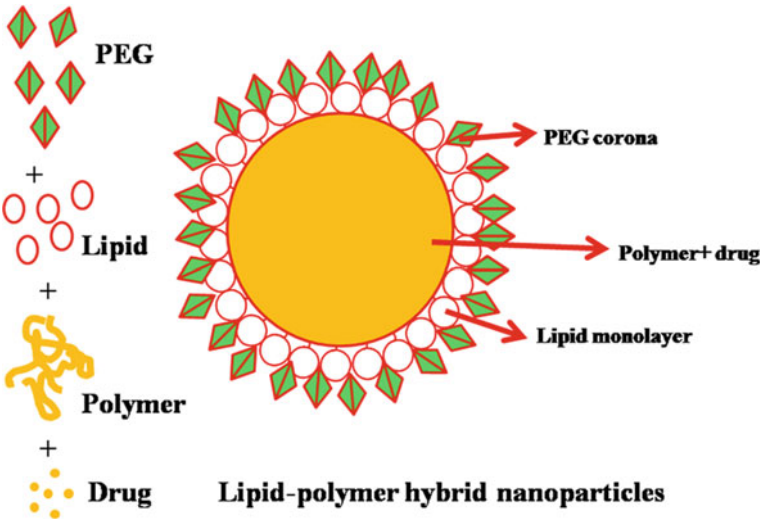

Fig. 16 Schematic representation of the preparation of LPN via one-step method

nanoparticles. The surface of the nanoparticle acts as site for self-assembly of lipids and lipid-PEG. The self-assembly of lipids are promoted through hydrophobic interactions which reduce the free energy of the system. The hydrophobic tails of the lipids project towards the hydrophobic polymer core, and the hydrophilic head will face the external aqueous environment. The lipid-PEG conjugate stabilizes the self-assembly process by inserting its lipid moiety into the lipid monolayer and PEG moiety outside the lipid monolayer and thereby providing a stealth corona to the nanoparticles. The self-assembly of lipids and lipid-PEG conjugates may be promoted by elevating temperature above the phase transition temperature of the lipids [10]. This is relatively quick and cost-effective compared to other existing processes (Table 4).

(Poly (lactic-co-glycolic acid) (PLGA), polybutylcyanoacrylate (PBCA) and methyl methacrylate sulfopropyl methacrylate (MMA-SPM), poly(methyl methacrylate) (PMMA), methyl methacrylate sulfopropyl methacrylate (MMA-SPM), polyethylene-polypropylene glycol (poloxamer 338) and PEGylatedtocopheryl succinate ester (TPGS 1000), human brain microvascular endothelial cells (HBMEC), efavirenz (EFV) and boosted lopinavir (lopinavir/ritonavir; LPV/r), sodium lauryl sulfate (SLS) or with cetyltrimethylammonium bromide (CTAB)) zidovudinephosphoryl-deoxycholyl didanosine (ZPDD), zidovudine (AZT), didanosine (ddI), ursodeoxycholic acid (UDCA), human retinal pigment epithelium (HRPE), sialic acid conjugated-mannosylated poly(propyleneimine) (PPI) dendritic nano-constructs. Fourth-generation PPI dendrimers, sialic acid conjugated PPI dendrimers (SPPI), mannose conjugated PPI dendrimers (MPPI) and dual ligand system, i.e. sialic acid conjugated-mannosylated PPI dendrimers (SMPPI), zidovudine (AZT), efavirenz (EFV) and lamivudine (3TC).

Table 4 Summary of different nanomaterials used for antiviral drug delivery

	Nanomaterial	Antiretroviral drug	The method of testing	Cells/tissue/organs	References
Synthetic polymers	PLGA	D4T	in vitro	Macrophages	[8]
	PBCA, MMA-SPM	D4T	in vitro	BMVECs	[71]
	PBCA, MMA-SPM	AZT, 3TC	in vitro	BBMECs	[72]
	PBCA, MMA-SPM	D4T, DLV	in vitro	HBMECs	[74]
	Eudragit RL 100	AZT	ex vivo	Wistar rat skin	[125]
	PLGA	AZT, 3TC	in vivo	Mice	[32]
	PHIC	AZT	ex vivo	Lymphoid tissue	[30]
	PHCA	AZT	in vitro	Macrophages	[82]
	PPG-5-CETE-TH-20	AZT	in vitro	release study	[17]
	PLA, PLA-PEG	AZT	in vitro	Macrophages	[83, 84]
	PLGA	3TC	in vitro	HepLL	[134]
	PMAA	3TC	in vitro	release study	[126]
	Poloxamer 388	RPV	in vivo	Mice and dogs	[7, 50]
	PLGA	NVP	in vitro	HBMECs	[73]
	Polysaccharide, PEG	NVP	in vivo	Mice	[116]
	PLGA	EFV	in vivo	PBMCs	[31, 117]
	PCL or PEO	DPV	ex vivo	Pig mucosa	[28]
Natural polymers	chitosan	3TC	in vitro	release study	[33, 99]
	squalene	ddC	in vitro	PBMCs	[49]
	gelatine	AZT	in vitro	reticuloendothelial system	[55]
	Mannosylated gelatine	ddI	in vivo	mice	[56, 58]
	chitosan	D4T	in vitro	Release study	[61]
Dendrimers	Mannosylated dendrimer	3TC	in vitro	macrophages	[36]
	tuftsindendrimers	EFV	in vitro	Monoc/macroph	[18, 35]

(continued)

Table 4 (continued)

	Nanomaterial	Antiretroviral drug	The method of testing	Cells/tissue/organs	References
	PPI, MPPI, SPPI, SMPPI	AZT	in vitro	macrophages	[39]
Liposomes	liposomes	ddCTP	in vitro	Monoc/macroph	[57]
	liposomes	AZT	in vivo	mice	[56, 58, 59]
	galactosylated liposomes	AZT	in vivo	mice	[133, 135]
	Mannosylated liposomes	AZT	in vivo	mice	[41]
	liposomes	D4T	in vitro	macrophages	[63, 64]
	Mannosylated liposomes	D4T	in vitro	macrophages	[62]
	galactosylated liposomes	D4T	in vitro	Monoc/macroph	[53, 54]
	liposomes	ddI	in vitro	U937	[67]
	liposomes	ddIMP	in vitro	PBMCs	[66]
	liposomes	ddC	in vitro	U937	[110]
	liposomes	ddCMP	in vitro	Monoc/macroph	[53, 54]
Miscellaneous	cyclodextrin	EFV	in vitro	U937	[9]
	micellesP-85	AZT, 3TC	in vitro	macrophages	[100]
	Macrophages	EFV	in vitro	monocytes	[52]
	CNT	3TC	in vitro	MT-4	[53, 54]
Drug conjugates	ZPDD	AZT and ddI	in vitro	macrophages	[60]
	UDCA–AZT	AZT	in vitro	HRPE	[26]
LPN	Cutina®HR	AZT	–	–	[70]
	lactoferrin	AZT, 3TC, EFV	in vitro	macrophages	[68]

2 Conclusions

AIDS and HIV infection has become a life-threatening pandemic. The ever-altering nature of the virus and its infection cycle has created many hurdles for creating an efficient drug delivery system. Several nanocarriers have been studied to enhance the bioavailability, circulation time and therapeutic potential of these drugs. Several types of polymeric, liposomal and hybrid nanoparticles have been synthesised and reported. Such nanosystems have shown great potential in terms of controlled/sustained release of drugs, improved bioavailability, increased circulation time and superior targeting ability. Such nanoformulations can be expected to bring considerable relief to AIDS patients and their caregivers. These systems provide a very bright outlook for the future of drug delivery for HIV/AIDS treatment and these formulations could be modified and extended to deliver drugs for numerous other disease that prevail all over the world.

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