International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 12, Special Issue 4, 2020

Full Proceeding Paper

TAILORING THE NANOPARTICLES SURFACE FOR EFFICIENT CANCER THERAPEUTICS DELIVERY

ARUSHI CHAUHAN[1], RAVI RANJAN[1], PRAMOD AVTI[1*], ARVIND GULBAKE[2#]

[1]Department of Biophysics, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India 160012, [2]Centre for Interdisciplinary Research, D. Y. Patil Education Society, Deemed to be University, Kolhapur, M. S., 416006, India
***Email: pramod.avti@gmail.com, arvind.gulbake@gmail.com**

Received: 20 Apr 2020, Revised and Accepted: 1 Jul 2020

ABSTRACT

Nanotechnology has tremendous advantages in many areas of scientific as well as clinical research. The development of nanoparticles (NPs) that can efficiently deliver drugs specifically to the cancer cells can help reduce normal cells toxicity and co-morbidities. Cancer can be treated by exploiting the unique physiochemical of the NPs, and modulating their surface modifications using ligands which further could be used as drug cargo vehicles. To enhance biocompatibility and drug delivery towards the target site, various modifications can be included to modify the surface of the NPs, such as carbohydrates, dendrimers, DNA, RNA, siRNA, drugs, and other ligands. These ligand-coated NPs have potential applications in the field of biomedical research, including diagnosis, contrast agents for molecular and clinical imaging (Magnetic Resonance Imaging (MRI), Computed tomography (CT), positron emission tomography (PET)), as cargo vehicles for drugs, increasing the blood circulation half-life, and blood detoxification. Further, the conjugation of anti-cancer drugs to the NPs can be efficiently used to target the cancer disease. This review highlights some of the features and surface modification strategies of the NPs, such as an iron oxide (IO), liposomes (LP)-based NPs, and polymer-based NPs, which show their effectiveness as cargo agents for cancer therapeutics.

Keywords: Cancer therapeutics, Dendrimers, Nanomaterials, Iron Oxide Nanoparticles, Lipid nanoparticles, Polyethyleneglycol, Polymeric nanoparticles, Polyvinyl alcohol, Transferrin

DOI: http://dx.doi.org/10.22159/ijap.2020.v12s4.40099. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The human body consists of trillions of cells, and each group of cells is designated for a specific function to sustain life. Healthy cells divide when they receive a chemical signal by various mechanisms, and the whole phenomenon is known as cell division. The cell division process is tightly regulated to maintain the normal homeostasis and is a critical issue in cancer due to the uncontrolled and unregulated proliferation of cell population [1]. Moreover, cancer cells can invade nearby tissues and get disseminated to distant locations in the body by the process called metastasis, thereby creating an unwarranted and imbalanced environment of normal homeostasis. The cancerous cells invade remote sites mostly via the bloodstream/lymphatic system, a process known as malignant neoplasms, which is a life-threatening situation and ultimately leads to death (fig. 1). The main goal of cancer treatment is to prevent uncontrolled cell proliferation and metastatic potential [2, 3]. Therefore, numerous therapeutic approaches are emerging to cure cancer [4, 5] based on molecular targets (receptors) such as overexpressed proteins and aggressive multiplication of DNA.

Some of the approved chemotherapeutic drugs available for the treatment of cancer include doxorubicin (DOX), paclitaxel (PTX), gemcitabine, and cisplatin, to name a few. Unfortunately, chemotherapy in clinics fails mainly due to toxic side effects and their bioavailability at the different target sites other than the specific target site [6]. Studies on chemotherapy failure in clinics also suggests the diverse phenomenon of multi-drug resistance [7]. To overcome the limitations of bioavailability, multi-drug resistance, alternate treatment strategies such as radiotherapy (external beam therapy) and molecular radiotherapy (using beta and alpha radiation) are emerging in the absence/presence of various drugs in clinical settings [8]. Instead, radiotherapy also has few limitations with its side effects associated with the use of alpha and beta radiation. The most common side effects during the radiotherapy treatment include the resistance, recurrence after initial treatment, and tumor lysis syndrome. The treatment of cancer in the clinics has to be more effective in the form of specific therapy such as chemo, immune, and radiotherapy. For clinical validation, there is a need for systematic clinical trials to provide opportunities and compelling goals for cancer treatment. However, various difficulties or challenges exist while executing clinical trials, including poor study design, poor trial execution, patient safety, dropouts, and reduced patients recruitment [9, 10]. Therefore, to overcome the challenges, especially with the treatment modalities carried out, cargo agents such as NPs for specific and versatile delivery platforms are needed to exploit the safety, efficacy, and effectiveness of the treatment. These treatment modalities should have strategies that rule out the consequences of bioavailability, tumor lysis syndrome, and multi-drug resistance.

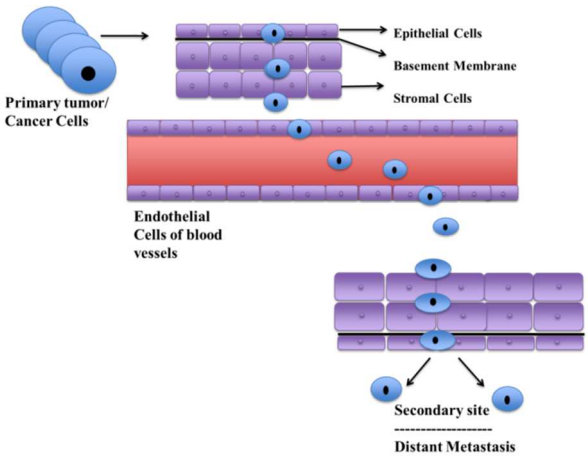

Fig. 1: Primary tumor and metastasis process

The use of NPs in the field of nanomedicine acts as a versatile therapeutic platform for the synthesis and development of drug targeting cargos for the treatment of various types of cancers [11, 12]. The versatility in the use of NPs depends on the use of a variety of materials such as metals, inorganic and organic, due to their ease

of synthesis, surface manipulations to carry desired functional groups, high binding affinity, ease of transport, which themselves act as therapeutic agents or carry the therapeutic agents and delivers especially to the tumor cells [13, 14]. NPs provide an efficient technology platform due to their flexibility and ease in tuning their biocompatible properties, synthesis of desired size and shape, tailoring various surface functional groups, and unique physio-chemical features [15, 16]. The conjugation of potential chemotherapeutic drugs with NPs has various advantages over the use of chemotherapeutic drugs such as transportation, specific targeting ability with reduced systemic toxicity, and enhanced drug accumulation inside the tumor [17-19]. The surface-modified-NPs also increases the absorption across the epithelial distribution and leaky membranes in the tumor to reach the optimal concentration very quickly in the tumor site as compared to chemotherapeutic drugs when used alone.

There are various types of NPs, such as lipid-based NPs, nanocapsule, polymeric NPs, metallic NPs, dendrimers, and LPs, emerging as useful tools in the clinical settings (fig. 2) [20, 21]. However, consideration of NPs based drugs in clinical practice remains unlikely due to various concerns such as possible toxicity issues, without exceptional regulatory guidance and compliance, cost-benefit attention, and decreasing interest for some health care staff. To date, different nanotechnology-based chemotherapeutic synthetic strategies are reported that could be considered for clinical use [22, 23]. Hence, we used different databases such as PubMed, Web of Science, Scopus, Ebesco for performing the search using the key terms such as lipid nanoparticles, polymeric nanoparticles, metallic nanoparticles, cancer, surface modifications to search for the relevant articles and considered.

Types of nanoparticles

Iron oxide (IO)-NPs

Iron oxide NPs (IONPs) have improved super paramagnetic properties and are extensively considered for various clinical applications [24]. The different types of IO used for the NPs synthesis include Fe_3O_4 (magnetite), α-Fe_2O_3 (hematite or antiferromagnetic), c-Fe_2O_3 (maghemite, ferrimagnetic), FeO (wustite, anti-ferromagnetic), γ-Fe_2O_3 and β-Fe_2O_3. However, Fe_3O_4 and γ-Fe_2O_3 NPs are the favorable and most commonly used chemical forms that are specially designed for various biomedical applications such as imaging contrast agents for MRI, thermal therapeutic tools [25, 26] and as cargo vehicles due to their features of improved biocompatibility and easy formulation [27-30]. These are structurally constituted, having nanocrystalline magnetite Fe_3O_4 or γ-Fe_2O_3 with a polymeric coating. The Fe_3O_4 and γ-Fe_2O_3 NPs hold complex spinal crystal structure depending upon the cation distribution where oxygen ion atom occupies a tight packing in cubic lattice and iron ions atom positioned at interstices. Some studies provide insights and reveal that magnetization occurs due to the exchange of electrons between Fe^{2+} and Fe^{3+} atom ions that cohabit in the octahedral structure [31]. The properties that make the IONPs unique is due to their crystallizability, size, shape, super paramagnetic properties and magnetization induced heat generation. Since the size and shape of IONPs are related to their inherent properties, therefore synthesis is an important step. There are several optimized methods for the synthesis of IONPs, which comprise the co-precipitation, microemulsion, sonochemical methods, hydrothermal synthesis, and thermal decomposition. Furthermore, other methods of IONPs synthesis include electrochemical synthesis [32], laser pyrolysis techniques [33], microorganisms, or magnetotactic and iron-reducing bacterial synthesis. Considering the formulation of IONPs for clinical use is a significant challenging aspect. It requires specific surface modification that renders them high biocompatibility in the biological environment, reduces self-aggregation over longer duration preservation, reduces metal-related biological/clinical toxicity, multifunctional properties to hold the drugs for therapeutic effects and antibodies attachment for specific targeting while retaining the intrinsic superparamagnetic properties. The reactive shell properties of IONPs are used for various functional groups attachments such as a range of organic ligands (carboxylic acid, Phosphonic acid) [34, 35] polymers (PVA, PEG and PAA), sugars (Dextran, Chitosan) and zwitterionic ligand.

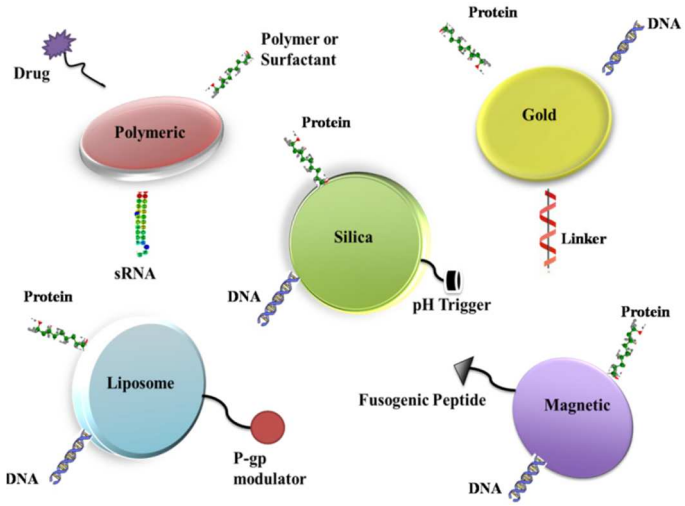

Fig. 2: Types of NPs and their multifunctional strategies

Further, other metallic/inorganic NPs (Gold, silica and Tantalum oxide), cross-linking besides engineering the surface coating layer is related to the nature of the NPs and their preferred biomedical applications [36, 37]. Besides, another group of researchers coated IONPs using small charged molecules, for example, folic acid to avoid macrophages uptake and enhance the heating to the cancer cell [36]. The *in vivo* kinetics and dynamics, and ultimately the fate of the IONPs, depends on the NPs and the type of the surface coatings, which determines the overall hydrodynamic size. Small NPs of approximately 20 nm with higher blood circulation half-life are usually excreted from the kidneys [38], and large NPs (150 nm) are quickly uptaken by the reticuloendothelial system (RES) predominantly by the liver and spleen. However, NPs with an intermediate size between 20-150 nm are mainly distributed in the heart, kidneys, and bone marrow [39].

Nanocrystalline magnetite (Fe_3O_4) cores have huge potential for biomedical applications in clinical cancer due to their properties that include biocompatibility, biodegradability, and simple and ease of synthesis [40]. There are two types of biocompatible layers that

can be considered to modify the surface of IONPs, i.e., organic and inorganic coatings [27]. The organic biocompatible based coating approaches are by either using a ligand exchange mechanism or physical assemblage/encapsulation [28]. Inorganic biocompatible coating involves the use of silica, Tantalum (V) Oxide. Gold NPs (GNPs) are inert and easily tailored by linking with the designed architecture of thiol (-SH) group ligands to render the best biocompatible properties [41]. Such types of coatings are used for therapeutic applications by attaching an antibody using the PEG linker to the Mag-GNP nanoshell [42]. IONPs coating with silica is performed by the Stober method or the reverse microemulsion [43]. The coated shells of IONPs allow performing various functions such as drug delivery vehicles in *in vivo* for the multimodal MRI and fluorescent imaging applications [42, 29].

In a Fe_3O_4 microemulsion of tantalum (V) oxide, a sol-gel reaction was carried out to obtain Fe_3O_4/TaOx core/shell multifunctional NPs [44]. Upon intravenous injection, such NPs exhibit long circulation half-lives. This rendered them as CT and MRI contrast agents to observe the changes associated with angiogenesis and the tumor microenvironment. Various researchers showed that multimeric ligand which can be bidentate or multidentate, for example, Dimercaptosuccinic acid (DMSA), containing bidentate-COOH groups provide excellent colloidal stability to IONPs in aqueous media and render water solubility and stability [43, 45]. These NPs exhibiting a hydrodynamic size of ~10 nm are highly stable between 6-8.5 pH ranges, do not self-aggregate in solution over long-standing, form highly homogenous solution, and are excreted by the kidneys. Natural ligands, like polysaccharides, can also interact with IONPs, which have many hydroxyl groups and carboxylic groups (-COOH), alginates, and amino acids [46]. Physical encapsulation of IONPs can also be achieved using LPs, micelles, and polymersomes via electrostatic interactions or van der Waals interactions. Such kind of biocompatible coatings is explicitly used in drug delivery for *in vivo* and *in vitro* therapeutic applications. Earlier anti-cancer drugs received much attention; due to the biocompatible nature of IONPs and are used as anti-cancer drug vehicles for the cancer therapeutic applications. Many anti-cancer drugs, for example, Doxorubicin (DOX), temozolomide (TMZ), and paclitaxel (PTX) are used with biocompatible coatings around IONPs and have been effectively validated *in vitro* and *in vivo* for their cancer treatment efficacy [47, 48].

Hequn Hao and colleagues [47] synthesized Fe_3O_4 nanocrystals using a co-precipitation technique in an alkaline medium with few modifications in which DOX-HCl aqueous solution was loaded onto Fe_3O_4 solution at room temperature in dark conditions followed by constant mixing at physiological pH for 12 h. Fe_3O_4 nanocrystals of size 10 nm were loaded onto BSA-DEX-FA NPs under high temperature, which triggers BSA gelation encapsulating the nanocrystals. Further, by diffusion technique, DOX was loaded onto BSA-DEX-FA, and the final formulation of NPs was obtained as DOX/Fe_3O_4/BSA-DEX-FA with an overall size of 100 nm that showed good solution homogeneity and stability. *In vitro* cytotoxicity studies using MTS assay in KB cells treated with DOX alone, and DOX loaded IONPs solutions having 1 µg/ml DOX at various intervals (24, 48 h and 72 h). These results showed a progressive decline in cancer cell proliferation in a dose and time-dependent manner. Furthermore, the tumor inhibition efficacy of DOX/Fe_3O_4/BSA-DEX-FA was evaluated in tumor mice models (18-22 g). Upon intravenous administration of DOX/Fe_3O_4/BSA-DEX-FA, and under the external magnetic field of 0.15T, the proper localization and accumulation of DOX loaded NPs into the tumor region was enhanced. Results obtained from these studies shows the tumor inhibition rate of about 63%, respectively. In comparison, with DOX alone, it was 55 %, respectively.

Temozolomide (TMZ) is a chemotherapeutic agent used for the management of glioblastoma. TMZ loaded IONPs functionalized with chitosan showed a hydrodynamic size of 50 nm [49]. Chlorotoxin (CTX) moieties are used as targeting ligands on these NPs. TMZ formulated IONPs exhibited higher stability at pH 7.4, followed by very long systemic circulation half-life, i.e., 7 times more than that of TMZ alone. A pre-clinical dose-response curve was analyzed in human U-118 MG cells by treatment with various concentrations (0-200 ng/ml) of TMZ, NP-TMZ, or NP-TMZ-CTX. This study showed great promise to convey a remedial dosage of NP-TMZ-CTX as compared to TMZ alone treatment at 72 h and showed 2-6 times much higher uptake into the cells and 50-90% reduction in the tumor cell proliferation.

Studies also suggest the preparation of IONPs using double emulsion capsule (DEC) stabilizers in the presence of surfactants such as PVA forming the DEC-IO complex. Paclitaxel (PTX) anti-cancer drug was loaded onto DEC-IO to form a complex of DEC-IO-PTX with a hydrodynamic size range of 75–200 nm. *In vitro* cell viability experiments in HeLa and MCF cells with DEC-IO-PTX treatment for 24 h showed IC_{50} values of 65±7% less as compared to DEC-IO *i.e.*90±15%. They have also explored a targeting ligand like peptide IV024 by DEC using EDC linker against several xenograft cancer models of lungs, breast, prostate, liver, and oral cancer. When the cells were targeted using IV024 with a DOX, and PTX loaded IONPs, cell viability of only 10% was observed within 24 h of treatment with DOX and 5% with PTX in HeLa and MCF-7 cancer cells. These results explored the role of IV024 peptide using IONPs loaded anti-cancer agent for targeting the cancer cells. Similar studies were also performed using anti-cancer drug DOX, DEC–IO–DOX and targeting peptide ligand IV024, IVO24–DEC-IO–DOX, in the same cancer cells and the cell viability was effectively reduced with peptide ligand IV024 [50].

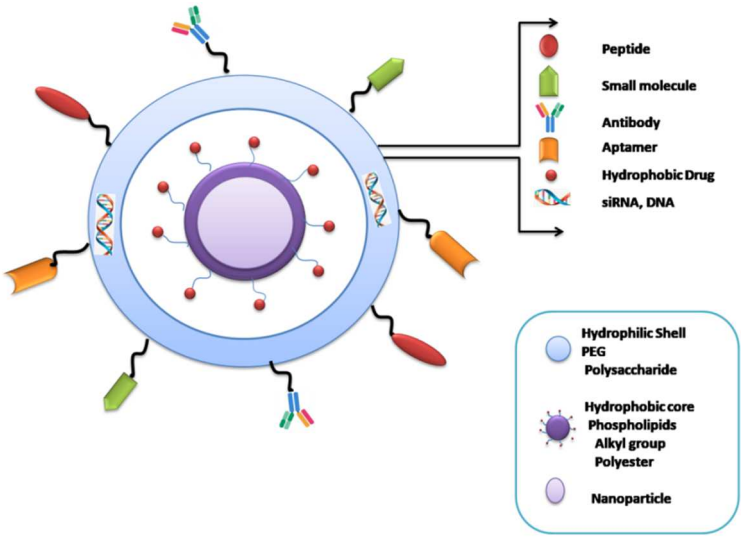

Fig. 3: IONPs and surface modifications

Liposome nanoparticles (LP-NPs)

LPs are prepared from lipids, generally composed of phospholipids, and used as colloidal drug delivery systems [51]. LPs are chemically made up of phospholipids and cholesterol. Furthermore, these LPs have multiple concentric bilayers with each lipid bilayer separated by aqueous media [52]. Primarily, LPs were implied to understand the substantial properties of cell membranes, which include lipids alignment in the bilayer, their physiochemical properties, and ion transportation through the biological membrane. There are various type of LPs such as multilamellar vesicles, constituted with phospholipid bilayer membrane unplugged by aqueous medium up to 5 µm size. Small unilamellar vesicle made up of aqueous partition enclosed with a mono lipid bilayer and the size of such LPs range from 20-100 nm [51, 52]. We know the majority of LPs components are chemically phospholipids and cholesterol, which make the majority proportion of the biomembranes. Such chemical characteristics of lipids regulate the major behavior of LPs. LPs preparations involve the use of phospholipids and the most commonly used phospholipids include egg, or soya, phosphatidylcholine, and synthetic phosphatidylcholine [53, 54]. Since naturally occurring phospholipids like egg or soya bean phospholipids have a significant extent of polyunsaturated fatty acid, they render the vesicles less stability than their synthetic equivalents. The molar proportion of phospholipid ranges from 55 to 100 % of total LPs constituents. The 2-distearoyl-sn-glycerophosphocholine (DSPE) is known to be the most common phospholipid in the LPs. The head region of DSPE is used to coordinate with other functional charged groups of other polymers such as polyethylene glycol (PEG) [55, 56]. However, phospholipid components alone of LPs make the sieve-like properties; therefore, the ratio of cholesterol determines the LPs formulation and their stability. The molar proportion of cholesterol, if varied between 30-45% of the total LPs component, determines the rigidity, elasticity, permeability, stability, and fluidity of the bilayer [54, 57, 58]. Furthermore, cholesterol also strengthens the LPs in terms of the rigidity and thereby influences the lipid bilayers phase transition properties. The increased rigidity influences encapsulated drug leakage from the vesicles. Some of the research groups also revealed that cholesterol avoids hydrolytic degradation of the lipid bilayer. Depending on the application of LPs, various other components also have been used in addition to phospholipid and cholesterol. The overall liposomal surface charge plays a crucial role in the cellular uptake mechanism. Studies show that the process of endocytosis mechanism easily takes positively charged or cationic LPs, whereas negatively charged and neutral LPs show low endocytosis uptake. However, negatively charged LPs are frequently used in drug delivery applications because negative surface charges can be recognizable by receptors present on various cells, including the RES. The charge on the liposomal surface also plays a crucial function in deciding the fate of the LPs intracellularly [59, 60]. While using the LPs in the clinical settings, PEG is the most widely used surface modifier to amplify blood circulation time due to its stealth properties (escaping the engulfing process and rapid clearance through the RES) and has demonstrated widespread application in the drug delivery applications for effective cancer treatment. The various synthetic techniques adopted for the preparation of LPs include-solvent removal, ethanol injection methods, emulsion, and detergent removal [59-61]. From these methods, the size distributions of LPs obtained are in the range of 25-1000 nm depending on the LPs method adopted. However, typical sizes between 50 to 200 nm are commonly used for a variety of biomedical applications. Furthermore, we know that LPs act as a hydrophilic, hydrophobic, and amphiphilic carrier, and accordingly, the hydrophobic or hydrophilic drugs can be used to entrap or encapsulate within the LPs resulting in effective cancer cell therapeutics [53, 55]. Therefore, both hydrophobic and hydrophilic drugs can be used to entrap or encapsulate within the vesicles. The hydrophobic drug gets intercalated within the lipid layers of the LPs, whereas hydrophilic drugs encapsulate in the central aqueous core. However, the encapsulation of chemotherapeutic drugs into LPs is commonly brought about into two different ways (1) passive loading–encapsulation of the drug at the time of vesicle formation and (2) dynamic loading–vesicle formation followed by drug trapping. LPs are known to be the most organic NPs approved for cancer treatment and usually have a great potential for targeting as delivery vehicles for chemotherapeutic drugs. Other applications of LPs include reduced transferrin (TF) elimination, enhance targeting specificity and reduce the chemotherapeutic agent's non-specific side effects [34, 62, 63].

Several liposomal based drugs are now available in market such as Doxil®/caelyx® (DOX), myocet® (DOX), lipodox® (DOX), daunoxome® (daunorubicin), depocyt™ (cytrabin) marqibo®, (vincristine), onco TCS (vincristine), onivyde®, doceAqualip and visudyne®. Usually, most of the liposomal formulations are used as intravenous injections, and their systemic administration leads to the rapid clearance from the circulation due which most of them show very short circulating half-lives. However, the circulation half-lives could be increased, if needed, in some cases of treatment strategies by using branched or long chains of PEGylation. The first example of liposomal NPs drug is DOX-PEGylated LPs (Doxil ®), which has shown reduced cardiotoxic side effects [22, 64]. Doxil ® is approved for numerous solid tumors, such as Kaposi's sarcoma, ovarian cancer, multiple myeloma, and metastatic breast cancer [38, 65]. Various studies revealed that PEGylated LPs-DOX enhances about 4 to 16 fold of drug efficacy in cancer cell treatment in comparison to free DOX. Some of the complex LPs systems have also been reported and are in the clinical trial.

Cyclic RGD and TF were also used to enhance specific binding to the tumors and efficient cellular uptake since TF is a possible ligand for effective delivery as it can cross the blood-brain barrier (BBB) easily. Studies have shown the introduction of multiple functional groups onto the LPs to create RGD/TF-Lpas cargo systems. This system is used for linking the PTX drug to form a new complex system that precisely targets the gliomas. Recently, varieties of monoclonal antibodies have been tagged to LPs for targeting various types of cancer (anti-HER2 long-circulating LPs are used to target HER2-over expressing tumors). Antibody CC52 against an *in vivo* model of rat colon adenocarcinoma CC531 conjugated with PEGylated LPs had high uptake levels in cancer. Studies have also shown that i. v. administration of (TAG)-72 conjugated with PEG-LPs effectively targeted and accumulated in LS174 T human colon cancer cells [66].

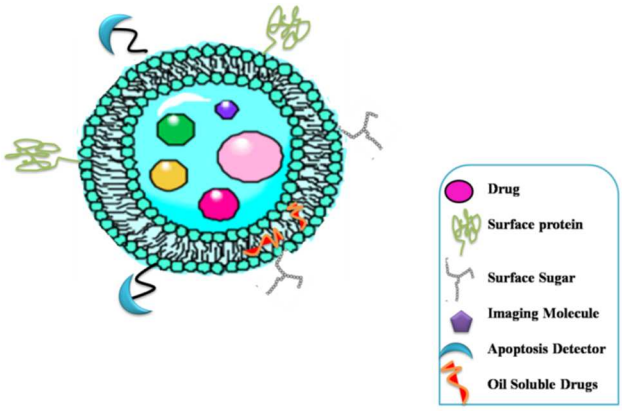

Fig. 4: Liposome based nanoparticles

Polymeric based NPs

Polymeric NPs are one of the most studied across all aspects of the field, including biomedical applications due to their facile synthesis [45, 67-70]. Polymeric NPs consist of the polymeric membrane, such as a hydrophilic and lipophilic surfactant. In polymeric NPs, natural and synthetic polymers such as N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), Polyethylene glycol (PLGA), PLA, chitosan and HA are used. Recent insight revealed that natural and chemically modified polymeric NPs drug delivery allow more accurate to target specific since the coating of the NPs with polymer enhances the quantity of drug-loaded also help in tissue/cell-specific recognition proteins which leads to a more targeted and efficient NPs. Such NPs play a vital role as a carrier and suitable for the chemotherapeutic drug. Utilization of a single polymer chain of polymeric nanoparticle in cancer therapy provides as a therapeutic agent or helps in chemical modification for drug conjugation [71]. Poly(lactide-co-glycolic acid) (PLGA) is a synthetic polymer known to have outstanding properties for *in vivo* targeting of cancer because of their biodegradability and bio−compatibility properties [72, 73]. PLGA is a commonly used synthetic polymer and widely preferred for the drug-loaded NPs preparation [74, 75]. Furthermore, hyaluronic acid (HA) is containing negative charge and non-sulfated glycosaminoglycan (GAG), which is seen in connective tissue, neural tissue, and epithelial cells. Due to its excellent features such as biocompatibility, biodegradability, and non-immunogenicity, HA has been extensively used and widely studied for cancer treatment [76]. The finding from various groups also suggests that the PEGylated-HA NPs reduces the uptake in the liver and shows extended blood circulation half-lives and enhanced the tumor accumulation in cancer cells [77]. *In vivo* studies indicates that the PEGylated-PAC NPs loaded with DOX showed a more significant chemotherapeutic effect with reduced toxicity as compared to the DOX alone treatment [78].

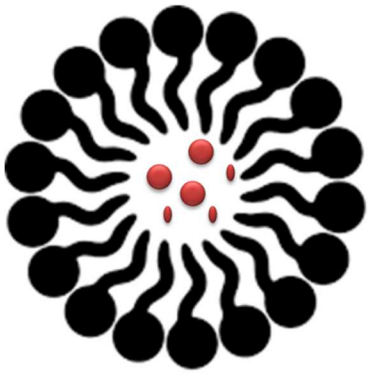

Fig. 5: Polymeric micelle

Challenges

NPs provide great opportunities in cancer therapy, leading to an improvement in cancer survival cases due to their high sensitivity and specificity. NPs based drug delivery in cancer therapy is an expanding field of research with the new technological advancements that has revolutionized medical research in the recent years. Though current scientific evidences shows promising results, however, there are few challenges of concern when it comes to the development of biocompatible NPs and their mode of treatments. Toxicity is of utmost importance and might occur due to various reactions taking place within the biological systems. Another critical challenge that limits the use of NPs-based drugs in clinical settings is the lack of adequate guidelines. Therefore, significant complications in the clinical application of nanomaterials are the estimation of the toxicities and mimicking the *in vivo* effects of nanoformulations. However, future advancements and research in this field will provide promising benefits in cancer treatment.

CONCLUSION

The cancer therapy that is available these days is not able to accurately target tumors and metastasis. Moreover, drug-resistance towards the clinically available and use of chemotherapeutic strategies is a major challenge. There is a need to develop strategies that could help target tumors more effectively and with reduced side effects. NPs such as IONPs, LPs based NPs and polymeric NPs can act as therapeutic tools for targeting cancers. However, the most recent strategies for making use of NPs as cargo agents for drug delivery in chemotherapeutics includes their ease of design and synthesis of desired sizes and shapes. The versatile nature and use of various types of NPs include the flexibility of surface modification by multifunctional agents/ligands as cargo agents for drug delivery. These surface-modified NPs shows potential in accumulating at the tumor target site (both *in vitro* and *in vivo*) with high efficacy and efficiency, can be modulated in the circulation for desired time durations and overcomes the phenomenon of drug-resistance. Such NPs design strategies are evolving and the recent evidences suggest that NPs are promising tools for cancer chemotherapeutics.

ABBREVIATION

Blood-brain barrier (BBB), Bovine serum albumin (BSA), Computed tomography (CT), Double emulsion capsule (DEC), Docetaxel (DEX), Dynamic light scattering (DLS), Deoxyribose nucleic acid (DNA), Doxorubicin (DOX), Folic acid (FA), Food and drug administration (FDA), Glycosaminoglycan (GAG), Good manufacture practice (GMP), Hyaluronic acid (HA), N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), Intravenous (I. V.), Iron oxide nanoparticles (IONPs), Liposomes (LPs), Magnetic nanoparticles (MNPs), Magnetic resonance imaging (MRI), Nanoparticles (NPs), Paclitaxel (PTX), Polyacrylic acid (PAA), Polyethylene glycol (PEG), Polylactic acid (PLA), Poly(lactide-co-glycolic acid) (PLGA), Polyvinyl alcohol (PVA), Reticuloendothelial system (RES), Transferrin (TF), Temozolomide (TMZ), Ultrasonography (US)

FUNDING

Dr. Gulbake acknowledges the receipt of the financial support provided by D. Y. Patil Education Society, Institution Deemed to be University, Kolhapur (Intramural Project Grant, DYPES DU/2017/2653).

AUTHORS CONTRIBUTIONS

Arushi Chauhan (AC) and Ravi Ranjan (RR) equally contributed in performing the search, collecting the data, drafting the manuscript and references. Pramod Avti (PA) and Arvind Gulbake (AG) conceived the idea, written and edited the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. Fischer T, Wilharm N, Hayn A, Mierke CT. Matrix and cellular mechanical properties are the driving factors for facilitating human cancer cell motility into 3D engineered matrices. Converg Sci Phys Oncol 2017;3:044003.
2. Suhail Y, Cain M, Vanaja K, Kurywchak P, Levchenko A, Kalluri R Kshitiz. Systems biology of cancer metastasis. Cell Syst 2019;9:109-27.
3. Xi W, Schmidt CK, Sanchez S, Gracias DH, Carazo-Salas RE, Butler R, *et al.* Molecular insights into division of single human cancer cells in on-chip transparent microtubes. ACS Nano 2016;10:5835-46.
4. Ramakrishna N, Temin S, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, *et al.* Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2–positive breast cancer and brain metastases: american society of clinical oncology clinical practice guideline. J Clin Oncol 2014;32:2100.
5. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, *et al.* EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618-29.

6. Oronsky BT, Carter CA, Oronsky AL, Salacz ME, Reid T. "No patient left behind": an alternative to "the War on Cancer" metaphor. Springer; 2016.
7. Wang Y, Dou L, He H, Zhang Y, Shen Q. Multifunctional nanoparticles as nanocarrier for vincristine sulfate delivery to overcome tumor multidrug resistance. Mol Pharm 2014; 11:885-94.
8. Schofield PN, Kondratowicz M. Evolving paradigms for the biological response to low dose ionizing radiation; the role of epigenetics. Int J Radiat Biol 2018;94:769-81.
9. Cartmell KB, Bonilha HS, Matson T, Bryant DC, Zapka J, Bentz TA, *et al.* Patient participation in cancer clinical trials: a pilot test of lay navigation. Contemp Clin Trials Commun 2016;3:86-93.
10. Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review. Contemp Clin Trials Commun 2018;11:156-64.
11. Ovais M, Raza A, Naz S, Islam NU, Khalil AT, Ali S, *et al.* Current state and prospects of the phytosynthesized colloidal gold nanoparticles and their applications in cancer theranostics. Appl Microbiol Biotechnol 2017;101:3551-65.
12. Piktel E, Niemirowicz K, Wątek M, Wollny T, Deptuła P, Bucki R. Recent insights in nanotechnology-based drugs and formulations designed for effective anti-cancer therapy. J. Nanobiotechnol 2016;14:39.
13. Ng VW, Avti PK, Bedard M, Lam T, Rouleau L, Tardif JC, *et al.* Miktoarm star conjugated multifunctional gold nanoshells: synthesis and evaluation of biocompatibility and cellular uptake. J Mater Chem B 2014;2:6334-44.
14. Bédard M, Avti PK, Lam T, Rouleau L, Tardif JC, Rheaume E, et al. Conjugation of multivalent ligands to gold nanoshells and designing a dual-modality imaging probe. J Mater Chem B 2015;3:1788-800.
15. Saleem J, Wang L, Chen C. Carbon-based nanomaterials for cancer therapy via targeting tumor microenvironment. Adv Healthc Mater 2018;7:1800525.
16. Wang Y, Sun S, Zhang Z, Shi D. Nanomaterials for cancer precision medicine. Adv Mater 2018;30:1705660.
17. Haley B, Frenkel E. editors. Nanoparticles for drug delivery in cancer treatment. Urol Oncol Sem Ori: Elsevier; 2008.
18. Palazzolo S, Bayda S, Hadla M, Caligiuri I, Corona G, Toffoli G, *et al.* The clinical translation of organic nanomaterials for cancer therapy: a focus on polymeric nanoparticles, micelles, liposomes and exosomes. Curr Med Chem 2018;25:4224-68.
19. Bi Y, Hao F, Yan G, Teng L, J Lee R, Xie J. Actively targeted nanoparticles for drug delivery to tumor. Curr Drug Metab 2016;17:763-82.
20. Avti PK, Kakkar A. Dendrimers as anti-inflammatory agents. Braz J Pharm Sci 2013;49:57-65.
21. Avti PK, Maysinger D, Kakkar A. Alkyne-azide "click" chemistry in designing nanocarriers for applications in biology. Molecules 2013;18:9531-49.
22. Barenholz Y. Doxil-the first FDA-approved nano-drug: from an idea to a product. Handb Harnessing Biomater Nanomed 2012:335-98. DOI:10.4032/9789814364270
23. Farooq MA, Aquib M, Farooq A, Haleem Khan D, Joelle Maviah MB, Sied Filli M, *et al.* Recent progress in nanotechnology-based novel drug delivery systems in designing of cisplatin for cancer therapy: an overview. Artif Cell Nanomed B 2019;47:1674-92.
24. Lam T, Pouliot P, Avti PK, Lesage F, Kakkar AK. Superparamagnetic iron oxide-based nanoprobes for imaging and theranostics. Adv Colloid Interface Sci 2013;199:95-113.
25. Singh G, Kumar N, Avti PK. Bioheat physics for hyperthermia therapy. Application of Biomedical Engineering in Neuroscience: Springer; 2019. p. 381-97.
26. Singh G, Kumar N, Avti PK. Computational evaluation of effectiveness for intratumoral injection strategies in magnetic nanoparticle assisted thermotherapy. Int J Heat Mass Tran 2020;148:119129.
27. Lam T, Avti PK, Pouliot P, Maafi F, Tardif JC, Rheaume E, *et al.* Fabricating water-dispersible superparamagnetic iron oxide nanoparticles for biomedical applications through ligand exchange and direct conjugation. J Nanomater 2016;6:100.
28. Lam T, Avti PK, Pouliot P, Tardif JC, Rheaume E, Lesage F, et al. Surface engineering of SPIONs: role of phosphonate ligand multivalency in tailoring their efficacy. Nanotechnology 2016;27:415602.
29. Lam T, Avti PK, Pouliot P, Tardif JC, Rheaume E, Lesage F, *et al.* Magnetic resonance imaging/fluorescence dual modality protocol using designed phosphonate ligands coupled to superparamagnetic iron oxide nanoparticles. J Mater Chem 2016;4:3969-81.
30. Wu W, Jiang CZ, Roy VA. Designed synthesis and surface engineering strategies of magnetic iron oxide nanoparticles for biomedical applications. Nanoscale 2016;8:19421-74.
31. Thorat ND, Bohara RA, Malgras V, Tofail SA, Ahamad T, Alshehri SM, *et al.* Multimodal super paramagnetic nanoparticles with unusually enhanced specific absorption rate for synergetic cancer therapeutics and magnetic resonance imaging. ACS Appl Mater Inter 2016;8:14656-64.
32. Schwaminger S, Bauer D, Fraga Garcia P, Wagner F, Berensmeier S. Oxidation of magnetite nanoparticles: impact on surface and crystal properties. Cryst Eng Comm 2017;19:246-55.
33. Wang S, Jiao Q, Liu X, Xu Y, Shi Q, Yue S, *et al.* Controllable synthesis of γ-Fe2O3 nanotube/porous rGO composites and their enhanced microwave absorption properties. ACS Sustain Chem Eng 2019;7:7004-13.
34. Chen J, Sun X, Shao R, Xu Y, Gao J, Liang W. VEGF siRNA delivered by polycation liposome-encapsulated calcium phosphate nanoparticles for tumor angiogenesis inhibition in breast cancer. Int J Nanomed 2017;12:6075.
35. Danafar H, Sharafi A. Co-delivery of sulforaphane and curcumin with pegylated iron oxide-gold core-shell nanoparticles for delivery to breast cancer cell line. Iran J Pharm Res 2018;17:480.
36. Ding W, Jin X, Ma B, Wang X, Lou C, Zheng J, *et al.* Determination of prussian blue nanoparticles in rat tissue in the presence of endogenous iron interferences by inductively coupled plasma–optical emission spectrometry (ICP-OES). Anal Lett 2020:1-14. https://doi.org/10.1080/00032719.2020.1762630
37. Tian X, Liu S, Zhu J, Qian Z, Bai L, Pan Y. Biofunctional magnetic hybrid nanomaterials for theranostic applications. Nanotechnology 2018;30:032002.
38. Guo T, Wu Y, Lin Y, Xu X, Lian H, Huang G, *et al.* Black phosphorus quantum dots with renal clearance property for efficient photodynamic therapy. Small 2018;14:1702815.
39. Tsoi KM, MacParland SA, Ma XZ, Spetzler VN, Echeverri J, Ouyang B, *et al.* Mechanism of hard-nanomaterial clearance by the liver. Nat Mater 2016;15:1212-21.
40. Liang Q, Wang YX, Ding JS, He W, Deng Ll, Li N, *et al.* Intra-arterial delivery of superparamagnetic iron-oxide nanoshell based chemoembolization system for the treatment of liver tumor. Discovery Med 2017;23:27-39.
41. Carvalho A, Fernandes AR, Baptista PV. Nanoparticles as delivery systems in cancer therapy: focus on gold nanoparticles and drugs. Applications of Targeted Nano Drugs and Delivery Systems: Elsevier; 2019. p. 257-95.
42. Nan X, Zhang X, Liu Y, Zhou M, Chen X, Zhang X. Dual-targeted multifunctional nanoparticles for magnetic resonance imaging-guided cancer diagnosis and therapy. ACS Appl Mater Interfaces 2017;9:9986-95.
43. Jang H, Lee C, Nam GE, Quan B, Choi HJ, Yoo JS, *et al. In vivo* magnetic resonance and dual fluorescence imaging of tumor sites by using dye-doped silica-coated iron oxide nanoparticles. J Nanopart Res 2016;18:41.
44. Ahn SH, Lee N, Choi C, Shin SW, Han Y, Park HC. Feasibility study of Fe3O4/TaO x nanoparticles as a radiosensitizer for proton therapy. Phys Med Biol 2018;63:114001.
45. Ma D, Chen J, Luo Y, Wang H, Shi X. Zwitterion-coated ultrasmall iron oxide nanoparticles for enhanced T 1-weighted magnetic resonance imaging applications. J Mater Chem B 2017;5:7267-73.
46. Lachowicz D, Szpak A, Malek Zietek KE, Kepczynski M, Muller RN, Laurent S, *et al.* Biocompatible and fluorescent superparamagnetic iron oxide nanoparticles with superior magnetic properties coated with charged polysaccharide derivatives. Colloids Surf B 2017;150:402-10.

47. Qasim M, Asghar K, Dharmapuri G, Das D. Investigation of novel superparamagnetic Ni0. 5Zn0. 5Fe2O4@ albumen nanoparticles for controlled delivery of anticancer drug. Nanotechnology 2017;28:365101.
48. Patitsa M, Karathanou K, Kanaki Z, Tzioga L, Pippa N, Demetzos C, *et al.* Magnetic nanoparticles coated with polyarabic acid demonstrate enhanced drug delivery and imaging properties for cancer theranostic applications. Sci Rep 2017;7:1-8.
49. Zhao M, van Straten D, Broekman ML, Preat V, Schiffelers RM. Nanocarrier-based drug combination therapy for glioblastoma. Theranostics 2020;10:1355.
50. El-Boubbou K. Magnetic iron oxide nanoparticles as drug carriers: preparation, conjugation and delivery. Nanomed J 2018;13:929-52.
51. Motomura M, Ichihara H, Matsumoto Y. Nano-chemotherapy using cationic liposome that strategically targets the cell membrane potential of pancreatic cancer cells with a negative charge. Bioorg Med Chem Lett 2018;28:1161-5.
52. Vassilev P, Tien HT. Planar lipid bilayers in relation to biomembranes. Structure and properties of cell membrane structure and properties of cell membranes: Volume III; 2018. p. 39.
53. Alavi M, Hamidi M. Passive and active targeting in cancer therapy by liposomes and lipid nanoparticles. Drug Metabol Person Therapy 2019;34:1-8.
54. Maeki M, Kimura N, Sato Y, Harashima H, Tokeshi M. Advances in microfluidics for lipid nanoparticles and extracellular vesicles and applications in drug delivery systems. Adv Drug Delivery Rev 2018;128:84-100.
55. Lopes NA, Pinilla CMB, Brandelli A. Pectin and polygalacturonic acid-coated liposomes as novel delivery system for nisin: preparation, characterization and release behavior. Food Hydrocoll 2017;70:1-7.
56. Pandey H, Rani R, Agarwal V. Liposome and their applications in cancer therapy. Braz Arch Biol 2016;59. DOI:10.1590/1678-4324-2016150477
57. Haeri A, Sadeghian S, Rabbani S, Shirani S, Anvari MS, Dadashzadeh S. Physicochemical characteristics of liposomes are decisive for their anti-restenosis efficacy following local delivery. Nanomedicine 2017;12:131-45.
58. Mastrotto F, Brazzale C, Bellato F, De Martin S, Grange G, Mahmoudzadeh M, *et al. In vitro* and *in vivo* behavior of liposomes decorated with PEGs with different chemical features. Mol Pharm 2019;17:472-87.
59. Wonder E, Simon Gracia L, Scodeller P, Majzoub RN, Kotamraju VR, Ewert KK, *et al.* Competition of charge-mediated and specific binding by peptide-tagged cationic liposome–DNA nanoparticles *in vitro* and *in vivo*. Biomaterials 2018;166:52-63.
60. Rajendran V, Rohra S, Raza M, Hasan GM, Dutt S, Ghosh PC. Stearylamine liposomal delivery of monensin in combination with free artemisinin eliminates blood stages of plasmodium falciparum in culture and P. berghei infection in murine malaria. Antimicrob Agents Chemother 2016;60:1304-18.
61. Mineart KP, Venkataraman S, Yang YY, Hedrick JL, Prabhu VM. Fabrication and characterization of hybrid stealth liposomes. Macromolecules 2018;51:3184-92.
62. Olusanya TO, Haj Ahmad RR, Ibegbu DM, Smith JR, Elkordy AA. Liposomal drug delivery systems and anticancer drugs. Molecules 2018;23:907.
63. Sutradhar KB, Amin M. Nanotechnology in cancer drug delivery and selective targeting. Int Sch Res Notices 2014;1-12. DOI:10.1155/2014/939378
64. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: an update. Bioeng Transl Med 2019;4:e10143.
65. Berger JL, Smith A, Zorn KK, Sukumvanich P, Olawaiye AB, Kelley J, *et al.* Outcomes analysis of an alternative formulation of PEGylated liposomal doxorubicin in recurrent epithelial ovarian carcinoma during the drug shortage era. Onco Targets Ther 2014;7:1409.
66. Zhu Y, Zhang J, Meng F, Deng C, Cheng R, Feijen J, *et al.* cRGD/TAT dual-ligand reversibly cross-linked micelles loaded with docetaxel penetrate deeply into tumor tissue and show high antitumor efficacy *in vivo*. ACS Appl Mater Interfaces 2017;9:35651-63.
67. Kim CH, Lee SG, Kang MJ, Lee S, Choi YW. Surface modification of lipid-based nanocarriers for cancer cell-specific drug targeting. Int J Pharm Investig 2017;47:203-27.
68. Pereira NRC, Loiola RA, Rodrigues SF, de Oliveira CP, Buttenbender SL, Guterres SS, *et al.* Mechanisms of the effectiveness of poly (ε-caprolactone) lipid-core nanocapsules loaded with methotrexate on glioblastoma multiforme treatment. Int J Nanomed 2018;13:4563.
69. Perez Herrero E, Fernandez Medarde A. Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy. Eur J Pharm Biopharm 2015;93:52-79.
70. Smith AG, Macleod KF. Autophagy, cancer stem cells and drug resistance. J Pathol 2019;247:708-18.
71. Olszowka M, Russo R, Mancini G, Cappelli C. A computational approach to the resonance Raman spectrum of doxorubicin in aqueous solution. Theor Chem Acc 2016;135:27.
72. Li B, Li Q, Mo J, Dai H. Drug-loaded polymeric nanoparticles for cancer stem cell targeting. Front Pharmacol 2017;8:51.
73. Silveira N, Longuinho MM, Leitao SG, Silva RS, Lourenço MC, Silva PE, *et al.* Synthesis and characterization of the antitubercular phenazine lapazine and development of PLGA and PCL nanoparticles for its entrapment. Mater Sci Eng 2016;58:458-66.
74. Ahsan SM, Thomas M, Reddy KK, Sooraparaju SG, Asthana A, Bhatnagar I. Chitosan as a biomaterial in drug delivery and tissue engineering. Int J Biol Macromol 2018;110:97-109.
75. Mahanta AK, Senapati S, Maiti P. A polyurethane–chitosan brush as an injectable hydrogel for controlled drug delivery and tissue engineering. Polym Chem 2017;8:6233-49.
76. Ni M, Xiong M, Zhang X, Cai G, Chen H, Zeng Q, *et al.* Poly (lactic-co-glycolic acid) nanoparticles conjugated with CD133 aptamers for targeted salinomycin delivery to CD133+osteosarcoma cancer stem cells. Int J Nanomed 2015;10:2537.
77. Hemshekhar M, Thushara RM, Chandranayaka S, Sherman LS, Kemparaju K, Girish KS. Emerging roles of hyaluronic acid bioscaffolds in tissue engineering and regenerative medicine. Int J Biol Macromol 2016;86:917-28.
78. Ke XY, Ng VWL, Gao SJ, Tong YW, Hedrick JL, Yang YY. Co-delivery of thioridazine and doxorubicin using polymeric micelles for targeting both cancer cells and cancer stem cells. Biomaterials 2014;35:1096-108.