Nanocarriers for drug Targeting

PROJECT TO BE SUBMITTED IN PARTIAL FULFILLMENT OFTHE REQUIRMRNT FOR THE DEGREE OF

BACHELOR OF PHARMACY

Submitted by

Akanksha Srivastava

B. PHARM (IV YEAR)

17SMAS102099

1712102007

UNDER THE SUPERVISION OF

Dr. AMRISH KUMAR

ASSOCIATE PROFESSOR

DEPARTMENT OF PHARMACY SCHOOL OF

MEDICAL & ALLIED SCIENCES

GALGOTIAS UNIVERSITY

GREATER NOIDA

JUNE, 2021

CERTIFICATE

This is to certify that the project work entitled **"NANOCARRIERS FOR DRUG TARGETING"** is a bonafide research work done by **AKANKSHA SRIVASTAVA** at Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida, under the supervision and guidance of **Dr. AMRISH KUMAR,** Associate Professor, School of Medical and Allied Sciences, Greater Noida. The work is completed and ready for evaluation in partial fulfillment for the award of Bachelor of Pharmacy under Galgotias University, Greater Noida during the academic year 2020-2021

Date:

Place:

Prof. Pramod Kumar Sharma
Dean
School of Medical and Allied Sciences
Galgotias University
Greater Noida (U.P.)

CERTIFICATE

This to certify that the project work entitled **"NANOCARRIERS FOR DRUG TARGETING"** by **AKANKSHA SRIVASTAVA** for the award of **"BACHELOR OF PHARMACY"** degree, comprises of the bonafide research work done by him at Department of Pharmacy, School of Medical & Allied Sciences, Galgotias University, Greater Noida under my guidance and supervision and to my full satisfaction.

Date:

Place:

Dr. AMRISH KUMAR
Associate Professor
School of Medical and Allied Sciences
Galgotias University
Greater Noida, (U.P.)
(Guide)

DECLARATION

I hereby declare that the project work embodied in this project entitled **"NANOCARRIERS FOR DRUG TARGETING"** was carried out by me under the supervision and guidance of **DR. AMRISH KUMAR,** Associate Professor, School of Medical and Allied Sciences, Galgotias University, Greater Noida. I have not submitted the matter embodied in this project for award of any other degree or diploma of any other university or institute.

Date:

Place:

Name and Signature of Candidate

ACKNOWLEDGEMENTS

Thankful and extremely grateful to the Almighty God for his overwhelming love and grace all through my completion of Bachelor of Pharmacy Degree from Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida, India.

Thankful to **Dr. Amrish Kumar**, Assistant Professor (Pharmaceutics) my project supervisor, who guided me through this work.

Many thanks to **Professor Pramod Kumar Sharma** (Dean, School of Medical & Allied Sciences), Dr. Vijay Singh (Head of Department), Mr. Rishabh Malviya, Dr. Aftab Alam, and all faculty members of Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University.

I extend my warming greetings to all the nonteaching Staffs members of Department of Pharmacy.

Akanksha Srivastava

B. PHARM (IV YEAR)

17SMAS102099

1712102007

Abstract:-

This paper focuses on the uses of Nanocarriers for Drug Targeting the simplest a pplication,, the various types of Nanocarriers program, their use, and future dire ction .Depresses for protein or peptide, but the effectiveness is greatly reduced d ue to enzymatic digestion and indigestion good for intestinal detection in the sm all intestine. In complex formulations, the installation of nanocarriers will prote ct the drug more sensitive and thus can greatly improve the effectiveness of oral drug delivery. Before being released, a nanocarrier needs to bypass many barrier s to the human body, including the intestinal and epithelial layer and endothelial cells. The exact mechanisms behind transcellular transmission have so far not be en fully understood. With most nanocarriers, the transcellular flow rate is insuffi cient to detect their efficacy in oral delivery.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

1 Introduction:-

The Nanocarriers colloidal carrier system contains submicron particles <500 nm.1 Nanocarriers has been extensively investigated in the last few decades as they have shown great confidence in the drug delivery industry. Nanocarriers, due to their high to high volume, have the ability to modify basic properties and drug performance. Improved pharmacokinetics and distribution of biodistribution, reduced toxicity, improved stability and durability, controlled release and local delivery of therapeutic properties are some of the things nanocarriers can incorporate into drug delivery systems inanimate or hybrid, sizes (small or large), shape (space, stick or cube) and other structures (cost of land, working groups, PEGylation or other cover, attached to target organizatios). The overall purpose of using nanocarriers in drug delivery is to effectively treat the disease with the following side effects.

Anticancer chemotherapeutics when combined with conventional drug delivery programspresent many different problems, including poor prescription drugs, severe toxicityand drug resistance. These barriers reduce the number of anticancer drugs. Nanocarrierbased platforms have enabled th e effective delivery of anticancer drugs to the intestine by exploiting the pathophysiology of tumor microenvelo, thereby greatly improving the therapeutic effects of oncological conditions. In additon, receptors targeting cells beyond the nucleus are also targeted by nanocarriers platforms decorated with targeting ligands. Many nanocarrierbased products have been approved for the treatment of a variety of plants, and many more are in various clinical trials. In the current review, we first discussed the characteristics of different types of nanocarriers (organic, inorganic and hybrid) and their importance in cancer treatment. We have then shown ways to identify and use the environment in nanocarriers to improve their visibility.

1.1 Hindrance in nanocarrier delivery to cancer cells

Delivery of drugs based on Nanotechnology often encounters many obstacles where they ultimately go. Subcutaneous skin cancer is a barrier to nanocarrier treatment delivery due to the hard and subsequent epidermal layer followed by several other layers that form the skin layers. Most therapies are trapped in the skin layer, therefore, pathogenic cells remain drug-free. Alternatively tumor biology plays an important role in the successful delivery of therapeutic agents to target cells. The translation structure and body structure of the plant tissue the successful deliver y of the nanocarrier is a leading point for the development of a highly effective drug carrier. Due to the rapid growth of tumor cells, transplantation of healthy cells also requires the supply of nutrients , nutrients and oxygen. Cells form new blood vessels.
Through the process of angiogenesis of continuous growth. Under hypoxic conditions, the cancer cell is deprived of oxygen again.
Some nutrients in the farthest part of the blood vessels. For intravenous administration, the nanocarrier has another set of problems arising from the macrophages and spleen and clears from the immediate circulation of the system. The whole process of nanocarrier delivery is followed by intra-tumoral infiltration, physical changes in the nanocarrier and then the lysosome followed

by the cytoplasm and nucleus thereafter. Successful delivery of a nanocarrier depends entirely on physicochemical particle size, land charge, density, environmental and physical condition of the target area. The highly processed nanoparticles (NPs) show the various ligands of the NP surface bonding with the linker shown in Figure i.

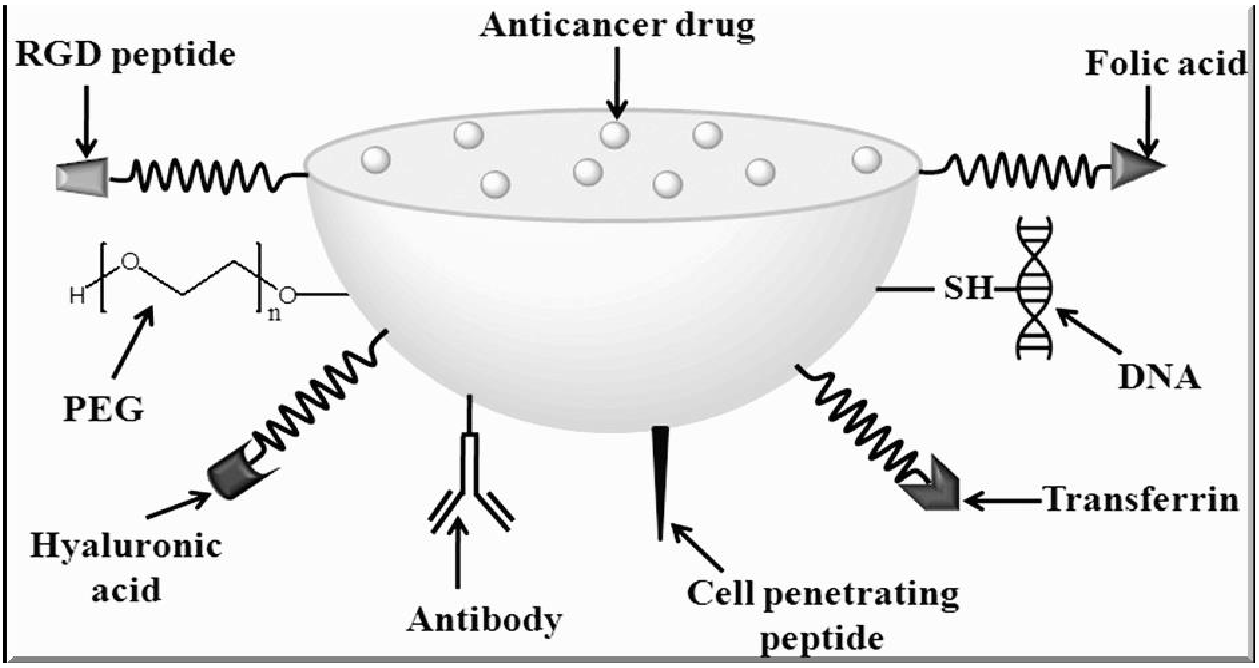


figure i. Engineered NP depicting various ligands for conjugation to NP surface through linker.

Table 1- Characteristic of different nanocarriers

Nanocarrier	Mode of synthesis	Size of nanocarriers (nm)	Properties of nanocarriers	Applications
Solid lipid nanocarriers (Kingsley et al. 2006)	High shear homogenization, hot homogenization, cold homogenization, ultrasonication, solvent emulsification, microemulsion, spray drying	50–100	Colloidal carrier, better stability, ease of upgradeability, biodegradable Low drug loading capacity, burst release	Drug delivery to liver cells both in vivo and in vitro, gene vector carrier, topical use, targeted drug delivery to solid tumors, antitubercular chemotherapy
Liposome (Sun et al. 2014; Mishra et al. 2010)	Mechanical dispersion, Solvent dispersion, detergent removal method	50–100	Phospholipid bilayer vesicle, Biocompatible, biodegradable, less toxicity	Trap hydrophilic and hydrophobic drug, optimal delivery of biologically active agent
Dendrimer (How et al. 2013)	Cascade reaction, either convergent or divergent approach, self-assembly	1–10	Radially symmetric, homogeneous, well defined, monodisperse hyperbranched molecules	Drug delivery, liver targeting, photodynamic therapy, neutron capture therapy, imaging, gene delivery
Polymeric nanocarriers (Lopez-Davila and Loizidou 2012)	Solvent evaporation, Emulsification/solvent diffusion, nanoprecipitation, salting out, supercritical fluid technology, dialysis, polymerization	10–100	Effective cell membrane permeation, stability in blood stream, biodegradable	High concentration of drug delivery, active and passive drug delivery, maintains stability of volatile pharmaceutical agent
Micelle (Bhatia 2016; Malam et al. 2009)	Supramolecular self-assembly, solvent/mechanical dispersion	10–100	Biostability, dynamic system, colloidal aggregate of amphiphilic molecule	Encapsulate either hydrophobic or hydrophilic drug
Carbon nanotubes (Muller 2000)	Chemical vapor deposition, laser ablation, carbon arc discharge	0.4–3	Hexagonal pattern, crystalline, third allotropic carbon sheet, single or multi-layer, dynamic strength, unique electrical and elastic property	Gene and drug delivery, peptide delivery, artificial implants, tissue engineering, cancer cell identification
Gold (Üner and Yener 2007)	Two phase synthesis, biphasic reduction	1–100	Multi-surface functionality, versatile,	Multi-surface functionality,

			excellent biocompatibility, less toxicity, surface plasmon resonance property, Fluorescence resonance energy transfer phenomenon	versatile, excellent biocompatibility, less toxicity, surface plasmon resonance property, Fluorescence resonance energy transfer phenomenon
Magnetic nanocarriers (Hallan et al. 2014)	Metal alkoxide hydrolysis, coprecipitation in microemulsion hydroxide coprecipitation, glycothermal synthesis, citrate gel process, glass crystallization	1–100	Superparamagnetism, chemical stability, high colloidal stability, magnetic moment	Magnetic separation, Magnetic Resonance Imaging, targeted drug delivery, hyperthermia, magnetic fluid, biosensing, Thermoablation

CHAPTER 2

SELECTED TUMORS AND THE USE OF NANOCARRIERS

Now, we discussed selected tumors and the use of nanocarriers in the appropriate tumor.

2.1 Organic nanocarriers

2.1.1 Solid lipid nanoparticles (SLNs)

SLNs are prepared by dispersing soluble lipids (s) dissolved in water, and emulsifiers (s) are used to stabilize dispersion. The two most commonly used methods for preparing SLNs are high-pressure homogenization and micro emulsification. SLNs provide a high lipophilic lipid matrix for drugs that will dissolve or dissolve.8 A variety of solid lipids include mono-, di- and triglycerides; fatty acids; free fatty alcohol; waxes and steroids used to prepare SLNs. SLNs are exactly the same as nanoemulsions except that different types of lipids are used in all formulations. Solid lipids at room temperature are used in SLNs instead of lipids (fats) used in nanoemulsions.

SLNs as nanocarriers offer many more benefits than colloidal counterparts, including nanoemulsions, liposomes and polymeric nanoparticles (PNPs). Some of the areas where SLNs get better points than their counterparts include controlled drug delivery, lack of biotoxicity, high drug charges, improved availability of water-soluble drugs, better and easier stability and greater productivity

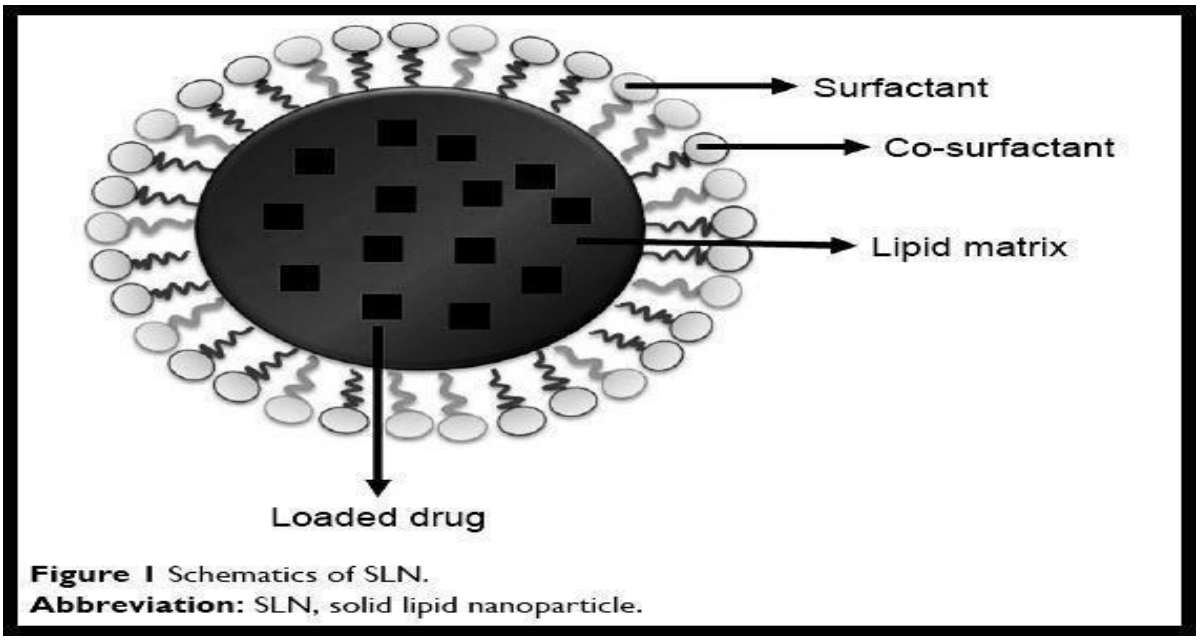


Figure 1 Schematics of SLN.
Abbreviation: SLN, solid lipid nanoparticle.

of Depending on the formulation SLNs (lipid, drug and surfactant) and production conditions (hot or cold homogenization), the drug can be distributed evenly in the lipid matrix (solid solution/compatible matrix model) of SLNs (Figure 1), embedded in the surrounding shell lipid spine (drug-enriched shell model) or embedded in a hole surrounded by lipid shell (a basic drug-enhancing model).

2.1.2 Liposomes

During the last few decades in biomedicine, liposomes have attracted a lot of attention, especially a s a drug delivery system for antitumor drugs. They demonstrated many advantages over conventio nal systems, such as extended drug delivery, active drug protection. Due to environmental factors, features of corrective operation of the product, prevention of early degradation of ancillary drugs, cost-
effective formulation of expensive drugs and effective treatment with reduced systemic toxicity.. Liposomes are spherical vesicles that have an aqueous core bound by lipid bilayers. They have sing le or multiple bilayer membrane assemblies madeof natural or synthetic lipids (Figure 2). Individu als with a bilayer membrane are referred to as small unimalarized vesicles or large unimalarized ve sicles depending on their size. If more than one bilayer is present, then it is known as multilaylar ve sicles. Liposomes vary in terms of composition, size, surface charge, and method of preparation. L iposomes are commonly used as model cells or carriers of various bioactive agents, including drug s, vaccines, cosmetics and nutraceuticals..

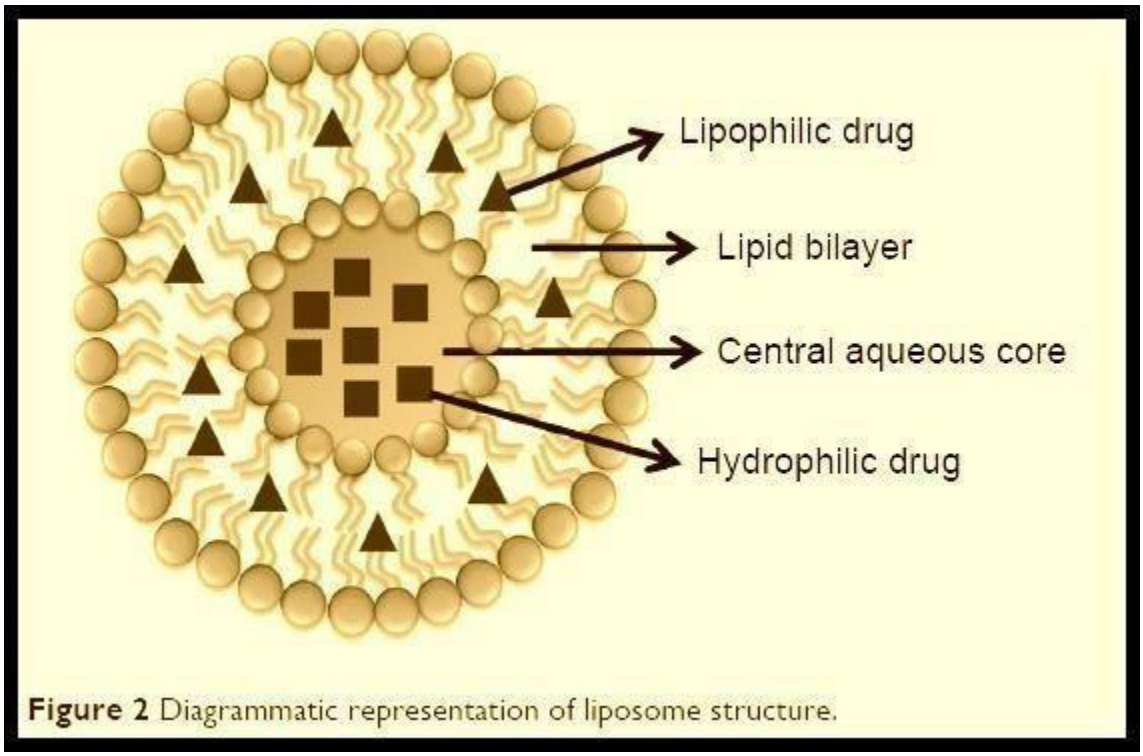


Figure 2 Diagrammatic representation of liposome structure.

The biodegradable and biocompatible composition of liposomes has made them excellent therapeu tic carriers. Moreover, their specific ability to contain both water-soluble and lipid-
soluble agents has correspondingly increased their use in biomedicine formulations in their aqueo us central part and in lamellae. Moreover, it increases the concentration of the drug inside the tumo r but reduces the concentration of the drug in normal tissues. Liposomes can also be attached to anti bodies or ligands to enhance target specificity.

2.1.3 Dendrimers

Dendrimers usually have macromolecule branches that have different arms from the center.Typically, they are produced using natural or synthetic materials, including sugars, nucleotides and amino acids. Their slower combinations enable them to align molecules with a typical branch pattern, a different molecular weight and a different number of clusters.
Dendrimers obtained with slowmoving techniques are different compared to those produced by polymerization processes due to well-structured and unusual branch patterns, respectively.

Dendrimers are the most likely drug delivery systems due to their unparalleled properties, including differential cell weight, increasing number of branching, bulk size, circular shapes and monodispersed macromolecules 1.514.5 nm. Normal molecule it has layers with large branches consisting of duplicate units, multiple functional end groups and a starting spine. Their architectural design offers more control over the shape of the dendrimer, the size, the height of the branch and the performance of the ground. Drugs and identification markers can be attached to alter earth function for specific purposes, which often involve direct contact with cell walls and living areas. Preoperative drug development focused on building drug combinations.Recently, dendrimers have been widely used in the field of biomedicine, including genetics, immunology, resonance imaging, vaccines and antiviral, delivery of antimicrobial drugs and anticancer.

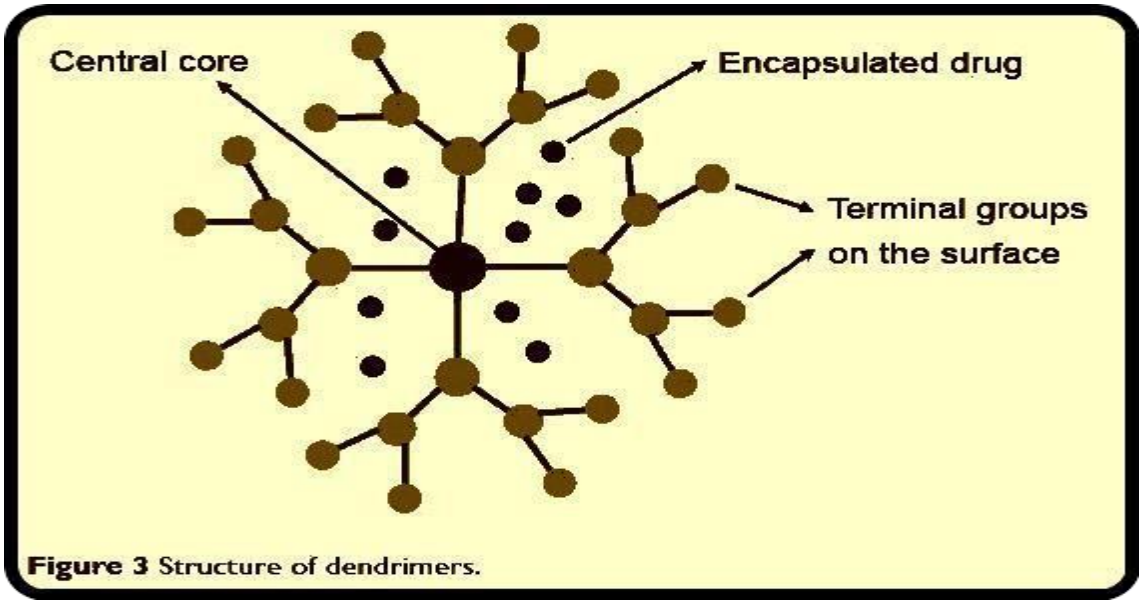


Figure 3 Structure of dendrimers.

Dendrimerdrug conjugate is formed when the drug is bound together in the dendrimer in the center or in the end groups and most often in the inner parts, that is, in the branches. The active filter of the drug is enhanced exponentially in the target area, when the drug is connected to multiple groups in the dendrimer edges. Basically, this is beneficial for the use of antiretroviral drugs. As a monodispersed, systematically controlled macromolecule with precise size and molecular weight, dendrimers-drug conjugate is the preferred carrier than conventional

polymeric drug delivery carriers. The drug and dendrimer link are especially important if the drug is attache d to external dendrimer groups. This is because the drug needs to be extracted in an effective way when the a ction is performed.Dendrimers have been used successfully to increase the effectiveness of doxorubicin as d escribed by Lai et al. They used photochemical internalization (PCI) technology, which is known to break d own the cytoplasmic membrane and enable the expression of macromolecule trapped in cytoplasmic vesicle s, leading to increased cytotoxicity to cancer cells.

2.1.4 PNPs

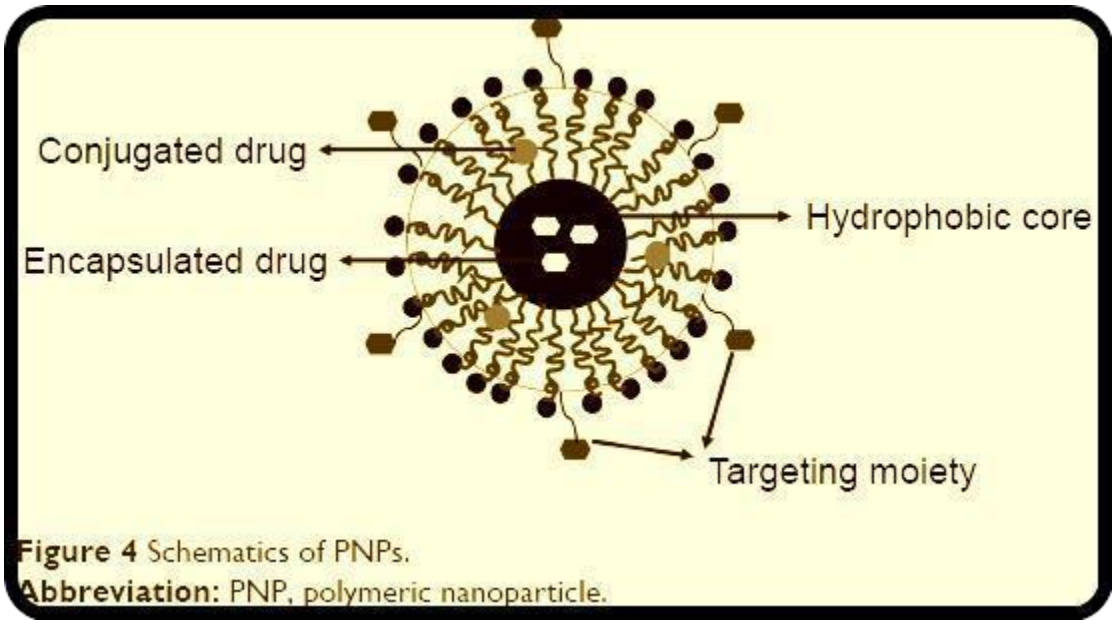


Figure 4 Schematics of PNPs.
Abbreviation: PNP, polymeric nanoparticle.

Over the past few decades, polymers have received a lot of attention in the drug delivery area as the y offer a number of attractive features in drug delivery. PNPs are solid, ananosised (10-1,000 nm) colloidal particles composed of decaying polymers. Depending on their construction org anization, PNPs can be divided into nanospheres (matrix type) or nanocapsules (A type of water st orage repository; figure 4). The Nanospheres type of PNPs disperse / binds the drug to the polymer matrix, while in the case of the nanocapsule of the PNPs, the drug is dissolved/disperses in an oil-liquid environment or water mixed with a strong polymeric membrane. In both types of PNPs, the r elease of adsorption or further chemical synthesis (matrix or capsule) is possible. Many approaches have been developed to prepare PNPs depending on the design and desired structures of PNPs. The se methods can be well divided into two phases, namely, dispersing of the remaining embedded pol ymers and direct column insertion of monomers. Methods that include the dispersion of the remain ing polymers included include solvent evaporation, salt, nanoprecipitation, dialysis and supercritic al fluid technology.

Many polymers have been used in the preparation of PNPs. As they decompose, these particles are reduced to individual monomers within the body and are therefore removed from the body by normal body processes . The most commonly used polymers include polylactic acid (PLA), polyglycolic acid (PGA), PLGA, PEG, polycaprolactone (PCL), N(2hydroxypropyl) methacrylamide (HPMA) copolymer, polyaspartic acid (PAA) and polyglutamic acid. However, the most commonly used natural polymers include albumin, alginate, chitosan, collagen, dextran, gelatin and heparin. In addition to the key features shared by all nanocarriers in cancer treatment, PNPs offer better endtoend and in vivo (blood), higher drug loading, distribution of compatible particle size, better and more manageable natural properties, higher drug distribution times and more release. Compared to colloidal counterparts such as polymeric micelles (PMs) and liposomes. All of these factors are highly desirable in the case of cancer treatment.

2.1.5 PMs

PMs have nanosised colloidal particles (10-100 nm) formed by self Assembly of synthetic amphiphilic dior triblock copolymers in a wet environment. Being naturally amphiphilic, di or block blocks and therefore contain hydrophobic and hydrophilic components. These block copoly mers when exposed to a liquid environment, in addition to a specific concentration (called critical micelle concentration [CMC]), form micelles. The hydrophobic part of the block copolymer forms the core of the micelle, while the hydrophilic part forms the shell of the micelles.

Thus, PMs have a spinal/shell structure consisting of a hydrophobic and hydrophilic shell (Figure 5) . The hydrophobic core of the PMs allows the incorporation of hydrophobic compounds and regulates the release areas of the PMs.

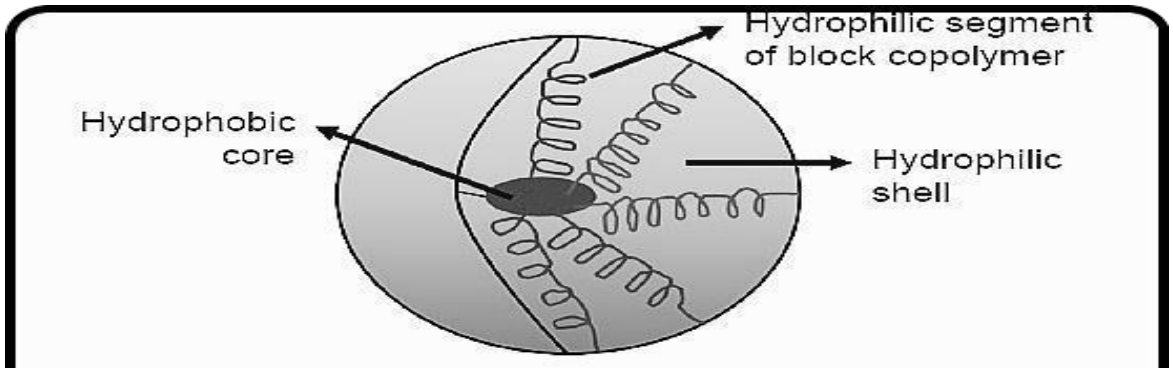


Figure 5 Structure of PMs.
Abbreviation: PM, polymeric micelle.

PMs offer promising nanocarriers for delivery of anticancer drugs. Since many anticancer drugs ar e usually water soluble (hydrophobic), PMs allow those hydrophobic anticancer drugs to be trapped in their columns, thus increasing water solubility. In addition, the hydrophilic shell of PMs Causes them to have periods of blood circulation by preventing the detection and subsequent uptake of PM by RES. Therefore, the small size (10–100 nm) and the duration of the

vivo cycle cause the PMs to accumulate specially in the plant area with an improved intensity and retention (EPR) effect (random identification). All of these effects improve bioavailability and treatment with hydrophobic anticancer drugs. In addition to random identification, active cancer identification with PMs is also possible by forming intelligent PMs (environment/dynamic PMs that respond to changes in pH, temperature, etc.) or by global mutation of tumor-induced PMs. To identify the ligand. Many cancer chemotherapeutic agents, including methotrexate, cisplatin, paclitaxel, docetaxel and doxorubicin, have been successfully developed for PMs.

2.1.6 Virus-based nanoparticles (VNPs)

VNPs or viral-like particles (VLPs) are nanosized (approximately < 100 nm), independent protein cages containing nanostructures similar to well-defined geometry (Figure 6) . Recently,, - VNPs (viruses such as nanocontainers) have been extensively studied for nanotechnological purposes , including drug delivery, genetic therapy, vaccination, thinking and identification. VNPs or protein cages (i.e., viruses) from a variety of sources including plant viruses (viruses. cowpea chlorotic mottle [CCMV] cowpea mosaic [CPMV] red clover necrotic mosaic virus [RCNMV], mosaic virus [TMV]) insect viruses (herd virus), bacterial viruses or bacteriophages (MS2, M13, Qβ) and animal viruses (adenovirus, polyomavirus) have been investigated for nanotechnology and drug delivery applications. As an emerging nanocarrier platform, VNPs offer a wide range of attractions including morphological similarity, biological compatibility, ease of use of space and availability of various sizes and sizes.

The potential for flexible chemical and genetic mutations on their surface enables VNPs to meet the needs of drug nanocarriers including incompatibility, hydrophilicity and advanced drug delivery training. Additionally, PEGylating surface VNPs may improve its broadcast time in the

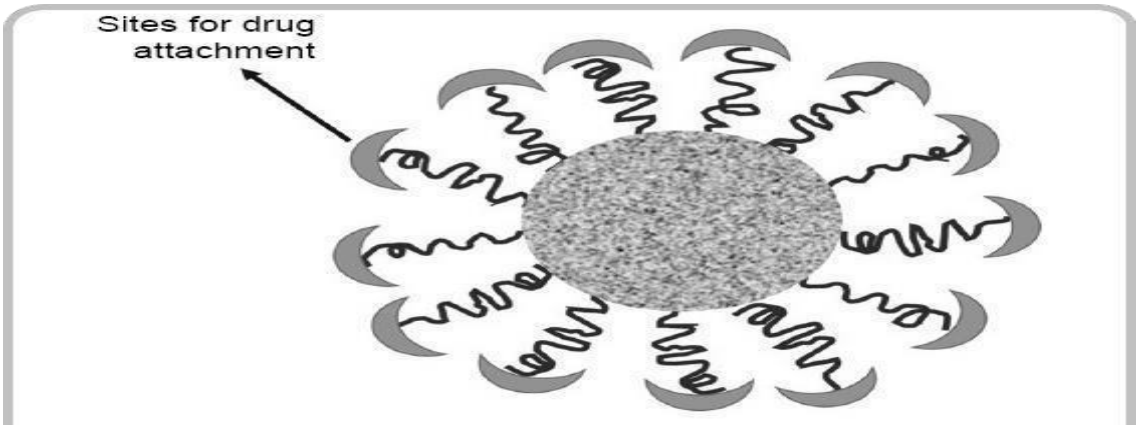


Figure 6 Structure of VNPs.
Abbreviation: VNP, virus-based nanoparticle.

host..In using drug delivery, drugs can be physically captured in VNPs or chemically injected into the surface of VNPs. In physical capture, a simple and natural process of reconstitution/ reintegration

of protein capsid is used to load drug load into VNPs. During chemical attachments, drug loads are loaded into VNPs by the cohesive attachment of drug molecules to specific sites (naturally present or enclosed) in capsid proteins. As a drug that carries nanocontainers, VNPs can be targeted for spe cific cancer purposes by exploiting the natural close proximity of certain receptors that are highly c oncentrated in various tissues (e.g., transferrin receptor [TfR]) or by altering the outer surface of na nocarriers with chemical or chemical processes.

2.2 Inorganic nanocarriers

2.2.1 Carbon nanotubes (CNTs)

CNTs are carbon offsets, free of charge, similar to the tube discovered by Iijima59 in 1991. CNTs belong to the fullerenes family (the third type of allotropic carbon) and are formed by wrapping graphene sheets into a tube- as a structure.60 CNTs can be divided into single-walled carbon nanotubes (SWCNTs) formed by folding a single sheet of carbon nanotubes. graphene or multi-walled carbon nanotubes (MWCNTs) are formed by folding several sheets of graphene into a tube-like structure (Figures 7A and B). CNTs have short-range measurements in nanometers and lengths that can extend more than a thousand times their diameter. Typically, the outer diameters of SWCNTs and MWCNTs are between 0.4-2 nm and 2-100 nm,respectively.

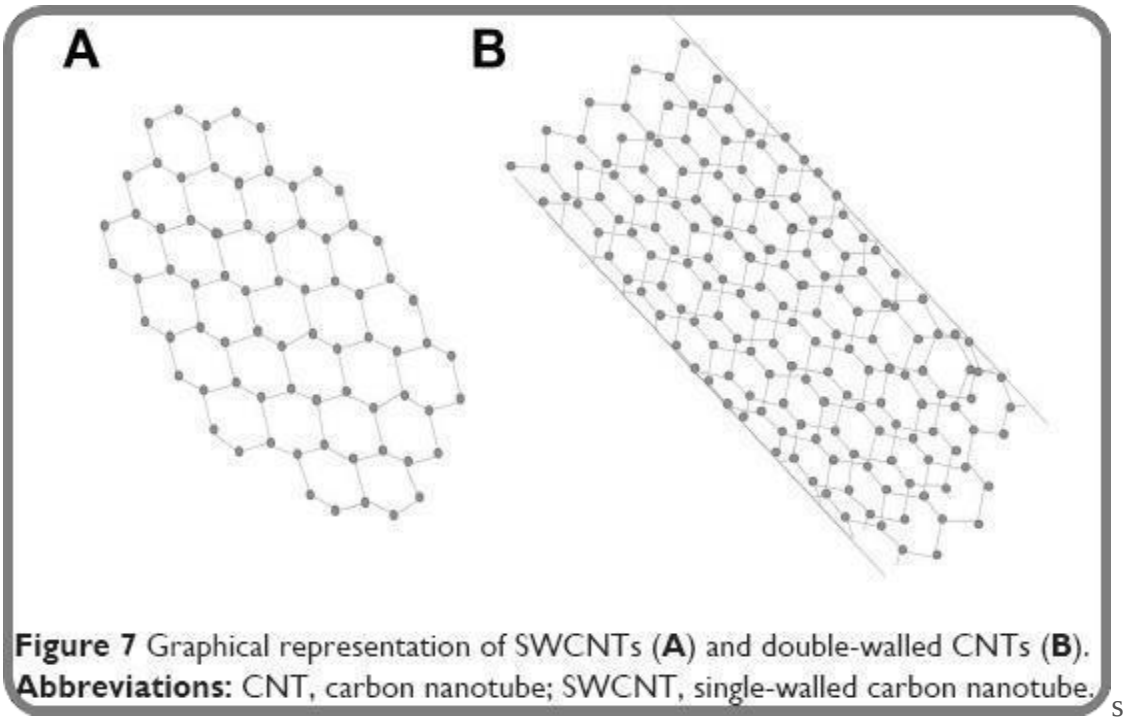


Figure 7 Graphical representation of SWCNTs (**A**) and double-walled CNTs (**B**).
Abbreviations: CNT, carbon nanotube; SWCNT, single-walled carbon nanotube.

s Othe r technique widely used in the production of CNTs includes arc extraction, laserablation and th ermal or plasma-enhanced chemical vapor deposition.

CNTs have certain unique environmental and physiological features that make them a promising carrier of drug delivery. Some of these features include nanoneedle structure, blank monolithic structure, high size ratio (length: width> 200: 1), ultrahigh surface, ultralight weight, high mechanical strength, high electrical conductivity and temperature and their strength of land reform

Due to their cell penetration capabilities, distinct physicochemical features, high drug loading, inte rnal stability, structural flexibility and earth efficiency (for various purposes), CNTs are one of the most suitable nanocarriers for cancer treatment. Anticancer drugs can be inserted into the inner spine of CNTs66 or can be attached, in combination or inconsistently, to the surface of CNTs.

2.2.2 Mesoporous silica nanoparticles (MSNs)

Silica materials (SiO2) have received expanded applications in the field of biomedicine due to their simple manufacturing processes and the availability of mass production. Among silica- synthetic materials, mesoporous silicas are very important in the delivery of drugs as they are able to handle a large amount of drugs due to their structure similar to bees with hundreds of pores (Fig. 8) .77 MS Ns local and pore volume, large loading capacity, controlling pore size ranging from 2 to 50 nm wit h small pore size distribution, good thermal and chemical stability and flexibility of loading drugs with hydrophilic and lipophilic properties, which make them promising the drug nanoscale carriers . In addition, the ease of use of controlled and targeted drug performance enables MSNs to improve clinical performance and reduce drug toxicity.

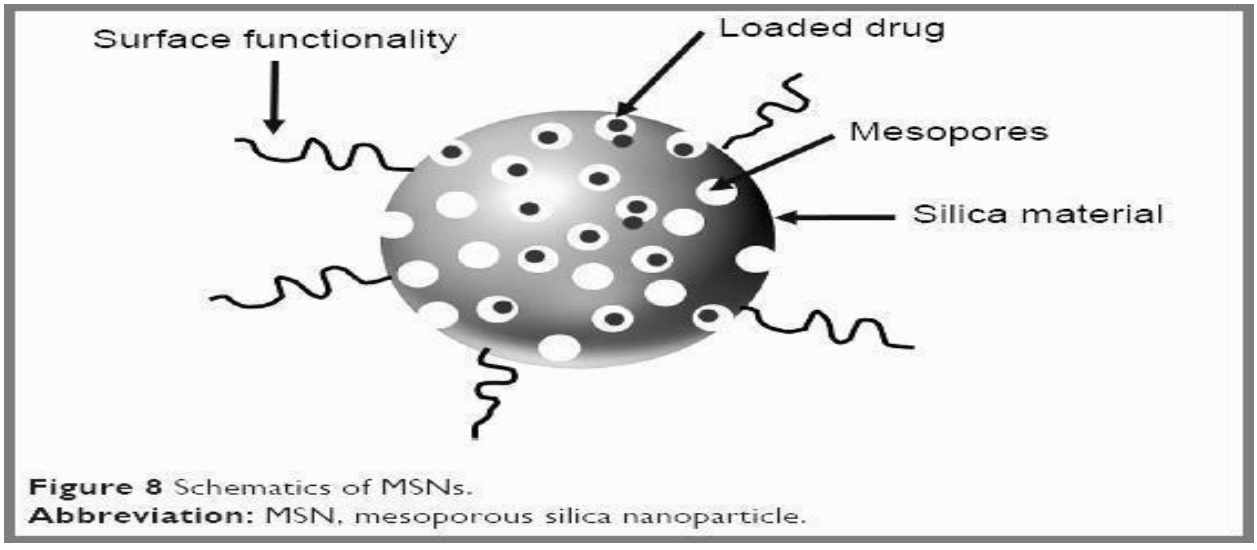


Figure 8 Schematics of MSNs.
Abbreviation: MSN, mesoporous silica nanoparticle.

The unique design and attractive properties of MSNs place this category of nanocarriers in an ideal environment for the delivery of anti-cancer drugs.

.

2.2.3 Metallic and magnetic nanoparticles

Since the discovery of iron nanoparticles in 1971, various nanoparticles derived from iron have found a way into clinical trials. Metal nanoparticles have been used in a variety of environmental applications, including electron microscopy probes to visualize cellular components, such as vehicle delivery drugs, proteins and peptides. Metal or silver nanoparticles such as gold or silver have material and electrical properties based on their size and shape. Gold nanoparticles act as a chemical senor when they combine with certain oligonucleotides to sense the corresponding DNA strands as they are detected by color change. Gold nanoparticles can be synthesized easily with drugs as well as probe molecules such as antibodies, enzymes and nucleotides. At present, magnetic nanoparticles are of great interest as they have distinct magnetic properties that have the potential to work earth, making them promising as magnetic resonance imaging (MRI) andas carriers for drug delivery needs.

Table2-Nanocarriers used for tumor treatment

Nanocarriers	**Drug**	**Name**	**Indication**	**Status**
Polymeric micelles	Paclitaxel	Genexol-PM	Breast,lung Pancreatic cancer Recurrent breast cancer	II-III IV
	Doxorubicin	NK911	Various	I-II
Nanoparticles	Albumin-Paclitaxel	Abraxane	Metastatic braincancer	Approved
	Doxorubicin Paclitaxel	Transdrug Nanoxel	Hepatocarcinoma Advanced breast cancer	Approved I
Polymer-drug conjugates	Paclitaxel	Xyotax	Breast ovarian cancer	II
		(CT-2103) PK1	Advance lung cancer Breast,lung,colon Various	III I I
	Doxorubicin Paclitaxel	Taxoprexin		II-II
Liposomes	Doxorubicin	Doxil	Ovarian,metastatic breast cancer,Kaposi sarcoma	Approved
	Daunorubicin Daunorubicin Vincristine	Myocet DaunoXome Onco-TCS	Breast cancer Kaposi sarcoma Non-Hodgkin Lymphoma various	Approved Approved Approved II
		Marqibo	Leukemia,melanoma	II

CHAPTER 3

NANOCARRIERS FOR CANCER-TARGETED DRUG DELIVERY

3. Nanocarriers for cancer-targeted drug delivery

3.1 Introduction

Cancer remains the leading cause of death worldwide, including cancer-related deaths in 2012. According to figures from the World Health Organization (WHO), the incidence of annual cancer cases is expected to rise from 14 million in 2012 to 22 million over the next two decades. Cancer is a path physiologically heterogeneous disease that progresses rapidly to an uncontrolled stage after onset. Although a variety of therapies, including immunosuppression, photo thermal, photodynamic, gene and hormone therapy show promising cancers in prenatal studies, however, surgery, radiation, and chemotherapy continue to be a line therapy. The first of many cancers. However, these focused therapies fail to control metastatic tissue reaching distant organs. With conventional chemotherapy, the next stage of cancer treatment is less specific in directing drugs to cancer cells that cause undesirable side effects in healthy tissues. Although generic cytotoxics are used to treat whole-body cancer in recurrent cancer, however, conventional anti-cancer drugs experience many side effects, including dehydration, complete biodistribution, high levels of toxins in normal cells, insufficient drug concentration in tumors or cancer cells and development of drug resistance.

3.2 Limitations of conventional chemotherapy

Treatment of local and metastatic cancer using antineoplastic drugs, especially those given with IV drugs, called chemotherapy is the first line of treatment. Although widely used in cancer treatment , chemotherapeutic drugs have limitations.

- Lack of specificity of neoplastic tissue causes severe damage to non-cancerous cells leading to serious adverse effects such as mucositis, suppression of bone marrow (immuno and myelosuppression), nausea, secondary neoplasms and reproduction. In addition, high-volume distribution of chemotherapeutics makes the delivery of the drug less specific to the tissues leading to abnormal concentration of a ntibodies against healthy lung tissue.
- Lack of selective action in action activities that are prominent in conventional chemotherapy. Most chemotherapy does not work on intracellular processes that are differ ent from lethal cells but on common pathways shared by neoplastic and normal cells. Ther efore, the cytotoxic and cytostatic mechanisms induced by these drugs also attack healthy non-cancerous tissues. Epirubicin (EPI), derived from Anthracycline,used in Hepatocellular carcinoma (HCC) causes DNA damage by disrupting cleavage-religation balance and increasing the concentration of covalent DNA topoisomerase II str uctures. As a result, apoptosis linked to p53 sensor DNA damage and activated caspase (activases) . However, long-term clinical use of EPI is limited due to indirect toxicity in normal tissues, especially cardiac toxicity associated with intramyocardial production of active oxygen species (ROS). The rate of rapid removal by the reticuloendothelial system (RES) reduces the proliferation of EPI in the tumor area and thus reduces drug efficacy. Therefore, there is an unmet need for the development of a non-toxic and more effective treatment for hepatocellular carcinoma (HCC).

Chemotherapeutic agents exert cytotoxicity due to the high dispersing volume of pharmacokinetic use of low-dose drugs. Low-molecular weight chemicals are rapidly released.

For this reason, high concentration is required to achieve a therapeutic effect that leads to toxicity. The low therapeutic index of chemotherapy means that the overcrowding required for effective tre atment often leads to more systemic side effects.

3.3 Advantages of nanotechnological drug delivery systems.

Nanotechnology is an emerging treatment platform that uses nanoparticles (NPs) for the diagnosis and treatment of cancer. NPs are used in cancer treatment because of their unique size, that is, usually 1-1000 nm, or perhaps within a suitable range of 5-200 nm. of drugs. Nanoranged size, large surface-to-volume ratios and functional surface capacity play a very important role in its biodistribution in vivo. The most common examples of nanocarriers in the delivery of chemotherapeutics include liposomes, polymeric nanoparticles, dendrimers, nano-shells, inorganic, nucleic acid based and magnetic nanoparticles (Figure 10). Nanoparticular drug delivery programs offer different cancer treatment benefits in free drug management from NPs:

- improve the treatment index of loaded chemotherapeutic agents compared to drugs a dministered in standard doses.
- increase drug use by achieving long-term government treatment standards.
- Reduce drug toxicity due to controlled drug withdrawal and improved drug pharmacokinetics by increasing drug solubility and stability.

3.4 EPR effect and its limitations

The result of EPR is the intermediate delivery of nanocarriers is considered to be a major improve ment leading to targeted anticancer treatment.

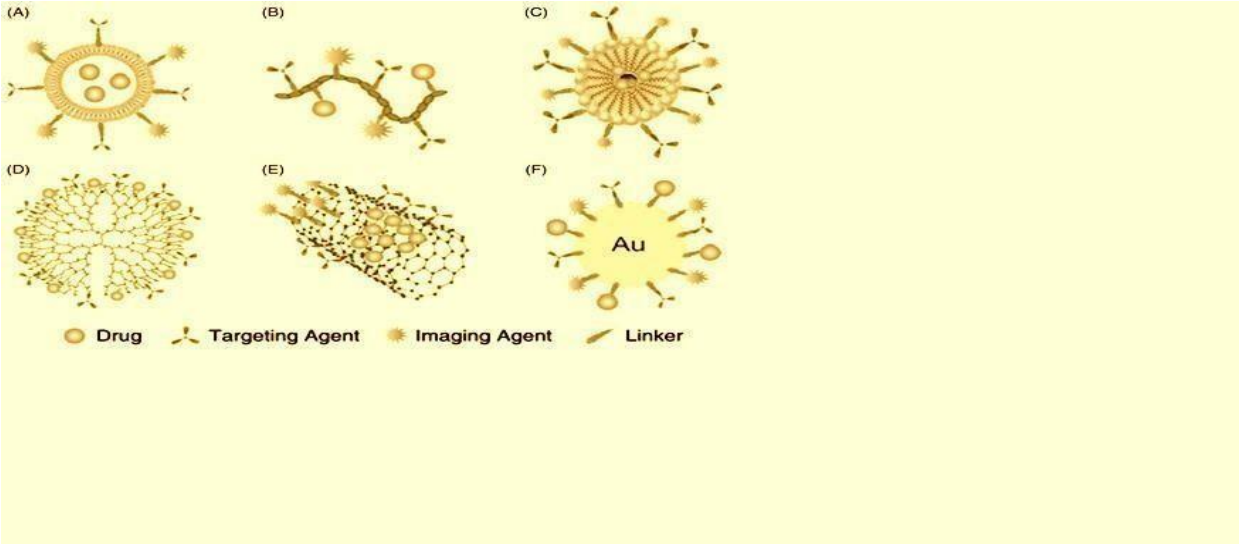


Figure 10. Commonly utilized nanomaterials for biomedical applications.
(A) Liposomes,
(B) Polymer Conjugate,
(C) Micelles,
(D) Dendrimers,
(E) Carbon nanoparticles
(F) Inorganic (metal) nanoparticles

The EPR outcome was first reported by Matsumura and Maeda and was shown in the following articles by Maeda . The group has shown that most hard tissues have damaged arteries and show strong blood vessels to ensure adequate supply of nutrients and oxygen to plant tissues for rapid growth. The EPR effect enables an increase in macromolecule greater than 40 kDa from the tumor vessel to the inner space leading to the accumulation of macromolecules.
However, strong binding to normal endothelial cells does not allow such a transition. Therefore, the effect of EPR provides tumor-targeted drug delivery, which is considered a paradigm promising the development of anticancer drugs. One of the doxorubicin-targeted liposomal formulation formulations, Doxil_ is clinically therapeutic for Kaposi's sarcoma and many other nanomedicines that rely solely on the effect of EPR on its identification of the tumor in clinical trials and pre-clinical studies.

Although the introduction of EPR cancer drugs has shown some effect on targeted nanocarrier delivery of chemotherapeutic agents, however, this strategy faces several challenges of drug delivery to tumor. First, the internal pressure of the air sets an important barrier that prevents nanocarriers from entering the tissue. Fluid pressure increases with plant growth as plasma fluids and proteins leak into the capillaries. The high protein content in the spatial space causes colloidal pressure to block the entry of any macromolecules from the bloodstream. Second, rapidly growing tumor cells compress the lymphatic arteries causing a reduction in interstitial drainage with the full benefit of fluid pressure. Third, the factor arises from the heterogeneity of body tissue. The central part of the tumor with tumor stem cells shows a small accumulation of nanocarriers compared to other parts of the tumor. The inclusion of the drug in this necrotic, middle part of the tumor is negatively affected by the EPR effect as the central part is hypo- vascularized with the effect of small vascular leakage.

Table 3- FDA approved nanomedicines for anti-cancer therapy

Trade Name	**Compound**	**Nanocarriers**
Abraxane	Paclitaxel	Albumin bound paclitaxel
DaunoXome	Daunorubicin	Pegylated liposome
Doxil	Doxorubicin	Pegylated liposome
Bexxar	anti- CD20 conjugated to idod ine131	Radioimmunoconjugate
Zevalin	anti- CD20 conjugated to yittr ium-19	Radioimmunoconjugate
Zeladex	Goserelin acetate	Polymer rod
Myoset	Doxorubicin	Non-pegylated liposome
Oncasper	PEG-L-asparaginase	Polymer-protein conjugate
Ontak	IL-2 fused to diphtheria toxin	Immuno toxin fusion protein
SMANCS	Zinostatin	Polymer-protein conjugate

CHAPTER 4

TARGETING MECHANISMS AND SURFACE FUNCTIONALIZATION ON NANOCARRIERS

Targeting mechanisms and surface functionalization on nanocarriers

Drug delivery includes random identification, **active targeting, pH specification, and temperature specification.**

4.1 Passive targeting

Unexplained targeting refers to the nanocarrier's ability to descend through the vascular system, tra pped, and accumulated in the tumor. This accumulation is caused by the durability and performance-enhancing properties of the poly (ethylene oxide) (PEO) coating other than most nanocarriers. PEO allows nanocarriers to travel through the leaky tissue of the plant, from which they cannot escape. The leaky tissue of a tumor is a network of blood vessels that form a tumor, consisting of many small holes. These pores allow nanocarriers in between, but also contai n more bends that allow nanocarriers to get trapped. When more nanocarriers are caught, the tree m eets in the plant area. PEO can have adverse effects on cell-nanocarrier interactions, weakening the effects of the drug, as many nanocarriers must be injected into cells before the drugs are released.

4.2 Active targeting

Active identification involves the installation of target modules such as ligands or antibodies on the surface of nanocarriers specific to specific types of cells around the body. Nanocarriers have such a high surface area to volume that allows multiple ligands to be placed in their places these target modules allow nanocarriers to be inserted directly inside the cells, but also have certain drawbacks. Millions can cause nanocarriers to become less toxic due to unspecified binding and good cost to ligands can reduce drug delivery once inside cells. Active identification has been shown to help overcome many drug resistances in tumor cells.

4.3 pH specificity

Certain nanocarriers will only release the drugs contained in certain pH ranges. PH specification also allows nanocarriers to deliver drugs directly to the tumor site. Abscesses are usually more acidic than normal human cells, with a pH of around 6.8. Normal tissues have a pH of around 7.4. Nanocarriers only release drugs at certain pH levels and can therefore be used to extract the dr ug only within acidic environments. High acidic environments cause the drug to be released due to its acidic environment which reduces the formation of nanocarrier. These nanocarriers will not release the drug in neutral or basic environments, directly in acidic areas of the plant while leaving normal immune cells untouched. This pH sensitivity can also be incorporated into

micelle systems by adding copolymer chains to the micelles determined to act on individual pH. These micelle-polymer complexes also help prevent cancer cells from developing resistance to multiple drugs. The low pH environment results in the rapid release of micelle polymers, which ca uses most of the drug to be released simultaneously, rather than gradually resembling other therapies.

4.4 Temperature specificity

Other nanocarriers have also been shown to deliver drugs effectively at certain temperatures. Since tumor temperatures are generally higher than body temperature, approximately 40 ° C, this temperature gradient helps to act as a site-specific delivery.

CHAPTER 5

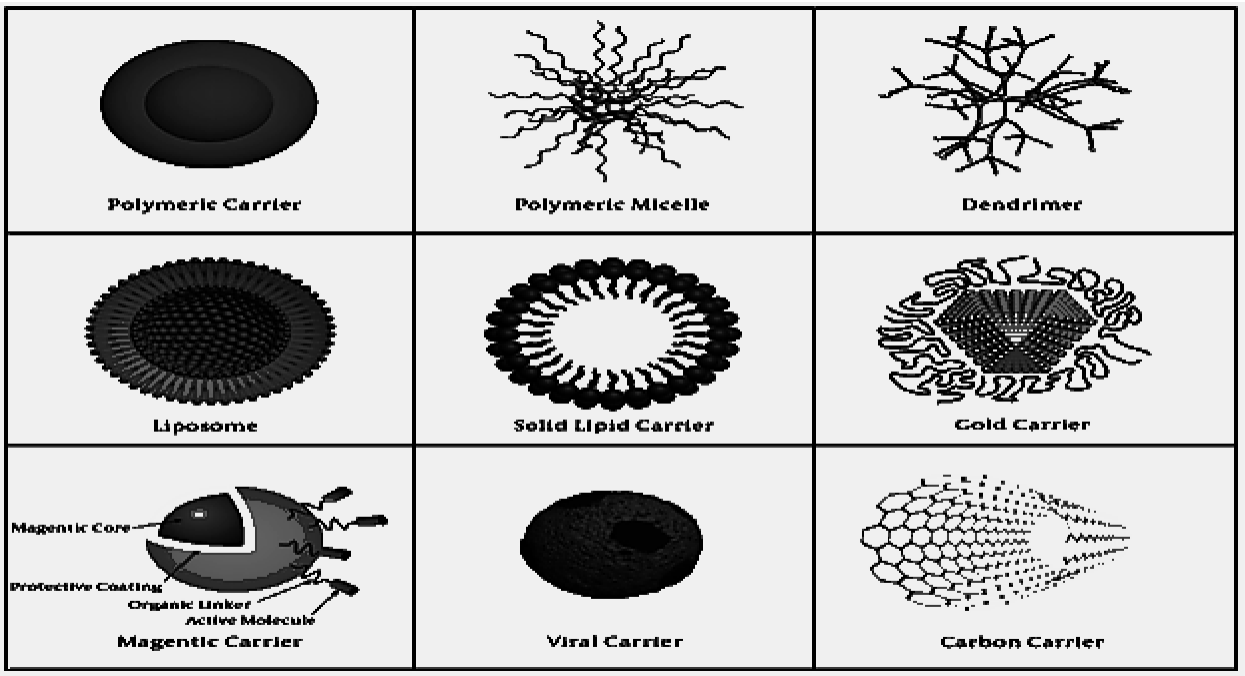
Types

5.1 Types:-

The nanocarriers found to date include **polymer conjugates, polymeric nanoparticles, lipid-based carriers, solid lipid carrier, dendrimers**, **magnetic conductor**, **virus carrier, carbon nanotubes, and -nanoparticles of gold**.

Lipid-carrying carriers include liposomes and micelles. The various types of nanomaterials used in nanocarriers allow hydrophobic and hydrophilic drugs to be introduced throughout the body. Since the human body contains a lot of water, the ability to deliver hydrophobic drugs successfully to humans is a major therapeutic benefit for nanocarriers. Micelles can contain hydrophilic or hydrophobic drugs depending on the shape of the phospholipids molecules. Some nanocarriers contain nanotube compounds that allow them to contain both hydrophobic and hydrophilic drugs.

Another potential problem with nanocarriers is unwanted toxins from the type of nanomaterial used. Inanimate nanomaterials can also be toxic to the human body when they come in contact with certain cell structures. New research is being done to develop more effective, safer nanocarriers. Protein-based nanocarriers show promise of therapeutic use because they occur naturally and often show less cytotoxicity than synthetic molecules.



Different Types of Nanocarriers

Table 4- Advantages and Disadvantages of different types of nanocarriers.

Types of Carriers	**Advantages**	**Disadvantages**
Liposomes	Biocompatibe Longer duration of circulation Amphiphilic	May trigger immune response
Carbon nanoparticles	Multiple functions Effici ent loading Water soluble and biocompatible Chemical modification	Toxicity
Polymeric micelles	Potential targeting Biodegrada ble, self assembling and bioco mpatible Efficient carrier system for hydrophilic drug Functi onal modification	Occasional Cytotoxicity Need of surface modifications
Dendrimiers	Uniformity in size, shape and branch length Tuned pharmacokinetics and biodi stribution. Targeting is achieved	Complex synthetic route
Metallic nanoparticles Gol d nanoshells	Uniformity in size, shape and branch length Tuned pharmacokinetics and biodi stribution Increased surface area, increased loading Targeting is achieved	Toxicity

CHAPTER 6

Future Perspective

Future Perspective

One of the major challenges of the latest developments in nanotechnology to be used for the treatment of various tumors/cancer is the expansion of new-generation drugs.

This expansion will ensure strong tumors regulation through contact with the ligand attach ed to the face and receptors in selected cells and tissues. However, it requires other obstacle to overcome such as lack of adequate technology, difficulty crossing the cell membrane, small drug window, control barriers and cost effectiveness.

Unfortunately, the typical recurrence of structuralextensions did not receive the expected patient compliance; however, nanocarriers have the potential to achieve specific targeted a nti-cancer drugs, both in the event that they become standard and subsequent agents.

Various targeted nanocarriers have developed an improved therapeutic effect on a variety of tumor animals. Specifically, 1201 120 ongoing clinical trials with multiple antibodies containing nanocarrier formation are under investigation. Similarly, today scientists are able to compare the type and location of a plant, which leads to the identification of appropriate therapies. In addition, if tumor cells have a circulatory system as is the case with lymphoma and leukemia, the carrier has a longer lifespan around half the life and higher potential for targeting more antigens. It is also expected that in the near future scientists will be able to make targeted cell combinations that can lead to improved therapeutic results at a reduced cost.

Although researchers have researched and developed many new drug delivery systems to achieve better drug use in patients, only a handful of these powerful drug delivery systems have reached the market. This may be due to significant gaps in the conversion of drug-laden nanocarriers. Therefore, it is important to switch to other traditional models to prevent these problems. In this regard, more serious efforts are needed to address other issues as a matter of urgency to achieve the innocent use of newly developed nanocarriers in clinical studies. This includes the development of standard in vitro certified nanoformulations and in vivo assay for effective performance, safety and potential toxicity.

CHAPTER 7

Conclusion

Conclusion

Nanotechnology was recently developed as one of the latest drug delivery systems. These nanocarriers have brought about a change in the delivery of cancer drugs by clearly identifying the tumor with as much firmness and effect of retention as needed. This exciting development in cancer treatment and the special development of many novel drug delivery systems has boosted the confidence of those who are struggling with tissue. It is believed that in the future, direct dose administration of drugs with high levels of nanocarriers and toxic side effects will not only emphasize the use of nanocarrier programs in anti-drug delivery but will also improve patient compliance.

REFERENCES

- Sun T, Zhang YS, Pang B, Hyun DC, Yang M, Xia Y. Engineered nanoparticles fordrug delivery in cancer therapy. *Angew Chem Int Ed*.
- Wong HL, Bendayan R, Rauth AM, Li Y, Wu XY. Chemotherapy with anticancerdrugs encapsulated in solid lipid nanoparticles
- Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. *Eur J Pharm Biopharm*.
- Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. *Adv Drug Deliv Rev*.
- Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations.
- Qureshi OS, Kim HS, Zeb A, et al. Sustained release docetaxel-incorporated lipid nanoparticles with improved pharmacokinetics for oral and parenteral administration. *J Microencapsul*.
- Yuan H, Miao J, Du Y-Z, You J, Hu F-Q, Zeng S. Cellular uptake of solid lipid nanoparticles and cytotoxicity of encapsulated paclitaxel in A549 cancer cells. *Int J Pharm*.
- Kakkar D, Dumoga S, Kumar R, Chuttani K, Mishra AK. PEGylated solid lipid nanoparticles: design, methotrexate loading and biological evaluation in animal models. *Med Chem Commun*
- Deshpande PP, Biswas S, Torchilin VP. Current trends in the use of liposomes for tumor targeting. *Nanomedicine*. 2013.
- Lee W-H, Loo C-Y, Traini D, Young PM. Nano-and micro-based inhaled drug delivery systems for targeting alveolar macrophages. *Expert Opin Drug Deliv*. 2015.
- orchilin VP. Recent advances with liposomes as pharmaceutical carriers. *Nat RevDrug Discov*. 2005.
- Kresge C, Leonowicz M, Roth W. Dendrimers and Dendrons. Concepts,Syntheses, Applications. Weinheim: VCH; 2001.
- Basu S, Sandanaraj BS, Thayumanavan S. Molecular recognition in dendrimers. In: Mark HF, editor. *Encyclopedia of Polymer Science and Technology*. 4th ed. John Wiley &Sons.
- Stiriba SE, Frey H, Haag R. Dendritic polymers in biomedical applications: from potentialto clinical use in diagnostics and therapy. *Angew Chem Int Ed*. 2002.
- de Groot FM, Albrecht C, Koekkoek R, Beusker PH, Scheeren HW. "Cascade-release dendrimers" liberate all end groups upon a single triggering event in the dendriticcore. *Angew Chem Int Ed*. 2003.

- Lai P-S, Lou P-J, Peng C-L, et al. Doxorubicin delivery by polyamidoamine dendrimer conjugation and photochemical internalization for cancer therapy. *J Control Release*.2007.
- Malik N, Evagorou EG, Duncan R. Dendrimer-platinate: a novel approach to cancer chemotherapy. *Anticancer Drugs*. 1999.
- Zhuo RX, Du B, Lu ZR. In vitro release of 5-fluorouracil with cyclic core dendritic polymer. *J Control Release*. 1999.
- Lee CC, Gillies ER, Fox ME, et al. A single dose of doxorubicin-functionalized bow-tie dendrimer cures mice bearing C-26 colon carcinomas. *Proc Natl Acad Sci U S A*. 2006.
- Bhadra D, Bhadra S, Jain S, Jain N. A PEGylated dendritic nanoparticulate carrierof fl uorouracil. *Int J Pharm*. 2003.
- Rao JP, Geckeler KE. Polymer nanoparticles: preparation techniques andsize-control parameters. *Prog Polym Sci 2011*.
- Bamrungsap S, Zhao Z, Chen T, et al. Nanotechnology in therapeutics: a focus on nanoparticles as a drug delivery system. *Nanomedicine*. 2012.
- Prabhu RH, Patravale VB, Joshi MD. Polymeric nanoparticles for targeted treatmentin oncology: current insights. *Int J Nanomedicine*. 2015.
- Wang X, Wang Y, Chen ZG, Shin DM. Advances of cancer therapy by nanotechnology .*Cancer Res Treat*. 2009.
- Hu CM, Aryal S, Zhang L. Nanoparticle-assisted combination therapies for effective cancer treatment. *Ther Deliv*.2010.
- Alexis F, Pridgen EM, Langer R, Farokhzad OC. Nanoparticle technologies for cancer ther apy. In: Schäfer-Korting M, editor. *Drug Delivery* Berlin, Heidelberg: SpringerBerlin Heidelberg; 2010.
- Zhu Y, Liao L. Applications of nanoparticles for anticancer drug delivery: a review. *J Nanosci Nanotechnol*.2015
- Pérez-Herrero E, Fernández-Medarde A. Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy. *Eur J Pharm Biopharm*. 2015
- Khuroo T, Verma D, Talegaonkar S, Padhi S, Panda AK, Iqbal Z. Topotecan–tamoxifen duple PLGA polymeric nanoparticles: investigation of in vitro, in vivo and cellular uptake p otential. *Int J Pharm*. 2014
- Wang H, Zhao Y, Wu Y, et al. Enhanced anti-tumor efficacy by co-delivery of doxorubicin and paclitaxel with amphiphilic methoxy PEG-PLGA copolymer nanoparticles. *Biomaterials*. 2011;
- Wang W, Chen S, Zhang L, et al. Poly(lactic acid)/chitosan hybrid nanoparticles for controlled release of anticancer drug. *Mater Sci Eng C Mater Biol Appl*. 2015
- Zhao D, Liu C-J, Zhuo R-X, Cheng S-X. Alginate/CaCO3 hybrid nanoparticles forefficient codelivery of antitumor gene and drug. *Mol Pharm*. 2012
- Gothwal A, Khan I, Gupta U. Polymeric micelles: recent advancements in the delivery of anticancer drugs. *Pharm Res*. 2016.

- Nakanishi T, Fukushima S, Okamoto K, et al. Development of the polymer micelle carrier system for doxorubicin. *J Control Release*. 2001
- Rapoport N. Physical stimuli-responsive polymeric micelles for anti-cancer drug delivery. *Prog Polym Sci*. 2007
- Ren J, Fang Z, Yao L, et al. A micelle-like structure of poloxamer–methotrexate conjugates as nanocarrier for methotrexate delivery. *Int J Pharm*. 2015.
- Li X, Yang Z, Yang K, et al. Self-assembled polymeric micellar nanoparticles as nanocarriers for poorly soluble anticancer drug ethaselen. *Nanoscale Res Lett*.
- Manchester M, Singh P. Virus-based nanoparticles (VNPs): platform technologies for diagnostic imaging. *Adv Drug Deliv Rev*. 2006
- Singh P, Prasuhn D, Yeh RM, et al. Bio-distribution, toxicity and pathology of cowpea mosaic virus nanoparticles in vivo. *J Co ntrol Release*. 2007.
- Ma Y, Nolte RJ, Cornelissen JJ. Virus-based nanocarriers for drug delivery. *Adv DrugDeliv Rev*. 2012
- Jabir NR, Tabrez S, Ashraf GM, Shakil S, Damanhouri GA, Kamal MA. Nanotechnology-based approaches in anticancer research. *Int J Nanomedicine*. 2012
- Douglas T, Young M. Viruses: making friends with old foes. *Science*. 2006
- Chen Z. Small-molecule delivery by nanoparticles for anticancer therapy. *Trends Mol Med*. 2010
- Iijima S. Helical microtubules of graphitic carbon. *Nature*. 1991
- Bianco A. Carbon nanotubes for the delivery of therapeutic molecules. *Expert Opin Drug Deliv*. 2004
- Madani SY, Naderi N, Dissanayake O, Tan A, Seifalian AM. A new era of cancertreatment: carbon nanotubes as drug delivery tools. *Int J Nanomedicine*. 2011
- Yan Y, Chan-Park MB, Zhang Q. Advances in carbon-nanotube assembly. *Small*. 2007
- Vardharajula S, Ali SZ, Tiwari PM, et al. Functionalized carbon nanotubes: biomedical applications. *Int J Nanomedicine*. 2012
- Iannazzo D, Piperno A, Pistone A, Grassi G, Galvagno S. Recent advances in carbon nanotubes as delivery systems for anticancer drugs. *Curr Med Chem*. 2013
- Ajima K, Murakami T, Mizoguchi Y, et al. Enhancement of in vivo anticancer effects of cisplatin by incorporation inside single-wall carbon nanohorns. *ACS Nano*. 2008
- Fabbro C, Ali-Boucetta H, Ros TD, Kostarelos K, Bianco A, Prato M. Targeting carbon nanotubes against cancer. *Chem Commun*. 2012
- Lay CL, Liu HQ, Tan HR, Liu Y. Delivery of paclitaxel by physically loading ontopoly (ethylene glycol)(PEG)-graft carbon nanotubes for potent cancer therapeutics. *Nanotechnology*. 2010
- Adeli M, Beyranvand S, Hamid M. Noncovalent interactions between linear-dendritic copolymers and carbon nanotubes lead to liposome-like nanocapsules. *J Mater Chem*. 2012

- Ji Z, Lin G, Lu Q, et al. Targeted therapy of SMMC-7721 liver cancer in vitro and in vivo with carbon nanotubes based drug delivery system. *J Colloid Interface Sci*. 2012
- Adeli M, Hakimpoor F, Ashiri M, Kabiri R, Bavadi M. Anticancer drug delivery systems based on noncovalent interactions between carbon nanotubes and linear-dendritic copolymers. *Soft Matter*. 2011
- Bhirde AA, Patel V, Gavard J, et al. Targeted killing of cancer cells in vivo and in vitro with EGF-directed carbon nanotube-based drug delivery. *ACS Nano*. 2009
- Arlt M, Haase D, Hampel S, et al. Delivery of carboplatin by carbon-based nanocontainers mediates increased cancer cell death. *Nanotechnology*. 2010
- Levi-Polyachenko NH, Merkel EJ, Jones BT, Carroll DL, Stewart JH. Rapid photothermal intracellular drug delivery using multiwalled carbon nanotubes. *Mol Pharm*. 2009
- Wang Y, Zhao Q, Han N, et al. Mesoporous silica nanoparticles in drug delivery and b iomedical applications. *Nanomedicine*. 2015
- Lu J, Liong M, Sherman S, et al. Mesoporous silica nanoparticles for cancer therapy: energy-dependent cellular uptake and delivery of paclitaxel to cancer cells. *Nanobiotechnology*. 2007
- Lu J, Liong M, Zink JI, Tamanoi F. Mesoporous silica nanoparticles as a delivery system for h ydrophobic anticancer drugs. *Small*. 2007
- Lebold T, Jung C, Michaelis J, Brauchle C. Nanostructured silica materials as drug-delivery systems for Doxorubicin: single molecule and cellular studies. *Nano Lett*. 2009
- Rosenholm JM, Peuhu E, Bate-Eya LT, Eriksson JE, Sahlgren C, LindenM.Cancer-cell-specific induction of apoptosis using mesoporous silica nanoparticles as drug-delivery vectors. *Small*. 2010
- Prabhakar N, Zhang J, Desai D, et al. Stimuli-responsive hybrid nanocarriers developed by controllable integration of hyperbranched PEI with mesoporous silica nanoparticles for s ustained intracellular siRNA delivery. *Int J Nanomedicine*. 2016
- Desai D, Zhang J, Sandholm J, et al. Lipid bilayer-gated mesoporous silica nanocarriers for tumor-targeted delivery of zoledronic acid in vivo. *Mol Pharm*. 2017
- Haley B, Frenkel E. Nanoparticles for drug delivery in cancer treatment. *Urol Oncol Semin Orig Investig.2008*
- Torchilin V. Tumor delivery of macromolecular drugs based on the EPR effect. *AdvDrug Deliv Rev*. 2011
- Torchilin VP. Targeted pharmaceutical nanocarriers for cancer therapy and imaging. *AAPSJ*. 2007
- Jain RK, Stylianopoulos T. Delivering nanomedicine to solid tumors. *Nat Rev ClinOncol*. 2010
- Bae YH, Park K. Targeted drug delivery to tumors: myths, reality and possibility. *JControl Release*. 2011

- Danhier F, Feron O, Préat V. To exploit the tumor microenvironment: passive andactive t umor targeting of nanocarriers for anti-cancer drug delivery. *J Control Release*.2010
- Patil Y, Sadhukha T, Ma L, Panyam J. Nanoparticle-mediated simultaneous and targeted delivery of paclitaxel and tariquidar overcomes tumor drug resistance. *J Control Release*. 2 009
- Allen TM. Ligand-targeted therapeutics in anticancer therapy. *Nat Rev Cancer*. 2002
- Pirollo KF, Chang EH. Does a targeting ligand influence nanoparticle tumor localization or uptake? *Trends Biotechnol*. 2008
- Sudimack J, Lee RJ. Targeted drug delivery via the folate receptor. *Adv Drug DelivRev*. 2000
- Martinez-Carmona M, Colilla M, Vallet-Regi M. Smart mesoporous nanomaterials for antitumorx therapy. *Nanomaterials*. 2015
- Choi J-S, Park J-S. Development of docetaxel nanocrystals surface modified with transferrin for tumor targeting. *Drug Des Devel Ther*. 2017
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011
- Hall JE. *Guyton and Hall Textbook of Medical Physiology*. Philadelphia, PA: ElsevierHealth Sciences; 2015.
- Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancerstatistics, 2012. *CA Cancer J Clin*.2015
- Anderson D, Najafzadeh M, Gopalan R, et al. Sensitivity and specificity of theempirical lymphocyte genome sensitivity (LGS) assay: implications for improving cancer diagnostics. *FASEB J*. 2014
- Meyerson M, Gabriel S, Getz G. Advances in understanding cancer genomesthrough second-generation sequencing. *Nat Rev Genet*. 2010
- Singh P, Singh A. Ocular adverse effects of anti-cancer chemotherapy. *J Cancer Ther Res*. 2012
- Aravind A, Varghese SH, Veeranarayanan S, et al. Aptamer-labeled PLGA nanoparticles for targeting cancer cells. *Cancer Nanotechnol*. 2012

- Abner AL, Recht A, Eberlein T, et al. Prognosis following salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stagebreast cancer. *J Clin Oncol*. 1993
- Lichter AS, Lippman ME, Danforth D, et al. Mastectomy versus breast-conserving therapy in the treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. *J Clin Oncol*.1992
- Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide , methotrexate, and fluorouracil in node-positive breast cancer – the results of 20 years of follow-up. *N Engl J Med*. 1995
- Zuur CL, Simis YJ, Verkaik RS, et al. Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer. *Radiother Oncol*.2008
- Adair JH, Parette MP, Altinoglu EI, Kester M. Nanoparticulate alternatives for drug delivery. *ACS Nano*. 2010
- Chawla JS, Amiji MM. Biodegradable poly (ε-caprolactone) nanoparticles for tumor-targeted delivery of tamoxifen. *Int J Pharm*. 2002
- . Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. Cell 2009;136:823–37
- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. Cancer J Clin 2010;60:277–300.
- . Peer D, Karp JM, Hong S, et al. Nanocarriers as an emerging platform for cancertherapy. Nat Nanotechnol 2007;2:751–60
- Kwon GS. Polymeric micelles for delivery of poorly water-soluble compounds. Crit Rev Ther Drug Carrier Syst 2003;20:357–403
- Luo Y, Prestwich G. Cancer-targeted polymeric drugs. Curr Cancer DrugTargets 2002;2:209–26
- . Nehoff H, Parayath NN, Domanovitch L, et al. Nanomedicine for drug targeting: strategies beyond the enhanced permeability and retention effect. Int J Nanomedicine 2014;9:2539–55
- Iwai K, Maeda H, Konno T. Use of oily contrast medium for selective drug targetingto tumor: enhanced therapeutic effect and X-ray image. Cancer Res 1984;44:2115–21
- Konno T, Maeda H, Iwai K, et al. Selective targeting of anti-cancer drug and simultaneous image enhancement in solid tumors by arterially administered lipid contrast medium.Cancer 1984;54: 2367–74
- Biswas S, Torchilin VP. Nanopreparations for organelle-specific delivery in cancer. Adv Drug Deliv Rev 2014;66C:26–41
- Torchilin V. Tumor delivery of macromolecular drugs based on the EPR effect. AdvDrug Deliv Rev 2011;63:131–5
- Giordano KF, Jatoi A. The cancer anorexia/weight loss syndrome: therapeutic challenges. Curr Oncol Rep 2005;7:271–6

- Mays AN, Osheroff N, Xiao Y, et al. Evidence for direct involvement of epirubicin in the for mation of chromosomal translocations in t (15; 17) therapy-related acutepromyelocytic leukemia. Blood 2010;115:326–30
- Torchilin VP. Drug targeting. Eur J Pharm Sci 2000;11:S81–91.