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Review Article

NANOTECHNOLOGY IN CANCER CHEMOTHERAPY

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Abstract

A growing attention is given to the Cancer. For such patients Antineoplastic agents had given systematically which destroys both cancerous and normal cell of the body which leads to side effect. Due to this non specificity, nanotechnology is applied for the cancer therapy. Nanotechnology as a delivery platform offer very promising application in drug delivery. Nanometer size drug delivery system, about 1/80,000 of the diameter of human hair is the design. Nanometer size provides cell entry and extravasiation and decreases renal elimination leads to increase in efficiency and potency of antineoplastic agent.

Drug delivery carrier matrix contain one or more therapeutic compounds, contrast enhancers, such as MRI agents, and permeation enhancers. The surface of the carrier is modified with ligands for selective targeting to diseased tissues and poly (ethylene glycol) to achieve a stealth delivery. Nanotechnological approach in drug delivery for cancer therapy includes a large variety of Drug Delivery Carriers such as liposome, Polymeric micelles, Biodegradable Nanoparticle are discussed with their fabrication and characterization. Cancer chemotherapeutic drug when used as liposomal drugs produce much better efficacy and safety as compared to conventional preparations. Passive nanovectors demonstrate *in vitro in vivo* studies for anti-tumour activity by using enhanced permeability and retention effect, further tumour accumulation and intracellular uptake is possible by active nanovectors. Also the external activation by applying magnetic field to the nanometer sized drug delivery system is discussed. Nanomaterials are mostly investigated in preclinical animal models. Future perspective of these nanomaterials is discussed.

Key Words: Antineoplastic Agents, Nanotechnology, Drug Delivery Carrier, Colloidal Drug Carrier.

Introduction:

Cancer is leading cause death in all over the world. Approximately 25% of registered death is due to cancer. It is a genetic disease in which cell undergo unchecked cellular proliferation, tissue invasion and metastasis.[1] Type of cancer depends on various factors including sex, age, genetic disposition and exposure to environmental carcinogen.[2] Carcinogenesis is the transformation of normal cell into neoplastic cell which involve mutation of either tumour promoter or tumour suppressor gene. Tumour promoter genes enhance proliferation or prevent the cell death while tumour suppressor genes inhibit cell cycle growth. Proto-oncogenes are normal gene associated with cell growth or cell division which becomes oncogene after mutation. These oncogenes are involved in initiation and development of cancer. The treatment of cancer is complex and dependent on the type of cancer concerned. Treatment includes; surgery, radiotherapy, chemotherapy, combinations thereof.[1]

Current anticancer therapy has some disadvantage such as;

- Non-selective with high toxicity against normal tissues (Fig I).
- Rapid elimination from the systemic circulation.
- Accumulation in non-targeted organs and tissues.
- Enzymatic and hydrolytic degradation.
- Inefficient cell entry.[3]

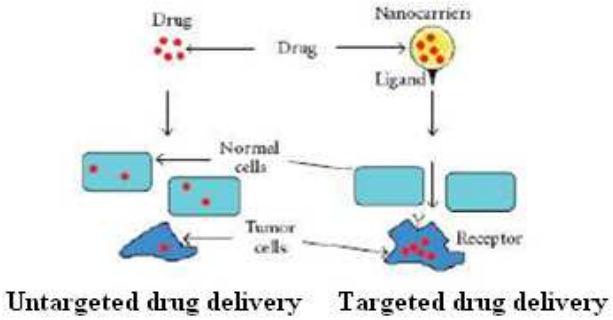

Figure I: Schematic diagram of Nanocarrier system for the site specific drug delivery[14]

Due to this non specificity, nanotechnology is applied for the cancer therapy. The prefix of nanotechnology derives from the 'nanos' – the Greek word for dwarf.[4] Nanotechnology refers to the interactions of cellular and

molecular components and engineered materials—typically clusters of atoms, molecules, and molecular fragments—at the most elemental level of biology.[5] A nanometer is billionth of a meter about 1/80,000 of the diameter of a human hair.[4] Nanotechnology as a delivery platform offer very promising application in drug delivery.[6] Nanotechnology has various applications in cancer through molecular tumour imaging, early detection, molecular diagnosis, targeted therapy, and cancer bioinformatics (Fig.II)[7]

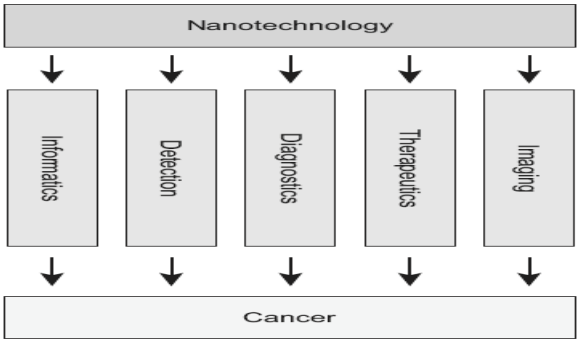

Figure II: Schematic diagram showing nanotechnology applications in cancer.[7]

Nanocarriers are used for cancer chemotherapy has various advantage over current Anticancer chemotherapy such as;

- Nanometer size provides improved cell entry and extravasation.
- Decreased renal elimination.
- Improved bioavailability of the anticancer agent.
- Increased solubility of water-insoluble anticancer agents.
- Provide a container that can hold agent within.[3]

Drug Delivery Device:

Drug Delivery Devices should be biodegradable, injectable, biocompatible and targetable and also control the release of anticancer drug over a sustained period of time. The upper size limit for nanocarrier should be approximately between 6 and 8 mm in diameter and the lower size limit is dependent on the goal of the delivery system.

Drug delivery carrier matrix contain one or more therapeutic compounds, contrast enhancers, such as MRI agents, and permeation enhancers. The surface of the carrier is modified with ligands for selective targeting to diseased tissues and poly ethylene glycol to achieve a stealth delivery (Fig. III).[3]

The ideal particulate carrier would have the capability to do the following

- To carry one or more therapeutic agents.
- To target through one or more conjugated antibodies or other recognition moieties.
- To image diseased tissue.
- To avoid biological barriers that can promote clearance from the systemic circulation.[3]

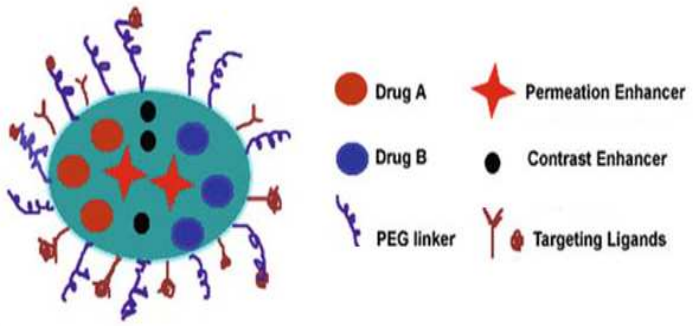

Figure III: Schematic presentation of a Drug Delivery Carrier Matrix[3]

Current Cancer Nanotechnologies:

A. Nanovector:

Nanovectors designed for drug delivery have a surface modified with biological materials, such as antibodies, that can be used to target a specific receptor in cancer cells.[8] Nanovectors are classified into three types;

1. First Generation: These are not targeted specifically against any biological molecule on the tumour cells.
2. Second Generation: These nanovectors were developed to recognize and target specific Biological molecules on the cancer cells
3. Third Generation: It is currently under development which is multi stage strategy based.
    i. First stage particle: These are biodegradable silicon microparticles which are having pores within them and pass through the circulatory system and recognize the disease specific endothelium.

ii. Second stage particles: These are multitypes of nanoparticle which are loaded within the first stage particles and are set free towards the tumour mass.[9]

B. Nanoparticle: Polyethylene glycol-coated gadolinium-based iron oxide nanoparticles have been used to target cancer cells and detect apoptosis using magnetic resonance imaging techniques. Magnetic fields are also induced to heat the iron oxide nanoparticles to kill the cancer cells.[8] The nanoparticles are typically between 20-150 nm or roughly 100 times smaller than most human cells[10] (Figure IV). The control of cell and tissue distribution of anticancer agents is the biggest advantage of nanoparticulate systems.[9]

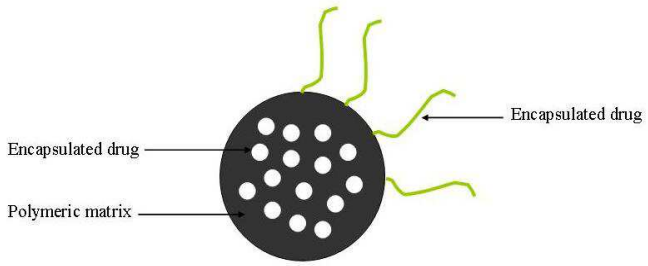

Figure IV: Schematic presentation of a Nanoparticle[15]

C. Gold Nanoparticles:

Gold nanoparticles have been used as contrast agents in vitro based on their ability to scatter visible light. In a subcutaneous model of colon cancer, it was demonstrated that systemically delivered gold nanoparticles (size, approximately 33 nm) conjugated to tumour necrosis factor accumulated in tumors.[7] (Fig. V)

Figure V: Schematic presentation of A: Gold Nanoparticles, B: Paramagnetic Nanoparticles[14, 19]

D. Paramagnetic Nanoparticles:

Paramagnetic nanoparticles are used for both diagnostic and therapeutic purposes. Diagnostically, paramagnetic iron oxide nanoparticles are used as contrast agents in magnetic resonance imaging. These have a greater magnetic

susceptibility than conventional contrast agents. And as a therapeutic purpose, iron nanoparticles coated with monoclonal antibodies directed to tumour cells can be made to generate high levels of heat after these accumulate in their target site by means of an alternating magnetic field applied externally which kills the cancer cells.[7] (Fig. V)

E. Solid Lipid Nanoparticles (SLNs):

They are particles of submicron size (50 to 1000 nm) made from lipids that remain in a solid state at room as well as body temperature. Various anticancer agents like doxorubicin, daunorubicin, idarubicin, paclitaxel, etoposide, etc have been encapsulated using this nanotechnological approach. Several obstacles frequently encountered with anticancer agents, such as a high incidence of drug resistant tumour cells can be partially overcome by delivering them using solid lipid nanoparticles.[7]

F. Liposome:

Liposomes are made up of lipids enclosing water core (Fig. VI). They increase the drug concentration at the tumour sites by passive targeting.[9] Cancer chemotherapeutic drug like amphotericin when used as liposomal drugs produce much better efficacy and safety as compared to conventional preparations. These liposome's can be loaded with drugs either in the aqueous compartment or in the lipid membrane. Usually water soluble drugs are loaded in aqueous compartment and lipid soluble drugs are incorporated in the liposomal membrane. The major limitation of liposome is its rapid degradation and clearance by the liver macrophages, thus reducing the duration of action of the drug. This can be reduced by coating the liposome with polyoxyethylene.[7]

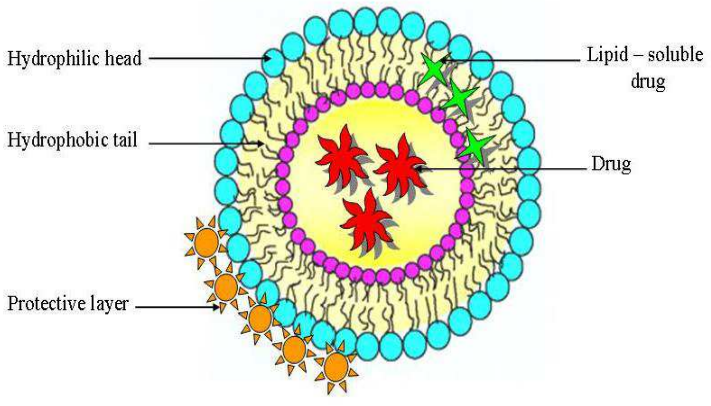

Figure VI: Schematic presentation of Liposome[15]

G. Dendrimer:

Dendrimers are artificial macromolecules with treelike structures in which the atoms are arranged in many branches and sub branches radiate out from a central core (Fig. VII). They are synthesized from branched monomer units in a stepwise manner. Thus it is possible to control their molecular properties, such as size, shape, dimension, and polarity, which depend on the branched monomer units.[7] Dendrimers are mainly used in the MRI of lymphatic drainage in mouse model of breast cancer.[9]

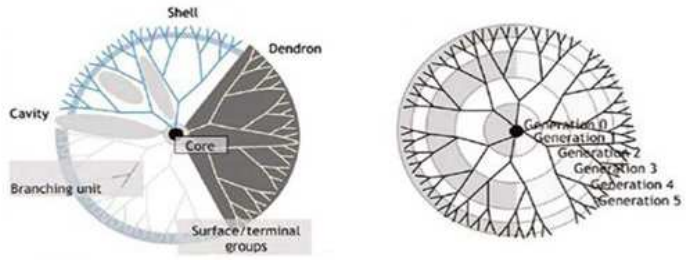

Figure VII: Schematic presentation of Dendrimer[15]

H. Nanoshells:

Nanoshell is a type of spherical nanoparticle consisting of a dielectric core which is covered by a thin metallic shells approximately 10–300 nm in dimension. Nanoshells are composed of a dielectric core, usually silica, surrounded by gold.[11] When nanoshells reach their target they can be irradiated to make the nanoshell hot — the heat kills the cancer cell.[12] These are used to kill venereal tumours in mice. When radiated with near-infrared light, the nanoshells heat up to 55º to 70º C, and are able to kill cancer cells thermally.[8]

I. Nanobiosensor:

A device used for detection of an analyte through combination of a sensitive biological component, transducer along with a detector component is termed as a biosensor which comprise of cancer specific antibody or ligands so that they can selectively capture cancer cells or target proteins. Nanobiosensors are useful for early diagnosis of cancer. They can also effectively be utilized for the detection of cancer agents such as environmental pollutants, pathogens and carcinogenic gases. The use of nanobiosensors in cancer clinical testing have been increased due to high speed and reduced cost for diagnosis, automation and multi target analysis.[9]

J. Nanocantilevers:

Nanocantilevers are flexible beams, resembling a row of diving boards that can be coated with molecules capable of binding to cancer biomarkers.[12] When specific biomolecules bind to nanocantilevers; deflection of beam takes place which is observed by laser light or other methods.[9]

K. Nanowires:

Nanoscale sensing wires that can be coated with molecules such as antibodies to bind to proteins of interest and transmit their information through electrodes to computers.[12] Silicon nanowires are one such real time detectors for simultaneous molecular binding effects.[9] Protein coated nanowires have potential applications in cancer imaging like prostate cancer, breast cancer and ovarian malignancies.[7]

L. Fullerenes:

Fullerenes are also called as "Bucky balls" were discovered in 1985.[7] A nanoscale structure, composed of carbon atoms arranged in a specific soccer ball- like architecture. Fullerenes are a form of carbon, which also forms nanotubes.[12] Both empty and metallo-fullerenes have low cyto-toxicity *in vitro* and *in vivo* and can be effectively used for drug design and delivery. The cage-like structure of fullerene is ideal for packing with anti-cancer drugs or even radiological materials to increase treatment efficacy for killing cancer cells.[8]

M. Nanotube:

Nanotubes are Cylinder-like assemblies of carbon atoms with cross-sectional dimensions in the nanometre range, and lengths that can extend over a thousand times their diameters[12] (Fig. VIII). They have unique chemical, size, optical, electrical and structural properties that make them attractive. Drug encapsulation has been shown to enhance water solubility, better bioavailability, and reduced toxicity.

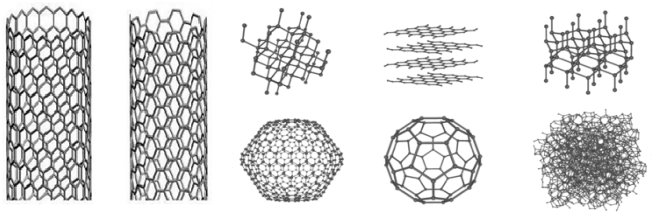

Figure VIII: Schematic presentation of Carbon Nanotube[11]

Advantages of nanotube are:

a) Efficient encapsulation of the drugs,

b) Successful delivery of said drugs to the targeted region of the body,

c) Successful release of drug.[11]

The surface of the nanotube is modified with proteins for cellular uptake. Then the nanotubes are heated with near-infrared light to kill cancer cells. Nanotubes have also been used as nano-bombs to destroy cancer cells *in vitro.* Nano-bombs may offer a highly effective method of killing cancer cells that are malignant as the temperatures attained in a localized way are much higher compared with other nanovectors used in thermal ablation of cancer cells.[8]

N. Quantum Dots:

Quantum dots are inorganic fluorescent semiconductor nanoparticels composed of 10–50 atoms with a diameter ranging from 2 to 10 nm (Fig. IX). Their sizes and shapes which determine their absorption and emission properties. They are widely studied for optical image application in living systems and are stable for months without degradation and alteration. Targeted ligands have been attached to QDs in order to achieve specific targeting for tumour cell labelling. Thus, they are assured to be chosen as long-term, high sensitivity and multicontrast imaging agents applied for the detection and diagnosis of cancer *in vivo.*[7]

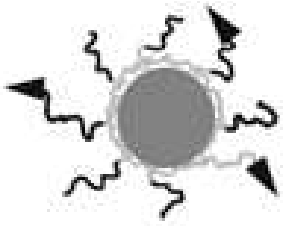

Figure IX: Schematic presentation of Quantum Dots[18]

General principles of drug targeting to cancer:

Passive targeting:

Passive targeting refers to the accumulation of drug or drug-carrier system at a particular site due to physicochemical or pharmacological factors. Carriers such as nanoparicles localize in the tumour tissue. This

occurs because as tumours grow and this process is known as angiogenesis. In normal tissues blood vessels are tight where as angiogenic blood vessels have gaps as large as 600–800 nm between adjacent endothelial cells. Drug carriers in the nanometer size range can extravasate through these gaps into the tumour interstitial space. Normal tissue vasculatures are lined by tight endothelial cells, thereby preventing nanoparticle drugs from escaping or extravasation, whereas tumour tissue vasculatures are leaking and hyperpermeable allowing preferential accumulation of nanoparticles in the tumour interstitial space called passive nanoparticle tumour targeting the carriers concentrate in the tumour, resulting in higher drug concentration in the tumour tissue. This is commonly referred to as enhanced permeability and retention effect (Fig. X).[7]

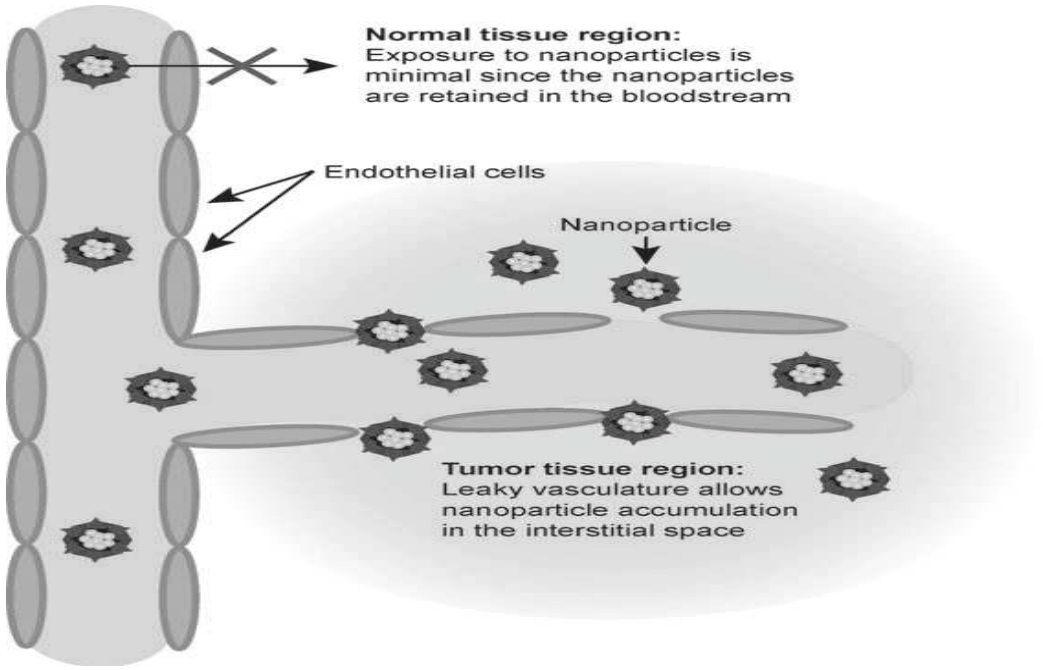

Figure X: Schematic diagrams showing Passive Targeting.[7]

Active Targeting:

Active targeting to the tumour can be achieved by molecular recognition of cancer cells either via ligand–receptor or antibody–antigen interactions. Nanoparticles and other polymer drug conjugates offer numerous opportunities for targeting tumours through surface modifications which allow specific biochemical interactions with the proteins/receptors expressed on target cells. It is essential to avoid drug uptake by the Reticulo Endothelial System (RES) so that they remain in the blood circulation and extravasate in the tumour vasculature.

Particles with more hydrophobic surfaces are preferentially taken up by the liver, followed by the spleen and lungs. Particles smaller than 100 nm and coated with hydrophilic polymers such as amphiphilic polymeric compounds which are made of polyethylene oxide such as poloxamers, poloxamines, or polyethylene glycol (PEG) are being investigated to avoid their uptake by the RES. To improve the efficacy of targeting cancer chemotherapeutics to the tumour, a combination of passive and active targeting are used. Also direct intratumoral injection of the carrier system is feasible if the tumour is localized and can be accessed for administration of a carrier system. The nanoparticle drug is internalized by tumour cells through ligand-receptor interaction. Depending on the design of the cleavable bond, the drug will be released intracellularly on exposure to lysosomal enzymes or lower pH (Fig. XI)[7]

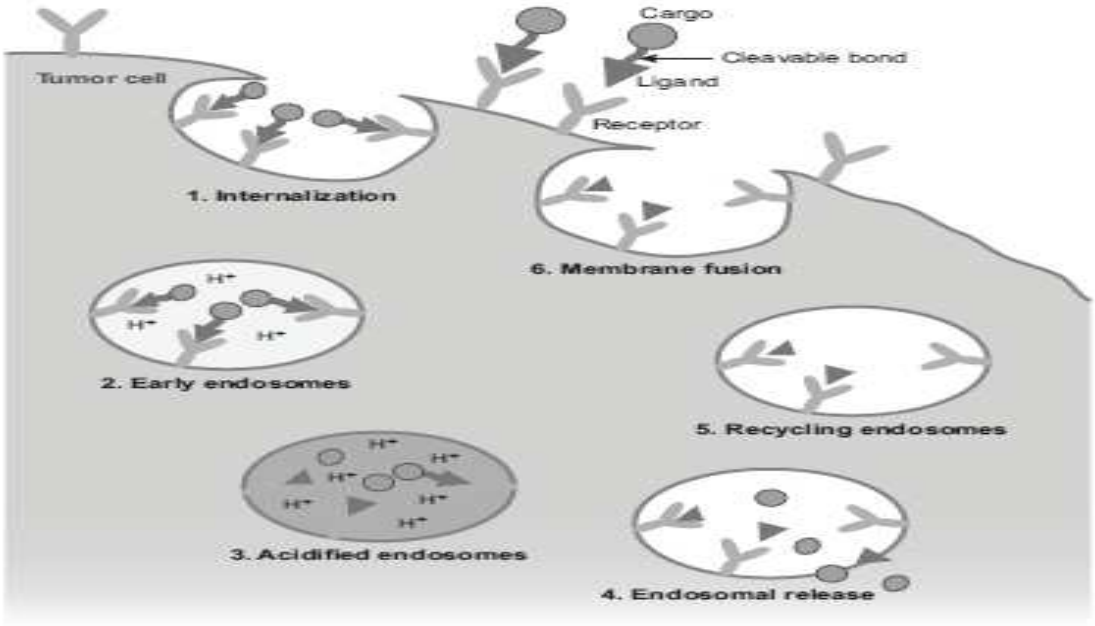

Figure XI: Schematic diagram showing Active Targeting[7]

Evaluation:

The physicochemical properties includes size, size distribution, surface and bulk morphology, surface chemistry, surface charge, drug encapsulation efficiency, and physical and chemical status of the drug encapsulated determine the therapeutic efficacy of the nanoparticle. Various techniques are used to analyze the physicochemical properties of nanomaterial (Table I). These techniques serve to evaluate the relationship between

physicochemical properties of nanomaterial and their interaction with blood components in the systemic circulation.[3]

Table-I: Evaluation of Nanomaterial.[3]

Sr. No.	Parameter	Method
1.	Size and Size Distribution	Dynamic Laser Light Scattering (DLS)
2.	Surface and Bulk Morphology	i. Scanning Electron Microscopy. ii. Transmission Electron Microscopy.
3.	Surface Composition	X-Ray Photoelectron Spectroscopy.
4.	Surface Charge	Measurement of Zeta Potential

Future perspective:

Nanomaterials are mostly investigated in preclinical animal models.[14] The Table II given below gives Nanomaterials in Clinical Trial.[15, 16, 17]

Table II: Nanomaterials in Clinical Trial[15, 16, 17]

Sr. No.	Name	Platform	Therapeutic Agent	Clinical Stage
1.	Doxil	Liposome	Doxorubicin	Approved
2.	DaunoXome	Liposome	Daunorubicin	Approved
3.	MCC465	Antibody Liposome	Doxorubicin	Phase I

4.	MBP-426	Transferrin-liposome	Oxaliplatin	Phase I
5.	Oncolipin	Liposome	Interleukin 2	Phase I
6.	L-Annamycin	Liposome	Annamycin	Phase I
7.	CPX-1	Liposome	Floxuridine	Phase II
8.	Aroplatin	Liposome	Oxaliplatin	Phase II
9	SPI-77	Liposome	Cisplatin	Phase II
10	Abraxane	Nanoparticle	Albumin-paclitaxel	Approved
11	Transdrug	Nanoparticle	Doxorubicin	Approved
12	Nanoxel	Nanoparticle	Paclitaxel	Phase I
13	Paclimer	Nanoparticle	Paclitaxel	Phase I

Conclusion:

Nanotechnology gives promising application in cancer chemotherapy. It also improves the bioavaibility of anti-cancer agent with minimum side effect. Targeting approach such as passive and active targeting approach is studied. In future, nanoscale device could detect cancer at its earliest stage and simultaneously deliver anticancer agent to the discovered tumour.

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