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Review Article

Targeted Delivery of Nanomedicines

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The role of targeting of the diseased region by a drug is emphasized. The rationale for resorting to nanomaterials as drug carriers is explained. A clear understanding of the biological environment, its degradation in diseased condition, and the interaction of the drug with it in normal condition and during illness lie at the core of successful drug delivery. Passive and active drug targeting approaches are differentiated. Commonly used drug targets, targeting ligands, and nanoscale systems are elaborated. Mechanisms of internalization of nanomedicines and circumventing P-glycoprotein mediated resistance are outlined. The paper presents an overview of the current scenario of targeted transportation of nanomedicines to the affected organ and suggests future research directions.

1. Introduction

The past few decades have witnessed unprecedented endeavours for developing nanomaterials as effective drug delivery vehicles. Undeniably, nanomaterials, generally smaller than 100 nm in at least one dimension, manufactured at the molecular level, in the form of nanoparticles, quantum dots, nanotubes, nanorods, or other versions, and composed of metals, semiconductors, natural or synthetic polymers, and lipids, have offered new opportunities for the improvement of medical treatment by impacting the science of drugs in a big way [1–6]. This paper describes the needs, design approaches, opportunities, and challenges of nanomaterial-based drug formulations for efficient transfer, targeting, and delivery. Although the treatment of the subject is general, the focus of the paper is on drug targeting for treating cancer.

Requirements of nanomaterials for drug transport and targeted drug delivery are highlighted at the outset. For efficacy of therapy, the drug should silently sneak to the afflicted portion, without any disturbance, accomplishing the healing. Furthermore, it should be able to discriminate between healthy and diseased portions, interacting selectively and solely with the diseased portion for curing purpose.

2. Nanomaterials as Drug Delivery Vehicles

The attractiveness of nanomaterials for drug delivery needs hardly to be reiterated [7–12]. Nanomaterials offer manifold advantages as drug transport and delivery vehicles. Evidently, the drug particles cannot reach the remote secluded areas of the body if they are large in size; for example, if a drug has to reach the body cells, the particles should be sufficiently small to penetrate and cross the cell boundary. Thus, first and foremost, the particles must have nanoscale dimensions. Only such low-dimensionality particles will be useful in these situations. In fact, nanoparticles are more suitable than microparticles for intravenous delivery because the tiny capillaries have 5-6 micron diameter, a range in which most microparticles or their conglomerations are impeded. For systemic circulation, the particle diameters should lie in the range of 10–100 nm. Then only access to various parts of the body will be available. Secondly, nanomaterials are consumed by cells easily than larger micromolecules, raising the drug effectiveness. The drug is integrated in the nanoparticle matrix or attached to the particle surface. As nanoparticles possess very high surface to volume ratios, the dissolution rate is increased according to *Noyes Whitney equation* relating the dissolution rate of solids to its properties and the dissolution medium;

for example, poorly soluble compounds like paclitaxel, cyclosporine, or amphotericin B show an augmented dissolution rate and absorption in the gastrointestinal tract when formulated as nanosuspensions. Thirdly, nanomaterials can be used for targeted drug delivery at the specific disease site, improving the uptake of a poorly soluble drug. Depending on the particle charge, surface properties, and relative hydrophobicity, nanoparticles are designed to adsorb preferentially on organs or tissues. Fourthly, nanomaterials help in lessening of undesirable side effects by a controlled release. Encapsulation of the drug in so-called nanospheres safeguards against degradation and prolongs exposure of the drug by restricted release. Therefore, use of nanomaterials in the pharmaceutical sector improves the overall therapeutic index, providing agreeable solutions for delivery problems (Table 1).

Negative aspects of the nanoparticles should also be mentioned. A disadvantage of nanosize is the possibility of removal of drug by filtration through the kidney. The effective pore size of the glomerular wall being 8 nm, large particles pass through far less frequently than the smaller ones. Thus the probability of removal through filtration can be decreased by carefully selecting nanoparticle size, keeping in mind the pore size in kidney.

3. The Need of Drug Aiming and Its Controlled Release

The notion of drug targeting must be carefully examined. Ideally, a drug administered, for example, by the oral route, should reach the diseased part of the human body stealthily without affecting the tissues and organs *en route*. After reaching the diseased part, it should release its ingredients at the exact moment in the correct dosage necessary to heal that part. Further, after the afflicted part is successfully cured, any remnant drug particles should be expelled from the body so that its normal functioning is not impaired. For anticancer drugs to be effective in treatment, they should, after administration, be able to reach the desired tumor tissues with minimal loss of their volume or activity in the blood circulation. Subsequently, after reaching the tumor tissue, drugs should have the ability to selectively kill tumor cells without upsetting normal cells, with a controlled release mechanism.

The aforementioned contention implies that a drug will be effective if it fulfills the following criteria (Table 2). (i) The drug should influence the diseased region solely, that is, it should have *no side or toxic effects*. (ii) The drug should not lose its ingredients on the way to its destination. If there is a loss of ingredients, they will have to be replenished by giving more drug to the patient leading to *overdosage effects*. (iii) Some targeting property should be built in the drug whereby it is guided towards its goal. This indicates the significance of drug targeting, which is the most craved but elusive goal in drug delivery science. It increases the efficacy and reduces toxicity of a drug by restricting its action to the treated tissue.

Table 1: Advantages of nanomaterials in drug delivery.

Sl. no.	Advantage
(1)	Ability to pass through narrow capillaries and accessibility of remote areas
(2)	Easily consumed
(3)	Delivery at specific sites by passive or active targeting
(4)	Easy encapsulation for protection or controlled release

Table 2: Ideal drug delivery characteristics.

Sl. no.	Characteristic feature
(1)	Absence of side effects
(2)	Biocompatibility
(3)	Stability and loss-free transit to affected part
(4)	Biodegradability

4. Understanding the Biological Environment

Needless to say that a thorough understanding of biological environment is necessary for designing and preparing nanoparticle-based formulations. Also, knowledge of interactions of nanomaterials with it is desirable. Key factors include target cell population, target cell-surface receptors, changes in cell receptors that occur with progression of disease, mechanism and site of drug action, drug retention, multiple drug administration, molecular mechanisms, and pathobiology of the particular disease under consideration.

5. Physiological Hindrance to Drug Targeting

The main obstacles to drug targeting are the physiological barriers, such as the mucus lining in the body. Other barriers like biochemical hurdles of target identification and pharmaceutical hurdles to devise appropriate techniques of conjugating targeting ligands to nanomaterials will be dealt with later.

The layers of mucus protecting sensitive tissues throughout the body have a detrimental side effect of forbidding entry to helpful medications. These mucus layers, known for trapping and removal of pathogens and other foreign materials, stall the localized delivery of drugs to many parts of the body, including the lungs, eyes, digestive tract, and female reproductive system. Since some viruses that were attracted to water and had a net neutral electrical charge were able to make their way through the human mucus barrier, nanoparticles were coated with polyethylene glycol (PEG), a nontoxic material dissolving in water and excreted benignly by the kidneys. PEG-coated, 200–500 nm particles could slip through a barrier of human mucus, which could render possible the delivery of chemotherapy, antibiotics, nucleic acids, and other treatment directly to the lungs, gastrointestinal tract, and cervicovaginal tract.

Blood Brain Barrier (BBB) is a semipermeable capillary membrane formed by the single layer of *endothelial* cells that line the inner surfaces of capillaries in the brain, allowing some materials to move across, but blocks others. Large

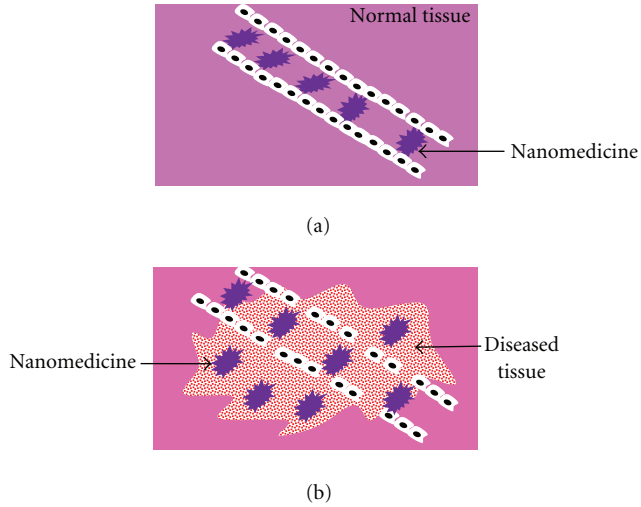

Figure 1: Passive drug targeting through seeping blood vessels in the cancerous part. (a) In the normal tissue, there are no ruptures and the drug travels steadily through the blood vessel. (b) In the tumour-affected region, the drug percolates through holes and accumulates in the tumour. Thus a high concentration of drug is built up in the later region, starting the healing action.

Table 3: Passive versus active targeting.

Sl. no.	Passive targeting	Active targeting
(1)	Utilizes the special deviated conditions prevailing in the diseased portion of the body	Depends on the species that is overexpressed during disease
(2)	Less selective	Highly selective
(3)	Restricted in use	Very versatile
(4)	More likely to produce side effects	Less likely to induce side effects

Table 4: Passive drug targeting scheme.

Sl. no.	Stepwise formulation
(1)	Studying the physiological conditions of diseased area
(2)	Preparation of the delivery carrier having a definite molecular weight (>30 kDa), molecular size (100–200 nm), possessing hydrophilicity and neutral charge
(3)	Adjusting the delivery system to be sensitive to pH, temperature, charge or an enzyme. The coating of the carrier is designed such that during circulation in blood, it is stable but when entering the capillaries in the tumor, where the temperature is slightly higher, the coating melts, and discharges the drug which accumulates in the tumor starting its action; such a carrier is said to be *thermosensitive*

molecules as well as low lipid (fat) soluble molecules do not penetrate into the brain. Molecules that have a high electrical charge are decelerated. However, lipid soluble molecules swiftly cross the BBB into the brain. The BBB is selectively permeable to oxygen, carbon dioxide, and glucose but does not allow movement of hydrogen ions across it. The BBB protects the brain internally in the same way as the skull saves it externally.

6. Drug Targeting Approaches

Two approaches are distinguishable, namely, passive and active targeting (Table 3).

6.1. Passive Targeting. Direct drug injection and catheterization are examples of passive drug targeting. *Passive targeting*, also known as *physical targeting*, is based on the preparation of a drug carrier complex that avoids removal through body mechanisms like metabolism, excretion, opsonisation, and phagocytosis, so that the complex remains circulating in the blood stream permitting its transmission to the target receptor by properties like pH, temperature, molecular size, or shape. Spontaneous drug accumulation in areas with leaky vasculature is a form of passive targeting (Figure 1). The physiology of diseased tissues, altered in different pathological conditions, is exploited for passively targeting drugs (Table 4).

Nanoparticles used in a drug delivery system should be large enough to thwart their speedy outflow into blood capillaries. But they should be small enough to escape capture by fixed macrophages stuck in the reticuloendothelial system, such as the liver and spleen. As the size of the sinusoid in the spleen and fenestra in the endothelial lining of the liver is 150–200 nm, and the size of gap junction between endothelial cells of the leaky tumor vasculature varies between 100 and 600 nm, the size of nanoparticles should be up to 100 nm to reach tumor tissues by passing through these two particular vascular structures [8].

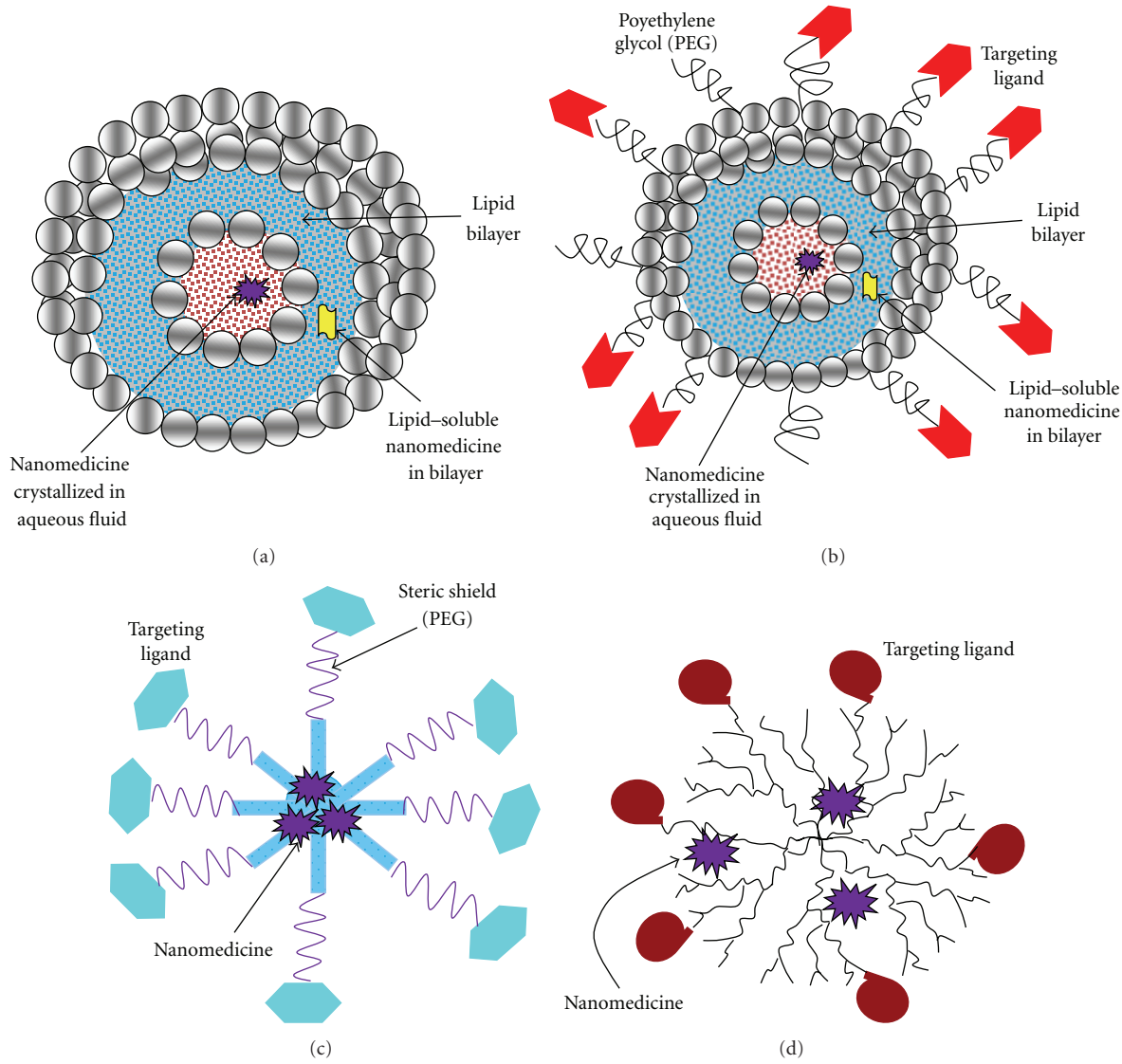

Figure 2: Representative nanoscale systems used for administering drugs: (a) liposome with drug inclusions in the aqueous fluid and bilayer, (b) liposome with targeting ligands and PEG, (c) polymer micelles, and (d) dendrimer.

Apart from size, the nanoparticles should have a hydrophilic surface to escape macrophage capture. This is achieved by coating the surface of nanoparticles with a hydrophilic polymer, such as polyethylene glycol (PEG), which shields them against opsonization by repelling plasma proteins.

The outcome of the release of various chemotactic factors from the infected/inflamed tissues is vascular remodeling to enable leukocyte extravasation, increasing the permeability for particulate drug carriers, for example, improved vascular permeability in inflammatory conditions allowing extravasation of the nanosystems and their discriminatory localization in the inflamed tissue. Considering cancer treatment, rapidly proliferating cancer cells demand the recruitment of new vessels (neovascularization) or rerouting of accessible vessels near the tumor to make available oxygen and nutrients. The consequent disproportion of angiogenic regulators such as growth factors and matrix metalloproteinases makes tumor vessels highly disordered and swollen with abundant pores showing bloated gap junctions between endothelial cells and compromised lymphatic drainage. These features are called the *enhanced permeability and retention effect* (EPRE). By this process, macromolecules, including nanoparticles, with a molecular weight above 50 kDa, selectively gather in the tumor interstitium [8].

An additional factor participating in targeting is the unique microenvironment flanking tumor cells, which is distinctly dissimilar from that of normal cells. Hyperproliferative cancer cells have an elevated metabolic rate. Consequently, the supply of oxygen and nutrients is, by and large, inadequate for them to sustain this rate. Therefore, tumor cells use glycolysis to acquire extra energy, producing an acidic environment. The pH-sensitive liposomes are designed to be stable at a physiological pH of 7.4 but are

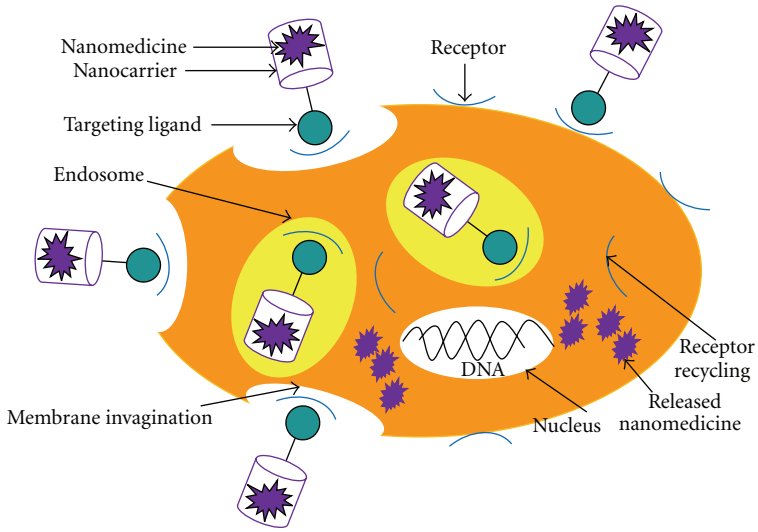

Figure 3: Diagram illustrating internalization of the nanomedicine by the cell. In the incipient stage, the medicine invaginates the cell membrane to seek entry into the cell. Inside the cell, it is enveloped by plasma membrane forming the endosome. From the endosome, the medicine contents and target ligands are released, spreading into the cell. While the medicine cures the disease, the ligands migrate towards the cell surface to participate in drug targeting, thus commencing a fresh cycle of activity.

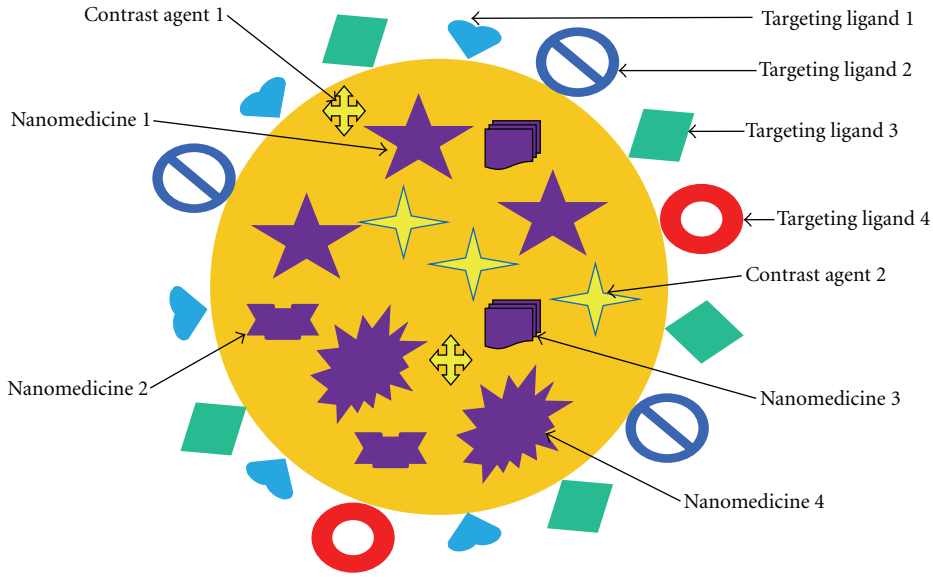

Figure 4: Conceptual visualization of a future multifunctional nanomedicine containing four different types of drugs, four targeting ligands, and two contrast agents for imaging to follow up the healing action of the drug.

degraded to release active drug in target tissues in which the pH is less than physiological values, such as in the acidic environment of tumor cells.

Gold nanoparticles have been immensely utilized in drug targeting [13–19]. *Photothermal therapy* using Au nanoparticles is a less insidious technique for the treatment of cancer and associated diseases. It employs a laser source, with a spectral range of 650–900 nm for deep tissue penetration, and Au NPs which absorb the optical irradiation and transform it into thermal energy on a picosecond time scale, inducing photothermal ablation. Gold nanorods are effective photothermal agents because they have a longitudinal absorption band in the near infra red (NIR) due to their surface plasmon resonance (SPR) oscillations. Other gold nanostructures such as nanoshells, nanocages, and nanospheres have also been used.

6.2. Active Targeting. In *active drug targeting*, moieties like antibodies, antibody fragments, and peptides are coupled to

drugs and delivery systems to act as homing devices for strapping to receptor structures expressed at the target site. This approach provides the widest opportunities and alternatives. Drug targeting by ultrasonic energy and magnetic field is also considered as active targeting [2].

Many active targeting drug conjugates use a ternary configuration composed of a ligand or antibody as a targeting moiety, a polymer or lipid as a carrier, and an active chemotherapeutic drug. In order to serve as tumour-specific targets, cell-surface antigens should be expressed entirely and homogeneously on all tumor cells, and not on normal cells. Further, they should not be discarded into the blood circulation. After binding to target cells, internalization occurs via receptor-mediated endocytosis, as explained in Section 10.

7. Drug Targets in the Body

The main targets in the body must be summarized (Table 5).

7.1. Receptors on Cell Membranes. Receptors on cell membranes allow specific interaction of drug carriers with cells facilitating their uptake via receptor-mediated endocytosis [2]. Folate receptors, which are differentially overexpressed in cells of cancers with epithelial origin, are applied to tumor-specific drug delivery in cancers including breast, ovary, brain, and lung malignancies. Further, as peptide receptors are expressed in gigantic quantities in some tumor cells, peptides/peptide analogs are conjugated to a drug carrier to allow tumor-specific targeting of cytotoxic agents, ensuring interaction with peptide receptors.

7.2. Lipid Components of Cell Membranes. Interaction of synthetic phospholipid analogs with cellular membranes alters the lipid composition, membrane permeability, and fluidity. In this way, signal transduction mechanisms are affected inducing apoptotic cell death.

7.3. Antigens or Proteins on Cell Surfaces. The diseased cells either express new proteins or exhibit differential (under/over) expression of the proteins found on normal cells. Monoclonal antibodies are used against these proteins. A utilizable tumor-specific antigen for drug targeting is the one expressed exclusively and similarly by all tumor cells. erbB2, a growth factor overexpressed in 20–30% human breast adenocarcinomas, on the tumor cell surface, has been used for immunotherapy with liposomal doxorubicin formulation coupled to anti-erbB2-antibody. The reason for its attractiveness is its ready accessibility, low expression on normal cells, and a consistent distribution within the tumor.

8. Targeting Ligands

These ligands include sugars, folic acid, peptides, and explicitly engineered antibodies, which interact with some degree of exclusivity with the specific receptors identified on particular cell types (Table 6) [22–35]. Existence of endogenous lectins on the epithelial cells of different gut regions is exploited for drug targeting using sugars. Overexpression of folate receptors on tumor cells allows targeting using folic acid as a targeting moiety. Peptides like vascular endothelial growth factor (VEGF) are used for targeting drugs to their specific receptors that are expressed profusely in different states of the disease. Antibodies are used against definite antigens/proteins expressed on the surfaces of cells.

Table 5: Drug targets.

Sl. no.	Target	Description
(1)	Folate receptor	A folate-binding protein. Folate receptor-targeted epothilone BMS 753493 contains an epothilone moiety linked to a single folate molecule. It delivers the antimitotic epothilone component into cells expressing folic acid receptors, frequently unregulated in tumor cells
(2)	Peptide receptor	A cell surface protein that binds peptides with high affinity
(3)	Cell membrane	Also called the plasma membrane, plasmalemma or "phospholipid bilayer", it is a semipermeable lipid bilayer found in all cells
(4)	Cell surface antigen	Antigens on surfaces of cells, for example, infectious or foreign cells or viruses; they are usually protein-containing groups on cell membranes or walls

9. Available Nanosystems

These are liposomes [27–29], polymeric micelles [30–33], polymer-drug conjugates [34], and dendrimers [35] (Table 7); see Figure 2. Some of the newer nanosystems include nanocages, nanogels, nanofibers, nanoshells, nanorods, and nanocontainers.

Liposomes are used to deliver immunomodulators, cytotoxic and antimicrobial agents to the macrophages by passive targeting. Activating factors such as cytokines are tied to macrophages to make them tumoricidal. The activated macrophages selectively annihilate tumor cells.

In a passive targeting therapy for the treatment of hepatic metastasis, anticancer drug-loaded polymeric nanoparticles are mainly concentrated in Kupffer cells in liver on intravenous injection. These Kupffer cells serve as reservoirs allowing protracted diffusion of anticancer drug into the neighboring tumor cells.

Polymeric micelles are novel carrier systems in drug targeting due to their increased loading capacities, stability in physiological conditions, and the possibility of engineering the core-shell architecture for diverse applications. Micelles with peptide/sugar moieties on the surface are used to aim at specific peptide receptors on cell surface.

Conjugation of a polymeric carrier to low molecular weight drugs rigorously changes its pharmacokinetic disposition at both the whole body and the cellular levels.

Table 6: Commonly used ligands in drug delivery.

Sl. no.	Name of the ligand	Definition	Characteristics
(1)	Sugar	Any of a class of sweet, soluble, crystalline carbohydrates, white when pure	The specificity of carbohydrate-protein interactions is much larger than that of many other ligand-binding systems, through its great ability to undergo site-specific modification. Use of carbohydrate ligands to target protein receptors at sites of localization, termed "glycotargeting," exploits the highly specific interactions of endogenous lectins with carbohydrates
(2)	Folic acid	A water-soluble vitamin, yellowish-orange, (C_{19} H_{19} N_7 O_6) belonging to the B-complex group of vitamins	Employed as a targeting moiety for anticancer drugs through covalent conjugation to drugs; the folate receptor-α is overexpressed in several human tumors, including ovarian, lung, brain, head and neck, and breast tumors
(3)	Peptide	Natural or synthetic, short polymer chain compound, containing two or more amino acids linked by the carboxyl group of one amino acid to the amino group of another	EGF-R peptide ligand (D4: Leu-Ala-Arg-Leu-Leu-Thr) is conjugated with a polyethylene glycol (PEG) lipid, and the lipid moiety of the peptide-PEG-lipid conjugate is inserted into liposome membranes by a postmodification process. D4 peptide-conjugated liposomes bind to and enter cells by endocytosis specifically and efficiently *in vitro* in a process apparently mediated by EGF-R high-expressing cancer cells (H1299) [20]
(4)	Antibody	An immunoglobulin, a specialized immune protein, generally found in the blood that detects and destroys invaders, like bacteria, and so forth; produced because of the introduction of an antigen into the body	anti-CEA (Carcinoembryonic Antigen) half-antibody conjugated lipid-polymer hybrid nanoparticles show enhanced cancer killing effect compared to the corresponding nontargeted nanoparticles [21]

These conjugates permit passive targeting of tumors via EPR effect. A polymer-drug conjugate bearing a targeting ligand is the galactosamine directed HPMA-tetrapeptidyl-doxorubicin, designed for treatment of liver cancer by targeting the asialoglycoprotein receptor on hepatocytes.

Table 8 presents some examples of anticancer nanomedicines.

10. Mechanisms of Internalization of Nanomedicine and Avoiding Drug Resistance

This occurs via receptor-mediated endocytosis in which the binding of the drug to a receptor is accompanied by the plasma membrane enveloping the two forming an endosome (Figure 3). When the pH in the endosome becomes acidic, it releases the drug particles which spread and enter the cytoplasm. The receptors thus liberated wander to the cell surface where they again partake in receiving more drug molecules. Thus a recycling of receptors takes place.

For the folate receptor, when a folate-targeted conjugate binds with folate receptor on the cell surface, the invaginating plasma membrane envelopes the complex of the receptor and ligand forming an endosome. The endosomes are transferred to target organelles. As the pH value in the interior of the endosome diminishes to become acidic and lysozymes are activated, the drug is released from the conjugate and enters the cytoplasm, provided that it has the acceptable physicochemical properties for crossing the endosomal membrane. Released drug is then carried by its target organelle depending on the drug. In the interim, the folate receptor set free from the conjugate returns to the cell membrane, initiating a second cycle of transport by fastening with new folate-targeted conjugates [8].

Drug resistance lowers its efficacy through the well-known *P-glycoprotein efflux pump*. This efflux is responsible for extrusion of toxic substances outside the cell. The ability of efflux system to recognize substances is based on physicochemical properties like hydrophobicity, aromaticity, and ionizable character instead of chemical properties such as ligand-receptor recognition. One suggested mechanism [8] of circumventing the efflux is that the drug being inside the endosome is able to evade recognition by the above pump. This mechanism essentially postulates that the avoidance of recognition by the pump occurs by virtue of confinement of the drug inside the endosome. Ligand-assisted targeting especially is more favourable against drug resistance because the drug internalization occurs via receptor-mediated endocytosis. However, the possibility of the drug being released from the lysosome and excreted out of the cell still exists.

Table 7: Common carriers of nanomedicines.

Sl. No.	Name of the carrier	Definition	Explanation and advantages
(1)	Liposome	Spherical vesicle with a phospholipid bilayer	It is used to convey vaccines, drugs, enzymes, or other substances to organs
(2)	Polymer miscelles	Nano-sized particle (~10 to ~100 nm) composed of block or graft copolymers, typically having a so-called core-shell structure. The core contains the drugs, while the shell interacts with the solvent making the nanoparticle stable in the liquid	Especially useful for poorly water-soluble pharmaceutical active ingredients. The stability of the drug is also increased. Undesirable side effects are lessened, as contact of the drug with enzymes in biological fluids is minimized
(3)	Dendrimer	A macromolecule with highly branched 3D structure, consisting of three main components: core, branches and end groups, and providing a high degree of surface functionality and versatility. It originates from the Greek *dendron*, meaning "tree"	It is small enough to enter cells carrying the drug. It has a great potential in drug nanoformulations for melanoma therapy owing to advantages, such as thermodynamic stability, high solubility in water, the controllable size (usually 1 to over 10 nm), morphology and functional groups on the surface, and uniform size distribution

Table 8: Anticancer nanomedicines.

Sl. no.	Name of the compound	Disease for which used
(1)	Liposomal doxorubicin	Ovarian cancer, AIDS-related Kaposi's sarcoma, and advanced breast cancer
(2)	Albumin-paclitaxel	Breast cancer
(3)	PEG-L-asparaginase	Leukaemia

11. Multifunctional Nanoparticles

Gao et al. [36], Choi et al. [12] have elucidated the use of a multifunctional nanoparticle with biomolecules conjugated to QDs for cancer targeting and drug delivery. In order to target cancerous cells, they conjugated A10 RNA, aptamer that recognizes prostate-specific membrane antigen (PSMA), to the QD. Doxorubicin (DOX), an anthracycline drug with fluorescent properties, was intercalated in the conjugate.

The aforementioned conjugate offers an enlivening method of imaging cancer cells. The intercalated DOX within A10 RNA conjugated to the QD quenches the fluorescence of both DOX and QD. When the QD-aptamer (DOX) conjugate finds the target cancer biomarker, it is captured into the cancerous cell through endocytosis. Upon liberation of DOX from the conjugate, both of them recuperate their fluorescent properties enabling imaging. Based on this design, the multifunctional nanoparticle is fabricated in such a way that cancer biomarkers become precisely detectable. Simultaneously, the drug is delivered into the cancer cell, giving high specificity.

12. Conclusions and Future Perspectives

Contemporary techniques for delivering nanomedicines at prespecified targets were described. Futuristic techniques were also envisioned. In future, two distinct roles for nanomedicines are envisaged: therapeutic and imaging. It is expected that multifunctional nanomedicines must be capable of treating diseases as well as aiding in imaging of healing parts to regulate the dosage (Figure 4). Then only the scourge of dreaded, devastating diseases like cancer can be eradicated. The area offers interesting promises and prospects in "not-too-distant" era.

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