Chapter 2
Surface Modification of Nanoparticles for Targeted Drug Delivery

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Abstract Over the course of recent years, nanoparticles have been the center of attention used to treat many health related diseases. Nanoparticles are used due to it being efficient and having the ability to overcome certain biological barrier such as tumor, malignant melanoma, and treating HIV. Nanoparticles are known to have many different manipulating structures and characteristics which gives these particles a huge advantage in treating cancer. Nanoparticles are also used in tumor suppression due to their extraordinary ability of modifying their cell surface. One of the other great advantages of nanoparticles is to treat malignant melanoma. Two of the main components used in malignant melanoma therapy is poly(ε-caprolactone) (PCL) and poly(ethylene glycol) (PEG). Both components being FDA approved, have extraordinary effects in drug delivery through nanotechnology if used in a conjugated manner. One of the barriers faced in malignant melanoma therapy is losing the ability to encapsulate and retain a drug if ligands on the surface adjust the chemical properties of the polymer, which can be overcome by the use of dopamine. Nanoparticles have been greatly advantageous in breaking through barrier of successful HIV therapy. To treat this retroviral disease, the use of solid lipid nanoparticles is made due to it being able to improve the long-term stability of colloidal nanoparticles.

Keywords Nanoparticles · Surface modification · Tumor specific delivery Quantum dots · Metallic nanoparticles

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1 Introduction

The utilization of nanoparticles with multifaceted properties is done in a wide array of biological applications. This encompasses gene and drug delivery for diagnostic and therapeutic purposes. Nanoparticles have shown to be very promising in the field of advanced drug delivery to specifically and rapidly target cells. Folic acid conjugated drugs target folate receptors-positive cancer cells. Research indicates that folate receptors upregulate 90% of ovarian carcinomas, also high to moderate levels in the brain, lung, kidney, and breast carcinomas. Folic acid is classified as a vitamin B which makes it imperative for cell survival as it has a role in the biosynthesis of nucleic acids. Folic acid has a high affinity ligand which complements conjugated anticancer drugs' differential specificity for folate receptors [1].

The extracellular matrix of tumors poses a biological barrier to the diffusion of advanced drug delivery systems and therapeutics. To overcome this obstacle, the surface of bromelain can be modified to increase the diffusion of silica nanoparticles across the tumor extracellular matrix. This is an ideal delivery method for cancer therapy as it is able to travel through the bloodstream and target the tumor site [2].

Therapeutic effects of chemotherapy on malignant melanoma can be enhanced using paclitaxel (PTX)-loaded methoxy poly(ethylene glycol)-b-poly(ε-caprolactone) nanoparticles (MPEG-b-PCL NPs) with modified surfaces contain polydopamine as a drug delivery carrier. This is a new therapy for treating malignant melanomas with anticancer drug loaded nanocarriers. This strategy has attracted much interest due to its high permeability to drugs, biocompatibility, non-cytotoxicity, and thermal products [3]. Similarly, PEGylated liposomes of PTX has also been developed with potential efficacy for treatment of ovarian cancer [4].

The preparation, characterization, and modification of lipid nanoparticles is essential for targeted cellular delivery methods. Previous research indicates that uncoated lipid nanoparticles of stavudine are effective in the treatment of HIV. Stavudine lipid nanoparticles with surface modification can serve as a drug delivery system for anti-HIV chemotherapy. This can be done both in vivo and in vitro [5]. This selective surface coating of lipid nanoparticles has proven to be very effective for specific targeting of infectious diseases. This technique helps overcome obstacles to HIV therapy at specific targets in the human body such the brain, spleen, bone marrow, etc. [6].

2 Surface Modification Using Cobalt Oxide Nanoparticles for Targeted Drug Delivery in Anticancer Treatments

Nanoparticles are solid and ranges in size from 1 to 100 nm. Manipulating the structure and characteristics of nanoparticles can affect their function introducing new techniques and technologies [7–9]. Nanoparticles (Table 2.1) vary to a great extent based on the properties of shapes, spatial arrangement, electronic configuration,

Table 2.1 Nanocarriers, constituents, and applications [12]

Nanoparticles	Definition
Liposomes	Spherical vesicles containing bilayered structure that can reassemble itself in aqueous systems. Few advantages of this nanoparticle is its ability to protect biomolecules along with their biodegradability and biocompatibility
Albumin-bound	Nanoparticle known for carrying hydrophobic molecules into the bloodstream. An advantage of using these nanoparticles include its ability to avoid solvent-based toxicities for therapeutics due to it naturally binding to hydrophobic molecules
Polymeric	Nanoparticles made from biodegradable and biocompatible polymers. In an aqueous solution, it has the ability to assemble itself into a core–shell micelle formation. The wide use of these nanoparticles is due to it having the ability to improve the safety and efficacy of the drugs they carry
Iron oxide	Nanoparticles known for being superparamagnetic. These molecules are very stable because they have an iron oxide core with hydrophilic coat of dextran. These nanoparticles are greatly advantageous because of its decreased toxicity and increased imaging sensitivity and specificity
Quantum dot	Nanoparticles that display optical and size dependent electronic properties. Quantum dots are known to be stable against photobleaching, have high efficiency, long lifetime, and emit bright colors. They have different biochemical specificities which can be excited and detected
Gold	Nanoparticles known to offer facile surface modification, biocompatibility, and many size and shape dependent optical and chemical properties. Due to these nanoparticles free electrons having the ability to interact with light, it enhances their light absorption, fluorescence, scattering, and surface-enhanced Raman scattering. It has great potential for infrared phototherapy because it can transfer absorbed light into heat

energetics, chemical reactivity, phase changes, catalytic capabilities, and assembly. Modifying the surface of nanoparticles for advanced drug delivery methods can alter its properties to target specific receptors in molecules on various types of cells [10, 11]. Nanoparticles are successful in biomedical and biopharmaceutical applications when their surface is synthesized and modified properly. In the solid phase, nanoparticles can be semicrystalline, amorphous, grain, or a mixture of the three. They can also be inorganic, organic, or a combination of the two. Additionally, the nanoparticles' structure can be comprised of multiple layers of different materials and when combined the structure is termed as nanocomposites. The creation of these nanocomposites can create a large number of nanoparticles that previously did not exist in nature. There are three types of nanoparticles that are created; nanoparticle composites, nanoparticle bulk composites, and composite nanofilms. These composite materials have a very successful track record in aerospace, sports, transportation, and defense. Nanocomposites are even used by developed nations to generate raw materials. There are even nanocomposites that are nanopolymers, inorganic–organic, or inorganic–inorganic. This variety allows for so many combinations to be made. The nanoparticles' method of preparation can be determined by its function, either chemical or physical. These methods can be further divided into liquid phase, gas phase, and solid phase methods based on the mechanism of the reaction.

Table 2.2 Anticancer treatments [6]

Anticancer drugs	Description
Chemotherapies	Known to kill cancer cells during their initial periods of division. This therapy is given through tablets or intravenous drip. Use of this therapy has many side effects, biggest being hair loss
Hormone therapies	Therapy used to stop the growth of cancer cells that are sensitive to hormones. Examples of this drug are: Tamoxifen and aromatase inhibitor. Few side effects related to this drug include: Bone pain, headaches, thinner hair, and nausea
Biological therapies	Known to target and kill specific types of cancer cells. Trastuzumab is known to be the biggest class of drugs in this category known to prevent breast cancer. Many side effects to this therapy are loss of appetite, hot flashes, skin changes, etc

Cobalt nanoparticles have catalytic, magnetic, and optical properties [13]. Cobalt oxide is mainly used as a biopolymer or organometal. These cobalt oxide nanoparticles have anticancer properties after surface modification. The cobalt oxide nanoparticles have great solubility in aqueous solutions and a decent hydrodynamic size. These nanoparticles have excellent uptake by cancer cells when combined with amide. Cobalt oxide nanoparticles are prepared by a thermal decomposition method after which surface modification of phosphonomethyl iminodiacetic acid (PMIDA) takes place [14]. These PMIDA-coated cobalt oxide nanoparticles can be coupled with folic acid. Methotrexate and doxorubicin are anticancer drugs that have been attached to folic acid nanoparticles that induce apoptosis in cancer cells. The above-mentioned drugs fall in class of chemotherapeutics. Other therapeutic classes used in cancer are hormones and biological therapies (Table 2.2).

Folate receptors are researched for tumor specific drug delivery. This research encourages preclinical and in vitro studies of tumors and therapeutic approaches on them. Myelogenous leukemia is a cancer that is now being treated using targeted folate receptor therapy [15]. Folic acid, which is an essential vitamin B, plays a vital role in anticancer drug targeting for folate receptors. Folic acid-conjugated drugs internalize folate conjugated compounds and bound folates through receptor mediated endocytosis. Folate receptor density increases indicate cancer. A variety of anticancer drugs have been evaluated based on their biological activity. In-spite of cobalt's role as a cofactor of vitamin B12, it can be used for anticancer treatment through surface modification. Research indicates that folate receptors appear to have important aspects of human medicine and physiology [16].

3 Use of Bromelain for Surface Modification of Silica Nanoparticles for Drug Delivery in the Tumor Extracellular Matrix

Bromelain is a digestive protein obtained from the stem or fruit of pineapple. The stem, fruit, and ananain–bromelain extracts are prepared differently and contain different compositions [17]. Bromelain has been used for ancient and modern

medicinal purposes to create various botanical preparations. Bromelain is mainly extracted from the stem. Its composition is a mixture of different components like phosphatase, peroxidase, glucosidase, cellulase, thiol endopeptidase, escharase, and other protease inhibitors. In vivo and in vitro research indicates that bromelain exhibits a multitude of antithrombotic, antiedematous, fibrinolytic, and anti-inflammatory activities. Bromelain is absorbable by the human body without losing proteolytic activity and major side effects. Bromelain has many therapeutic benefits and can be used in treatments to diagnose bronchitis, angina, sinusitis, pectoris, surgical trauma, wound debridement, thrombophlebitis, and increased absorption of antibiotics. Bromelain additionally possesses anticancer properties influences apoptotic cell death [18]. Even though the mechanism of bromelain is not known completely, bromelain has been accepted universally as a therapeutic agent because it is safe to use has minimal side effects. Bromelain has a high therapeutic value due to its pharmacological and biochemical properties. Bromelain has also been used for the treatment of a variety of health issues and is also a nutritional supplement. The human body is able to absorb a massive 12 g per day of bromelain without any major side effects. Bromelain is absorbed through gastrointestinal tract of humans and has a half-life of 6–9 hours. Bromelain produces side effects of a variety of antibiotics and increases bioavailability. These properties of bromelain show promising capabilities for anticancer drugs and therapeutic strategies [19]. Bromelain contains a mixture of cysteine proteases which proteolytically blocks activation of extracellular regulated kinase-2 in T cells of intracellular signal transduction pathways [20]. The product that is extracted from stem bromelain is taken from the pineapple juice and cooled using ultrafiltration, centrifugation, and lyophilization. The rest of the extract is available commercially to the public as a cream, capsule, powder, and tablet. The extract is available in its purest form or through multi enzyme combinations such as Phlogenzym, traumanase, and debridase [21]. In recent research it has been shown that bromelain is able to modulate key pathways that aid in malignancy. New research also indicates that anticancer activity of bromelain has a direct impact on cancer cells and their microenvironment. Properties of bromelain are mainly due to its protease components. Bromelain extracts have proteolytic enzymes which are called glycoprotein along with many minerals, protease inhibitors, organic solvents, colored pigments, and organic acids. Proteinases are the most active components from the bromelain extract and account for about 2% of the proteins. The pH range of these extracts spans from 4.5 to 9.5. During the various stages of cancer development, it has been discovered that inflammation is a common side effect. Research shows that when the inflammation from cancer progression is reduced, then the cancer itself is reduced and inhibited from progressing further. Bromelain has also been shown to downregulate PGE-2 and COX-2 expression in murine microglial cells along with leukemia cells. Bromelain is also found to enhance the function of cells that are responsible for inflammation suppression in the body. They do this by upregulating beta interleukins, alpha tumor necrosis factors, and gamma interferons of the peripheral blood mononuclear cells in humans. These results show that bromelain intensifies the immune response and helps with cellular stress during cancer formation. CD44 expression is greatly enhanced during

cancer cell spreading however bromelain usage has shown to reduce CD44 on tumor cells in humans. It also further benefits humans as it stops inflammation from migrating to other parts of the body. Bromelain also activates natural killer cells to further reduce inflammation caused by cancerous cells. Bromelain treatments greatly reduce the growth of carcinoma in the gastrointestinal tract and reduce cancer cell survival. The human body is able to absorb a massive 12 g per day of bromelain without any major side effects. Bromelain is absorbed in a highly potent form in the gastrointestinal tract and is around 40% of the total bromelain consumed. Research also indicates that bromelain is stable in the highly acidic stomach juice of humans even after 4 full hours. There are pathways that bromelain activates for malignant tumors. The bromelain targets inflammatory, immune, and hemostatic systems during cancer formation and progression stages. Bromelain extracts used for treatment on adenocarcinoma, lung carcinoma, and tumor cells are extremely efficient because they tumors showed signs of regression in just 24 hours. Bromelain overall has much potential and has already proven effective for cancer prevention and cancer regression.

In contrast to other nanocarriers, silica particles possess their own properties to deliver drugs to a range of organic systems, specific organs, and target sites. Silica particles offer a more stable, stealthy, and biocompatible alternative. A range of drugs can be readily encapsulated within the silica particle by a method of fusing sol-gel polymerization through emulsion chemistry or spray-drying. Sol-gel emulsions allow for the synthesis of nanocarriers that are necessary for handling biological material, allow ample temperature processing, and distribution of homogenous drugs. In contrast spray-drying poses challenges including size limitations, low yields, and segregation of the carriers' surface [22]. Silica nanoparticles can be synthesized and tailored to accommodate anticancer drugs. Silica nanoparticles are a popular form of nanoparticles used for targeted cancer therapy due to their simple surface modification through bromelain. Surface ligands similar to antibodies, folate acid, and polypeptides can selectively recognize tumor cell surface markers differentiating them from normal cells [23]. In an experiment, folate was used to deliver albumin with tamoxifen to a tumor target site through an in vivo method with a silica nanocarrier. The results indicated a significant reduction in the tumors volume compared to an uncoated particle [24]. Silica nanoparticles have been proven to have higher penetration within the tumoural tissues [25].

The preferred drug delivery for cancer treatment is prepared to efficiently circulate through the bloodstream, target the tumor site, and release into the subendothelial space [26]. This is a fundamental technique to achieve effective diffusion of the therapeutic drug to the internal matrix of the tumor and maximize efficiency of treatment. Aside from tumor vascularity there are other biological barriers which prolong the diffusion of nanocarriers that induce therapeutic effects. The tumor extracellular matrix (ECM) consists of laminin, collagen, proteoglycans, elastin, hyaluronic acid, and other structural proteins that inhibit effective diffusion of drugs to a great extent. However, particles with unique properties have shown to successfully

navigate through the tumor ECM with the assistance of surface modification. Taking into account that the tumor ECM is susceptible to protease action, research has led to the development of surface coating a synthetic nanocarrier with proteolytic properties. The effective nanocarrier is a mesoporous silica nanoparticle coated with bromelain, cysteine, and sulfhydryl proteases. This concoction enhanced diffusion ability upon contact with the tumor ECM and increased the therapeutic efficiency of the nanoparticle.

4 Surface Modification of MPEG-B-PCL Nanoparticles for Malignant Melanoma Therapy

There are two major issues when discussing the construction of drug delivery devices from amphiphilic block copolymers: biodegradability and biocompatibility. These two factors must be considered when developing these drug carriers. Two components used in the development of polymeric carriers are poly(ε-caprolactone) (PCL) and poly(ethylene glycol) (PEG). Hydrophobic PCL has been approved by the United States Food and Drug Administration (FDA) for medical uses is highly useful in biomedical research because of its high permeability to many drugs, nontoxicity, and biodegradability. On the other hand, PEG is a nontoxic, hydrophilic polymer, which has also been approved by the FDA for medical uses. This component is known for its low cell adhesion, low protein absorption, and other biomedical properties, most of which lead to the prevention of premature elimination of carriers from the bloodstream and increased systemic circulation times. These copolymers, when used together, have remarkable effects in drug delivery through nanotechnology [27].

Modifying the surface of a membrane is very effective in a way which improves antifouling performance. By increasing the hydrophilicity of a surface, we are able to observe improvement in the antifouling ability of the membrane especially because many natural substances have hydrophobic properties. Essentially, the increasingly hydrophilic surface acts as a buffer layer to prevent substances from disrupting the membrane. There have been a number of experiments to find a proper hydrophilic polymer, but recently a new one has surfaced. Polydopamine coating has drawn attention from a large number of scientists because of its extensive properties. It's self-polymerization, special recognition, and high anchoring ability add to the surface hydrophilicity while also keeping a thin layer on the membrane [28]. This polydopamine-mediated surface modification is highly important because the versatility and effectiveness of the coat allow for chemically functional substrates to be used in clinical applications [29].

Polymerization is incredibly efficient at functionalizing the NP surfaces but using dopamine has its added advantages compared to others. Most processes include coupling agents, reactive linkers, or prefunctionalization of the polymer, all

of which can lower the efficiency of the NP. Prefunctionalized polymers run the risk of losing the ability to encapsulate and retain a drug if ligands on the surface adjust the chemical properties of the polymer itself. Dopamine alleviates this issue because it is a relatively simple surface modification method and can be applied to a multitude of drug carriers [30].

Oxidative self-polymerization is a useful method that can be used to form thin polymer films, especially when modifying surfaces with dopamine. This specific method can be used to create a variety of polydopamine-coated planar substrates.

Oxidative self-polymerization of silicon with dopamine to form the PDA capsule was shown by Postma et al. ([31], Fig. 1 of this reference); they showed the oxidative self-polymerization of silicon with dopamine to form the PDA capsule. PDA capsules that surround chemical surfaces are vital to the application of NPs in medicine because they help decrease toxicity toward cells in the body. The fact that the PDA coated capsules benefitted the cells makes the method a promising one for drug delivery applications in medicine. As a result of its directness, efficiency, and generalizability, the PDA method can be expected to become common in application of nanoparticle delivery systems [31].

Malignant melanoma is a combative type of skin cancer that has been found to be more prevalent today than ever before. Throughout the past two decades alone, the occurrence and mortality rate have risen dramatically, well above other types of cancer. Interestingly, this skin cancer can be treated surgically when it is in its primary form but once metastasis occurs, it becomes much more difficult for surgery to have its full therapeutic effect. For this reason, there is an increased demand for higher efficiency in chemotherapy methods for malignant melanoma.

Cancer nanotherapeutics are advancing in the right direction in order to solve severe problems such as nonspecific biodistribution and targeting, lack of water solubility, poor oral bioavailability, and low therapeutic indices. These nanoparticles (NPs) are able to distribute their respective drugs directly to cancer cells by using the unique pathophysiology of tumors (Table. Along with this passive system, there is an active targeting system in place which includes antibodies directed at specific tumor targets in order to increase the selectivity of the NPs [32]. The use of NPs is very advantageous because they have high encapsulation efficiency, high drug loading capacity, minor drug leakage, and sustained release. Some drugs that can be delivered using NPs are docetaxel, puerarin, PTX, and doxorubicin. Although PTX is said to have significant effects in the treatment of malignant melanoma on paper, its extremely poor water-soluble property, low bioavailability, and high toxicity have drastically lowered its use in clinical settings. The drug Taxol® is a formulation of PTX that is prescribed in malignant melanoma therapy but there are many negative side effects that come with its use as a result of the drug vehicle Cremophor-EL. There are detrimental increases in cardiotoxicity, nephrotoxicity, and hypersensitivity in patients who take this drug. In order to reduce side effects, efforts have been escalated to replace this carrier for PTX delivery.

5 Nanoparticles for Cellular-Based Applications of Stavudine

Nanoparticles helped a major barrier to successful HIV therapy but also poses a challenge of delivering the drug at target sites such as the spleen, brain, and bone marrow. Nanoparticles that are based on solid lipids have shown to greatly improve solubility and bioavailability of therapeutic molecules by penetrating through to cellular viral reservoirs. Although surface characteristics and sizes may be the major determinants of the clearance kinetics and bio distribution of colloidal lipid particles; chemical coupling of such ligands is usually difficult, due to the absence of reactive groups at the surface of carriers. Nanoparticles that have selective retention are (10–250 nm) in size. In lipophilic composition, feasibility of production of ultrafine size nanoparticles, solid lipid nanoparticles (SLNs) can be used as carriers for delivering antiretroviral drugs. There is a variety of nanocarriers such as bioconjugates, dendrimers, liposomes, and nanoparticles have been evaluated as potential targeted drug delivery systems by numerous scientist [33]. The size-flow-filtration phenomenon that is usually limited to only tumors, the reticuloendothelial system, and possibly lymph nodes like mentioned early is a passive target of nanoscale carriers. Certain HIV receptors such as CD4, coreceptors (CCR5 and CXCR4), and other receptors are relatively specific for macrophages that provide potential valuable surface targets for drug delivery to all susceptible cells in patients that are diagnosed with HIV [34].

In previous research it has already been demonstrated that lectins play an important role in biological recognition events and can bind to intestinal mucosa and facilitate as well as transport across cellular barriers. In other findings, polysaccharide coatings have been considered an alternative to the other coatings. To be added, they have specific receptors in certain cells or tissues that are involved in tissues addressing and transport mechanism. Research on drug delivery systems that help enhance drug bioavailability by prolonged residence at the site of absorption owing to increase epithelial contact [34]. Bioadhesive that have been found to date are synthetic macromolecules, in the form of micronanoparticles or macronanoparticles that interact with mucosal surface and are hence referred to as mucoadhesive. The adhesion for this reason of a mucoadhesive polymer to some mucosal tissue will therefore be limited, by the time of turnover by the mucus gel layer to only a few hours. To solve this problem, polymeric drug carriers can be attached to certain cytoadhesive ligands that then bind to epithelial surfaces through only specific receptor mediated interactions. To help comprise a structurally diverse class of proteins that are found in organism ranging from all types of viruses and plants to humans are comprised from lectins [35]. Solid lipid nanoparticles (SLN) are an alternative colloidal drug delivery system to polymer nanoparticles. SLNs are usually produced by high-pressure melt emulsification. If a formula contains shear and temperature sensitive compounds, then the harsh productions process is not applicable. For this reason, subsequent adsorptive SLN loading might be a promising alternative. To improve the long-term stability of colloidal nanoparticles, scientists

have been using a method called free-drying that has been considered an advanced and reliable technique. SLNs that are found suitable for parental administration are then converted into dry products.

Stavudine falls in a class of medications called nuclear reverse transcriptase inhibitors. This works by decreasing the amount of HIV in blood. While this medication is used for HIV, it still can cause serious or life threatening lactic acidosis meaning that a build-up of acid in the blood that needs to be treated in a hospital. This is seen more commonly in women, or if a woman is pregnant the risk of taking this medication is higher. Interactions with other HIV treatments require dosage modifications but are relatively rate with NRTIs. On the flip side, concomitant use of either didanosine or lamivudine with stavudine can exacerbate mitochondrial toxicities or otherwise result in diminished antiviral activity. Combinations of stavudine and zidovudine have shown to be antagonistic in previous clinical studies.

6 Toxicopharmacological Aspects

Stavudine, which is a thymidine nucleoside analog, in which vitro exhibits an antiretroviral activity against both HIV-1 and HIV-2 (Table 2.3). Stavudine triphosphate exerts antiviral activity when stavudine is phosphorylated by cellular kinases. HIV replication that is inhibited by stavudine triphosphate takes place by the two following mechanisms:

1. Inhibition of HIV reverse transcriptase by competing with the natural substrate, thymidine triphosphate.
2. It is inhibited by viral DNA synthesis that causes DNA chain termination. In addition, stavudine triphosphate may inhibit cellular DNA polymerases, particularly mitochondrial DNA polymerase γ.

Table 2.3 Aspects of stavudine

Stavudine applications	Stavudine is an oral medication, used for the treatment of infections with HIV. It belongs to the class of drugs called reverse transcriptase inhibitors
Dosage of stavudine	Recommended dose for adults is 40 mg every 12 hours for those weighing 60 kg
	Newborns up to 13 years of age should take 0.5 mg/kg every 12 hours
Side effects of stavudine	A decrease in blood cells
	Muscle pain (myopathy)
	Pancreatitis
	Liver failure
	Metabolic disturbance (lactic acidosis)
	Also damages nerves and can cause a severe peripheral neuropathy
Generic name for stavudine	Zerit

As far as toxicology is concerned, most doses are given orally. A single oral dose of stavudine that is up to approximately 500 times the recommended human dose did not show severe toxicities in animal studies. Rather, there are some long-term effects of stavudine administration which includes decreased red blood cell count, sometimes accompanied by decreased hemoglobin and hematocrit and hepatic alterations (liver enlargement with centrilobular hepatocellular hypertrophy), are clearly indicated in these studies. Although there may be liver enlargement seen in the studies, stavudine does not have any inducing effect on cytochrome P450, and thus the increase in liver weight is likely due to induction of some other protein or enzyme system. Carcinogenicity studies conducted over 24 months that were performed in mice and rats. On the basis of the results from both studies that were conducted, the liver was identified as the main target organ for the development of neoplasm lesions.

7 Conclusion

The use of nanoparticles in applications of drug delivery has become widespread because of various types of surface modifications. As seen in malignant melanoma therapy, surface-modified PTX-loaded NPs are capable of giving off less side effects and a higher therapeutic efficiency. The same can be said of NPs modified with stavudine or bromelain as well. These surface modifications lower the toxicity of the NP, increase the permeability of a membrane to drugs, and increase biodegradability. Moreover, drug delivery methods are looking more promising as we develop stronger methods to increase nanotechnology and its uses in the world of medicine.

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