Chapter 12
Surface Modification of Nanoparticles to Oppose Uptake by the Mononuclear Phagocyte System

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Abstract Drug delivery has become an important aspect of medicine field with invention of specific potent molecules. New possibilities by understanding the disease pathways are emerging for its treatment and prevention at early basis. This provides development of customized systems that are designed to achieve specific control. This chapter provides an overview of recent advances in surface modification of nanoparticles to oppose uptake by mononuclear phagocytic system in order to achieve targeted drug delivery.

Keywords Targeted nanotechnology · Surface modification · MPS

1 Introduction

A successful drug delivery depends on the release of an optimal dose of the drug at the required site over a given time period without any side effects. Over the years researchers have investigated novel drug delivery approaches in order to develop ideal drug delivery systems. Genetic mutations and intracellular infections are major challenges of intracellular diseases. Targeted drug delivery provides accumulation of drug concentration into specific regions of interest in the body after successful delivery. It is also referred to as smart drug delivery sometimes, with an ability to bind specifically to the desired site of action. However, the task of targeting a desirable site in vivo is challenging. Here, the challenge is on three fronts: first to find the target for the disease; second to find the appropriate drug molecule to bind to that target and treat the disease; and thirdly to find an appropriate means to carry the drug to the specific site in a stable form.

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Efficient treatment of intracellular disease relies on the development of small drug molecules or development of nanoparticulate drug delivery system which can diffuse through the intracellular compartment via cell membrane. Limitations associated with development of new small drug molecules persists which increases the gap between understanding of disease mechanism and development of new drug molecules. Nanoparticles with size in nano range have attended much attraction in various fields of medicine [1]. These nanoparticles with specialized functions have opened up the doors for development of more advanced technologies. Nanoparticles offer advantages such as good colloidal stability, effective encapsulation, protection of drug molecules against enzymes and hydrolysis, and ease of preparation method [2]. Thus, nanomedicine (application of nanotechnology in medicine) industry is flourishing day after day where in the medicine works at nanoscale in cellular structures of body. Nanoparticles with their functional chemistry can overcome biological barriers and target even single cell entities for treatment. However, one needs to investigate and understand the clinical interaction of nanoparticles with body system for better efficacy.

Nanocarriers as targeted drug delivery were firstly proposed by Paul Ehrlich in the nineteenth century. In 1960s, firstly nanoparticles were investigated for vaccination processes and then till date various nanotechnology based pharmaceutical products have flourished the market and still many are under investigation [3]. Over the years, many versatile nanocarriers has been investigated successfully with various active molecules for targeted drug delivery including liposomes [4], solid lipid nanoparticles [5], gold nanoparticles [6], silica nanoparticles [7], carbon nanotubes [8], micelles [9, 10], dendrimers [11], nanogels [12], nanoemulsion [13], and nanocrystals [14]. Figure 12.1 demonstrates a schematic representation of various nanoparticles with efficiency to target various organs.

Recent advancement in nanotechnology has influenced diagnosis and treatment procedures of complex diseases like cancer and HIV to a great extent [15–19]. Along with such complex diseases, promising efforts are made in development of novel therapies for the treatment of cardiac and other diseases intended for site-specific administration of drug molecules with minimal side effects [20–24].

Clearance kinetics and biodistribution of nanoparticles are governed by their surface properties and particle size. Small size nanoparticles with size less than 5 μm will be taken up by mononuclear phagocytic system (MPS) in liver and spleen. Surface modification of nanoparticles has received much attention as promising approach in recent years for efficient drug delivery [25–27]. Smart nanocarriers modified to have surfaced positive charge will interact with surface negative charge of cells rapidly and efficiently, which helps endocytosis to occur easily, thereby supporting targeted drug delivery. The choice of polymeric materials plays a major role in preparation of such specific modified nanoparticles. Unique property of nanoparticle is attributed to the polymeric properties utilized in preparation. Thus, here the nanoparticles are modified for specific objectives to be fulfilled while intended for targeted drug delivery. Surface modification of nanoparticles renders specific characteristics on the surface such that it will orient itself toward specific site in the body. Surface modification of nanoparticles is done by simply coating of core with

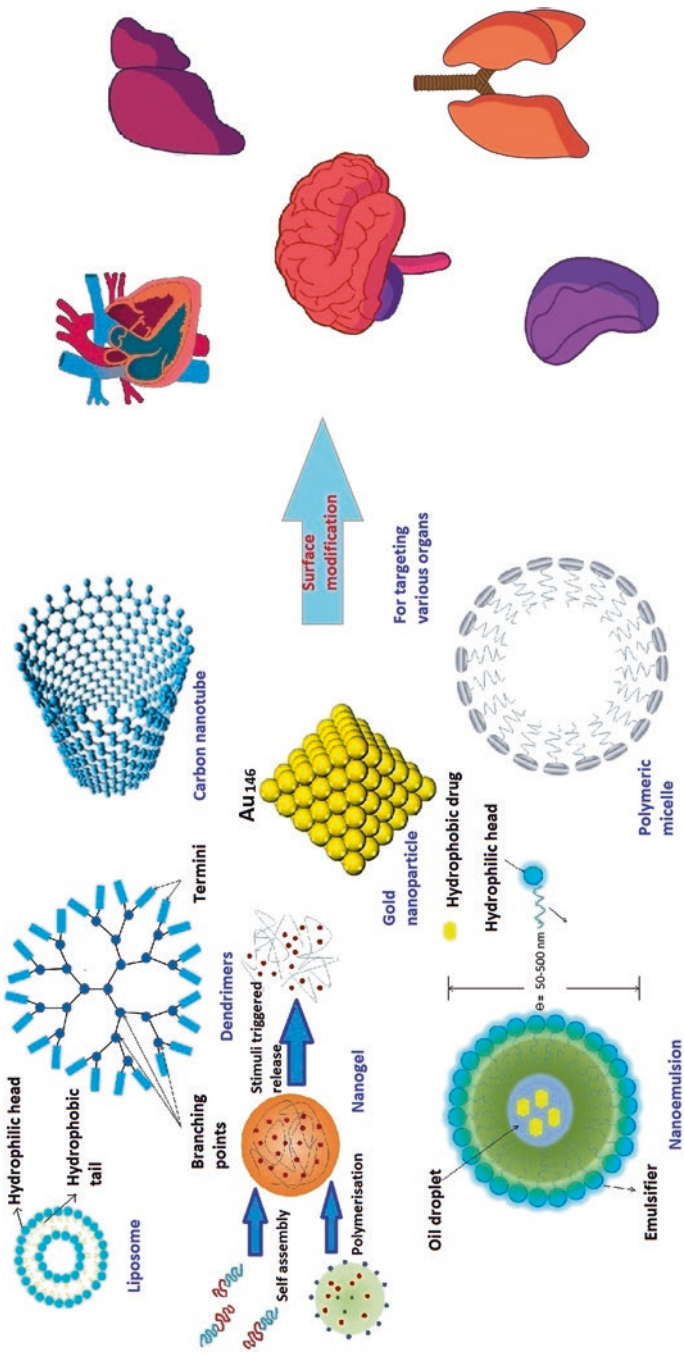


Fig. 12.1 Various nanocarriers capable to target important organs after surface modification

hydrophilic polymers intended for long circulation in body, and/or coupled with specific ligands or proteins for targeted drug delivery in specific site [28–31]. In general, smart use of nanoparticles has revolutionized formulation and delivery of drugs. This chapter focuses on the application of various nanocarriers in targeted drug delivery systems. Emphasis is given to surface modification by using functional agents which enables nanoparticles to oppose the mononuclear phagocytic system and circulate for prolonged time in blood, recognize the environmental properties of the body, communicate and respond appropriately, and also deliver the active molecule to the intended site of action.

2 Surface Modification for Functionalised Nanoparticles

Polymeric nanoparticles are widely utilized in targeted drug delivery. Most synthetic polymers used in the preparation of modified nanoparticles are hydrophobic. Our body recognizes such hydrophobic systems as a foreign material and coats them with blood components, mainly opsonins. Such opsonized modified nanoparticles are readily taken up by the mononuclear phagocytic system (MPS) or reticular endothelial system (RES), peculiarly in the liver [32]. However, when phagocytic system is not targeted, the goal of surface modification turns to protection from MPS/RES. To overcome this problem, new strategies are worked out directing the nanoparticles with targeting capabilities. Mirshafiee et al. (2016) investigated impact of precoating of protein on nanoparticles. They utilized precoating of gamma-globulin which impeded the binding of opsonins on their target cell surface receptors of macrophages, thereby making the nanoparticles available for site-specific delivery [33].

2.1 Prolonged Circulation of Nanoparticles

Long circulating nanoparticles can be obtained by coating the surface with hydrophilic polymers. Such coating prevents opsonization of nanoparticles and thereby protect from MPS/RES uptake [34–36]. Coating with polyethylene glycols (PEGs) is well known for preparing stealth nanoparticles. Such PEG coating provides a protective layer on the surface of nanoparticles which has ability to repel the absorption of opsonin proteins. Steric forces play an important role in such repulsion phenomena which leads to steric stabilization, reducing surface–surface interaction and thereby blocking the initiation of opsonization process [37]. Surface charge density, chain length, and shape of polymers are found to influence the macrophage uptake and surface hydrophilicity of nanoparticles thereby leading to their long circulation in body [38]. Figure 12.2 demonstrates effect of surface charge density of hydrophilic polymer on opsonization. Gref et al. (2000) described advantages of PEGylation of nanoparticles. Nanoparticles without surface modification showed presence of

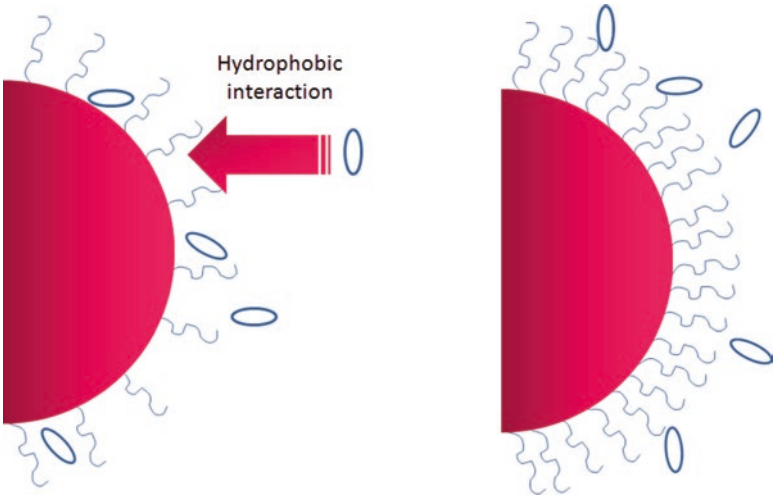


Fig. 12.2 Opsonization prevented due to surface charge density of hydrophilic polymer

apolipoproteins. Further, they reported effect of chain length of PEG on opsonization process on nanoparticles. The results suggested an optimal range of molecular mass of polymer between 2 and 5 kDa which reduced plasma protein adsorption [39]. Dos Santos et al. (2007) reported PEG-Lipid conjugates with prolonged circulation. Further effect of various molecular weights was analyzed on circulation lifetimes to protein binding. The results demonstrated that as little as 0.5 mol% of 1,2-distearoyl-sn-glycero-3-phosphatidylethanolamine (DSPE) modified with PEG having a mean molecular weight of 2000 (DSPE-PEG2000) substantially increased plasma circulation of liposomes [40]. Particle size of nanoparticles also determines the protein corona and thereby influences phagocytic uptake [41, 42]. Biopolymers especially proteins forms a protein corona that is colligated with the nanoparticles. Larger nanoparticles incline to adsorb more protein as compared to lower sizes and thus were found to be readily taken up by the phagocytic system [43, 44].

Poloxamers are another class of polymers which have gained much attention in surface modification and preparation of nanoparticles. These triblock copolymers composed of hydrophilic polyethylene oxide (PEO) chains linked to hydrophobic backbone of polypropylene oxide (PPO), that is, PEO-PPO-PEO when used for the stabilization of nanoparticles, the PEO segment forms an entangled structure which helps the nanoparticles to remain masked from the phagocytic system [45]. Here, PEO shows affinity toward the particle surface, whereas PPO remains on the outer side forming a polymeric star like conformation. At bulk polymer concentrations the polymer concentration reaches to a plateau. The thickness of the adsorption of polymer depends on the hydrophobicity of the particle surface and hydrophilic–lipophilic balance of the poloxamer type. For instance, poloxamer 188 forms a 20-nm thick layer on PLGA (poly (lactic-co-glycolic acid)) nanoparticles. At concentrations equal or more than CMC, growth in thickness of the layer is observed

which is attributed to hemimicelle adsorption [46]. Stolnik et al. (2001) demonstrated the effect of surface coverage of poloxamer 407 on biological fate of nanoparticles. Increase in the surface coverage resulted in increase in volume fraction of PEO chains in the adsorbed layer. This in turn ensued into reduced protein interaction with the nanoparticle surface leading to prolonged in vivo circulation [47]. Poloxamine-coated nanoparticles are reported to have increase in vivo circulation and reduction in uptake by liver [48].

Thus coating or surface modification via hydrophilic polymers effectively prevent uptake of nanoparticles by preventing opsonization and thereby increasing the circulation time. However, control of physiological processes of the body is difficult which in turn limits these applications.

2.2 Localization of Nanoparticles

Surface modification of nanoparticles for site-specific drug delivery can be divided into two groups, passive targeting and active targeting. In passive targeting the drug entry is based on enhanced permeation rate in the tumor tissue. It is widely known that because of several abnormalities resulting into healthy tissue, the resulting tumor tissue comprises a leaky blood vessel network. The tumor blood vessels lack pericytes and comprise highly multiplying endothelial cells. Enhanced permeation in the tumor tissue facilitates an opportunity for tumor targeted drug delivery [49]. Enhanced permeation rate can be mediated by several mediators including bradykinins, nitric oxide, vascular endothelial growth factor, cytokines, prostaglandins, and matrix metalloproteinases [50]. From various studies it has found that tumor possess pore size ranging between 380 and 780 nm [51–53]. Greish and coresearchers reported high tumor targeting efficiency of pirarubicin micelles made up of copoly(styrene-maleic acid) with little toxicity. The conjugate showed higher accumulation in tumor tissue by enhanced permeation rate effect [54]. Yang et al. (2011) reported antitumor efficacy of PEG-liposomal oxaliplatin in xenograft tumor bearing mouse model for colorectal cancer. The results demonstrated that following intravenous administration liposomal conjugate was found to accumulate in the tumor via leaky tumor vasculature [55].

In context with other organs, after intravenous administration nanoparticles are rapidly cleared by MPS/RES and then accumulated in liver and spleen [56]. This natural process can be utilized as site-specific drug delivery for both organs/a single organ. Tammam et al. (2012) reported tacrolimus biodegradable nanoparticles for liver and spleen targeting. The results of the study concluded that poly(lactic) acid (PLA) nanoparticles (NP) of tacrolimus was successfully targeted to liver and spleen via RES which proved beneficial in graft survival with reduced side effects. Release pattern of tacrolimus from PLA-NP determined by the dialysis bag method demonstrated 77 ± 45.72% drug release within 4 days [57]. But when MPS/RES is to be avoided so as to target the tumor other than liver or spleen, other approaches are investigated.

Gu and coresearchers investigated PEGylated mesoporous silica nanoparticles (PEG-MSN) to target doxorubicin to liver. From the study it was observed that uptake of PEG-MSN of doxorubicin was significantly higher than that of MSN of doxorubicin benefited from the galactose receptor-mediated endocytosis phenomenon [58]. The amphiphilic property of PEGs with good solubility is responsible for better biocompatibility for cell membranes. Therefore, PEG-coated nanoparticles show higher efficiency to penetrate compared to unmodified nanoparticles [59].

Drug delivery by passive targeting undergoes non selective uptake by organs which may lead to unnecessary accumulation of drugs resulting into severe adverse effects. Therefore, active targeting becomes indispensable for delivery drug to right cells. Active targeting is based on positive interactions between antibody/ligand and antigen/receptor molecules. Thus, the drug delivery system is manipulated to improve its distribution pattern and target to the specific biosite. The attachment of specific ligand on nanoparticles facilitates site-specific drug delivery. Ligands are conjugated on the surface of nanoparticles with chemical strategies which can find the tumor cells as a target at the same time excluding the healthy cells, leading to minimal adverse effects of chemotherapy [60].

Many researchers have demonstrated that attachment of folate groups as ligands on the surface of nanoparticles results into enhancement cellular uptake by tumor tissues, as a function of surface density balance against PEG steric resistance [61, 62]. Quintana et al. 2002 developed a therapeutic nanodevice intended to target tumor cells through the folate receptor. Folic acid and methotrexate were covalently linked to the surface of ethylenediamine core polyamidoamine dendrimer. The results demonstrated improved targeting to 100-fold by successful surface modification using ligand based approach [63]. Quadir et al. (2017) reported folate-targeted nanoparticles loaded with doxorubicin that target the folate receptor-over-expressing tumor cells. The system comprised pH-responsive polymeric part which drives the nanocarrier and ligand conjugated PEG unit which targets the folate receptor. The results demonstrated suppression of tumor growth due to successive accumulation of drug in tumor cells [64].

Drug delivery to brain is a challenging task for researchers due to complex structure of blood–brain barrier (BBB). Poly (lactic-co-glycolic acid) (PLGA)/polylactic acid (PLA) is widely utilized to prepare nanoparticles to target brain. However from the studies it is demonstrated that modified nanoparticles show enhanced brain uptake as compared to unmodified PLGA/PLA nanoparticles [65, 66]. Song and coworkers demonstrated brain drug delivery system by attaching lactoferrin (a multifunctional protein) on silica nanoparticles. Nanoparticles were further modified with PEG to reduce protein absorption. The results suggested enhanced transport efficacy of the nanoparticles across BBB. Maximum efficacy was found with nanoparticles less than 25 nm in diameter [67]. Wang et al. (2010) reported trimethylated chitosan (TMC) surface-modified PLGA nanoparticles for brain delivery. TMC was covalently linked to the surface of nanoparticles via carbodiimide mediated linkage. Average diameter of nanoparticles were of 150 nm and were found to accumulate in the cortex, paracoel, third ventricle, and choroid plexus epithelium, while no brain uptake was observed with unmodified PLGA nanoparticles [68].

2.3 Some Other Examples of Nanocarriers for Targeted Drug Delivery by Surface Modification

The types of nanocarriers mentioned here are the most challenging and frequently used surface-modified nanopharmaceuticals for targeted drug delivery. Table 12.1 enlists marketed surface-modified targeted nanopharmaceuticals.

Carbon based nanoparticles such as carbon nanotubes have exhibited a prominent application in site-specific drug delivery. Carbon nanotubes are low dimensional carbon nanoparticles having unique physical and chemical properties. Lu et al. (2012) developed conjugates of multiwalled carbon nanotubes and iron oxide magnetic nanoparticles as dual targeting nanocarrier of doxorubicin. Further, the nanoparticles were functionalized with poly(acrylic acid) through free radical polymerization conjugated with folic acid ligand. Site-specific drug delivery was achieved under the guidance of magnetic field and through ligand receptor interactions. The results showed enhanced cytotoxicity toward U87 human glioblastoma cells as compared to free doxorubicin [78]. Hou et al. (2016) reported graphene oxide loaded with mitoxantrone with aim to reduce drug resistance in cancer. The nanoparticles were functionalized using hyaluronic acid and pluronics. The results suggested enhanced uptake of nanosheets by MCF-7/ADR cells via receptor mediated endocytosis [79].

Gold nanoparticles with size ranging between 1 and 100 nm are extensively studied for drug and gene delivery. In a recent study, PEGylated doxorubicin gold nanoparticles were prepared to target glioma cells. Ligand-based functionalization was carried out to mediate the system to penetrate blood–brain barrier. Angiopep-2, low density lipoprotein receptor related protein-1 enabled the system to target to the glioma cells in brain [80]. Another research utilized peptide TAT modified gold nanoparticle of an anticancer molecule in order to assess multi drug resistance and thereby its antiproliferative activity [81]. Locatelli et al. (2014) reported multifunctional polymeric nanocomposites containing two cytotoxic agents, alisertib and silver nanoparticles. Further the nanocarrier was conjugated with chlorotoxin, an active targeting 36-amino acid-long peptide that specifically binds to MMP-2, a receptor overexpressed by brain cancer cells. The results suggested reduction in the tumor area when studied using cell line U87MG [82]. Figure 12.3 describes surface-modified gold nanoparticle formation for targeted drug delivery.

In contrast to conventional nanoparticles, *mesoporous nanoparticles* are porous in interior region. They are nontoxic in nature, easily modified, have large loading capacity and are biocompatible. Polydopamine-based surface modification method was employed to prepare doxorubicin loaded mesoporous silica nanoparticles. Peptide CSNRDARRC conjugation was carried out to enhance the therapeutic effects on bladder cancer. The results suggested recognition of human bladder cancer cell line HT-1376 by the modified nanoparticles and thereby highest cellular uptake due to receptor ligand interaction [83]. Figure 12.4 describes schematic diagram of surface modification of mesoporous nanoparticles.

Table 12.1 demonstrates few examples of marketed/under research surface-modified targeted nanopharmaceuticals

Product	Drug	Formulation	Mechanism	Application	References
Doxil®	Doxorubicin	PEGylated nanoliposomes	Passive target to tumors by EPR effect	Ovarian cancer, Kaposi's sarcoma, multiple myeloma	[69]
Abraxane®	Paclitaxel	Albumin-bound paclitaxel nanoparticles	Albumin receptor (gp60)-mediated transcytosis across endothelial cells	Various cancers like breast cancer, pancreatic cancer, and lung cancer	[70]
Myocet®	Doxorubicin	Liposome encapsulated	Passive target to tumors by EPR effect	Breast cancer	[71]
DaunoXome®	Daunorubicin	Liposome encapsulated	Passive target to tumors by EPR effect	HIV-related Kaposi's sarcoma	[72]
EndoTAG-I	Paclitaxel	Cationic liposome	Targets activated tumor endothelial cells with negative charge	Breast cancer/ pancreatic cancer	[73]
Aurimmune (CYT-6091)	TNF-α (Tissue necrosis factor)	TNF-α and PEG bound to colloidal gold nanoparticles	TNF-α plus EPR	Advanced cancer	[74]
CRLX101	Camptothecin	Polymeric nanoparticles made up of cyclodextrin and PEG	Linkage hydrolysis	Various cancers	[75]
BIND-014	Docetaxel	Polymeric nanoparticles of PLA coated with PEG attached with ligands targeted to PSMA (prostrate-specific membrane antigen)	Ligand mediated	Various solid malignancies	[76]
Genexol®	Paclitaxel	Micelles composed of block copolymer poly(ethylene glycol)-poly(D,L-lactide)	Passive targeting via EPR effect	Metastatic breast cancer, lung cancer	[77]

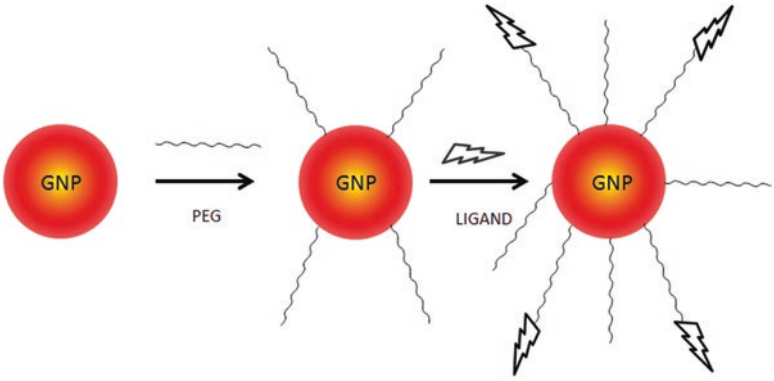
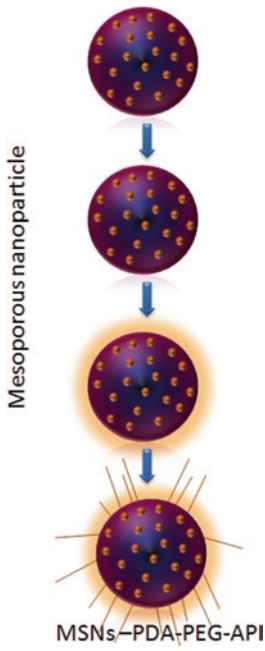


Fig. 12.3 Gold nanoparticles, surface modification by PEG and ligand attachment for site-specific drug delivery

Fig. 12.4 Mesoporous nanoparticle for site-specific drug delivery after surface functionalization



Lipid nanoparticles have emerged as new possible carrier systems to deliver drugs. Choice of lipids can alter the biopharmaceutical characteristics of the drug molecule taken and thus changes its circulation. Paclitaxel loaded solid lipid nanoparticles were prepared to target lung cancer. Surface functionalization of nanocarriers was carried out using lectin conjugation. Nanoconjugates were found to be rapidly taken up by A549 cells through receptor-mediated endocytosis [84]. Neves et al. (2016) reported loaded solid lipid nanoparticles of resveratrol, a neuroprotective compound. Further the nanocomposites were functionalized by

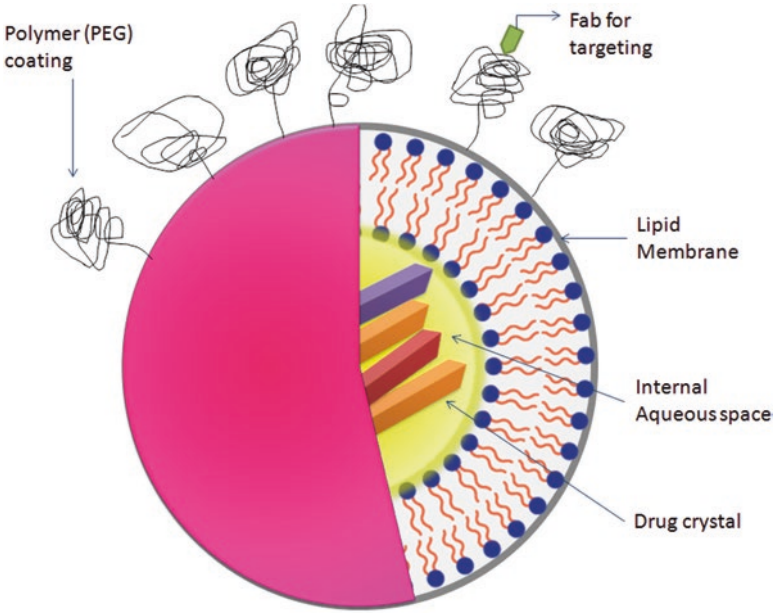


Fig. 12.5 Diagrammatic representation of surface-modified liposome. Statement: The authors hereby declare that all the figures in the chapter are not taken from any source and are self-drawn or modified

apolipoprotein E which are recognized by LDL receptors over expressed on the blood–brain barrier. The results demonstrated permeability of resveratrol-loaded solid lipid nanoparticles functionalized with apolipoprotein E through hCMEC/D3 monolayers with a significant increase (1.8-fold higher) [85].

Dendritic molecules have played an emerging role in targeted drug delivery strategies. With capacity of the peripheral molecules to under surface modification with antibody, or proteins, dendrimers are capable to host several molecules. Zong et al. (2012) reported multifunctional generation 5 polyamidoamine dendrimers of methotrexate. Folic acid conjugation was done for the complex to get bind selectively to the over expressed folate receptor on tumor cells [86].

Liposomal drug delivery system has been implied as another promising nanocarrier system for site-specific drug delivery. The aqueous core and the lipidic shell enable the system to encapsulate both hydrophilic and hydrophobic molecules. Antibody-modified liposomes were evaluated for in vivo antitumor activity of timosaponin AIII. The results suggested higher selectivity of CD44 liposomes toward CD44 tumor positive cells and thereby exhibited stronger tumor inhibition [87]. Figure 12.5 describes a diagrammatic sketch of the liposomal targeted drug delivery.

Novel nanocarriers like *micelles* have emerged as an important class of targeted drug delivery systems for delivery of various chemotherapeutics. One such work reported comprises a polymeric micelle system of paclitaxel to tumor targeting

delivery. Micellar formulation consist of sodium cholate and monomethoxy poly (ethylene glycol)-block-poly (D,L-lactide). Significant antitumor efficacy of paclitaxel micellar formulation was observed in mice bearing BEL-7402 hepatocellular carcinoma and A549 lung carcinoma [88].

3 Future Perspectives

Over the past few years, nanomedicine has emerged as a versatile tool for the targeted drug delivery system. Various nanocarriers have been investigated for sustained, controlled, and targeted effects. However, surface functionalization of nanocarriers has provided an extra merit in the targeted delivery system approaches. Such modification enables the unit to direct toward the specific site by avoiding MPS/RES uptake (to the level of receptors in the cells). Thus, target to specific cells is now possible approach via surface modification of nanocarriers. Looking forward on this, surface modification of nanocarriers represents the future of nanotechnology in the area of targeted drug delivery systems.

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