

Chapter 6

An Overview of Paclitaxel Delivery Systems



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Abstract As per the World Health Organization, cancer is the second leading cause of death globally and is responsible for an estimated 9.6 million deaths in 2018. More than 2 million cases of lung and breast cancer have been reported in 2018. Paclitaxel is a natural product based anti-mitotic agent useful for the treatment of lung cancer, ovarian cancer and breast cancer. Paclitaxel exhibits low oral bioavailability due to poor aqueous solubility and poor permeability. Paclitaxel is the first blockbuster anticancer drug with annual sales of more than US \$1 billion in 1997. Taxol[®], Abraxane[®] and Genexol PM[®] are commercial injectable preparations of paclitaxel with a drug loading of not more than 17% w/w. The toxicity issues of Cremophor[®] EL used in Taxol[®] led to the development of different delivery systems sans Cremophor[®] EL. The maximum tolerated dose of Taxol[®] is 135 mg/m². Taxol[®] exhibited hypersensitivity reactions and required use of special IVEX-2 filter to avoid leaching of plasticizer into the product. Genexol PM[®] was physically unstable and was ineffective against multidrug-resistant tumor treatment. Abraxane[®] exhibited limited tumor exposure, tumor uptake, tumor regression and higher half-maximal inhibitory concentration.

In this chapter, we reviewed the literature of paclitaxel delivery systems. Micelles, liposomes, nanoparticles, lipid systems, microparticles, emulsions, solid dispersions, cyclodextrin complexes, implants, prodrugs and hybrid systems have been reported for paclitaxel delivery. The major points of our analysis of the literature are (1) Efficiency of solubility enhancement of paclitaxel was found in the decreasing order for prodrugs, mixed micelles, cyclodextrin complexes and solid dispersions, (2) The oral bioavailability enhancement for nanoparticles, micelles and emulsions of paclitaxel was found to be 7-fold, 5-fold and 4-fold respectively, (3) Decreasing order of reduction in tumor growth was found in emulsion, liposome, prodrug and nanoparticulate delivery system of paclitaxel as compared to that with Taxol[®], (4) Genexol PM[®] and Abraxane[®] do not require special filters to avoid leaching of plasticizer into the product, (5) Genexol PM[®] and Abraxane[®] being free from Cremophor[®] EL do not exhibit hypersensitivity reaction, (6) Paclitaxel mixed

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micelles composed of poly (ethylene glycol-co-lactic acid) and D- α -tocopheryl polyethylene glycol 1000 succinate were effective against multidrug-resistant tumor cells in contrast to Genexol PM[®], (7) Recombinant chimeric polypeptide conjugated paclitaxel nanoparticles exhibited 2-fold systemic tumor exposure, tumor uptake as compared to Abraxane[®] and almost complete tumor regression, (8) Paclitaxel loaded polycaprolactone-co-D- α -tocopheryl polyethylene glycol 1000 succinate nanoparticles exhibited 8-fold lower half maximal inhibitory concentration as compared to Abraxane[®], (9) Paclitaxel delivery systems such as implants, nanoparticles, solid dispersions, lipid nanoparticles and micelles have been reported with more than 20% drug loading, (10) The maximum tolerated dose of Genexol PM[®] and Abraxane[®] could be increased from 135 mg/m² to 300 mg/m², and (11) Orally effective paclitaxel formulations such as DHP107 and Oraxol[®] are under phase II clinical trials.

Keywords Paclitaxel · Delivery system · Stimuli sensitive delivery · Targeted delivery · Natural product · Anticancer

6.1 Introduction

Paclitaxel is a potent broad-spectrum anticancer drug. Paclitaxel is a diterpenoid molecule with a central 8-member taxane ring. Paclitaxel was initially isolated from the bark of *Taxus brevifolia*, family: *Taxaceae* (the Western Yew tree). The pure form of paclitaxel was isolated in 1969. Paclitaxel is used in the treatment of breast, ovarian, lung cancer, head and neck cancer. Paclitaxel belongs to class IV of the biopharmaceutical classification system, the most difficult category for drug delivery.

The year-wise publication trend for paclitaxel delivery as per the SciFinder search engine is given (Fig. 6.1). The publication trend reveals that the number of publications have increased 10 times in the last 20 years.

Paclitaxel was extracted from the bark of the western yew tree *Taxus brevifolia*. It was identified as one of the active constituents of this plant in 1967. The structure of the compound was elucidated by Wall and Wani 1996. Its cytotoxic activity was reported against human KB carcinoma cell line and mouse leukemia cells. The availability of the compound was limited because of its low yield from the western yew tree. So, Robert A. Holton and his research group came up with a semi-synthetic pathway by which docetaxel was produced from 10-deacetyl baccatin, which was present in abundant quantities in *Taxus baccata* (Alqahtani et al. 2019). A synthetic method for paclitaxel using C7 protected baccatin III with tricyclic ketone have been reported (Holton et al. 1994).

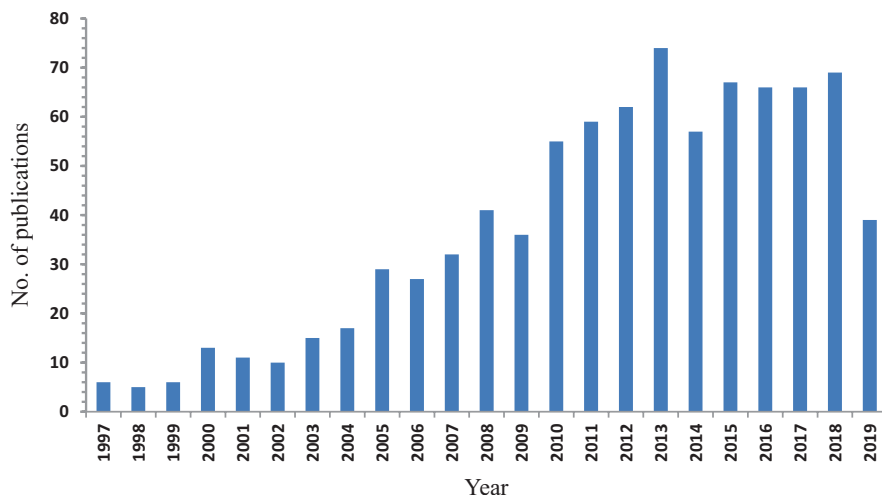


Fig. 6.1 Year-wise publication trend for paclitaxel delivery; this trend has been obtained from SciFinder search on June 24, 2019 using publication year trend; note the increase of publications for paclitaxel delivery over period of 1997–2019; the publication trend signifies demand for newer delivery options for paclitaxel; the existing paclitaxel commercial products lack safety, targeting to specific organs and patient inconvenience due to injections

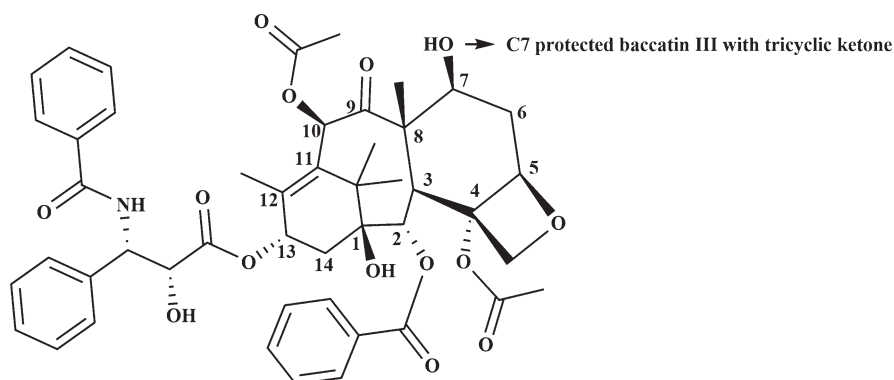


Fig. 6.2 Chemical structure of paclitaxel and C7 protected position for synthesis of paclitaxel using baccatin III; paclitaxel was extracted from Yew tree initially hence alternative semi-synthetic method using highly abundant baccatin III in the bark of *Taxus wallichiana* var. *mairei* has been discovered by protecting baccatin III at C7 position and coupling tricyclic ketone to yield paclitaxel

6.1.1 Chemical Structure of Paclitaxel

Paclitaxel is a diterpenoid compound containing a taxane ring along with other hydrophobic substituents. The empirical formula of paclitaxel is $C_{47}H_{51}NO_{14}$. The chemical structure of paclitaxel is given (Fig. 6.2).

IUPAC name of the compound is (1S,2S,3R,4S,7R,9S,10S,12R,15S)-4,12-bis(acetyloxy)-1,9-dihydroxy-15-[[[(2R,3S)-2-hydroxy-3-phenyl-3-(phenylformamido)propa-1-en-1-yl]oxy]-10,14,17,1-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.0³.10⁴.7]heptadec-13-en-2-yl]benzoate (Weaver 2014).

Paclitaxel has a unique mechanism of action which differs from other anticancer agents such as vinca alkaloids. Paclitaxel causes polymerization of microtubule and makes these highly stable. Stabilization of microtubules inhibits cell division leading to cell death (Schiff et al. 1979).

6.1.2 Problems Associated with Paclitaxel

Paclitaxel is practically insoluble in water with an aqueous solubility of 0.00556 mg/mL. Paclitaxel is hydrophobic in nature with a Log P value of 3.54 but has poor permeability. The molecular weight of paclitaxel is 853.9. The high molecular weight of the drug might be responsible for the poor permeability. The consequence of poor solubility and permeability of the drug is poor oral bioavailability. Paclitaxel is a substrate for P-glycoprotein which is responsible for drug efflux. High molecular weight of the drug has been attributed to drug efflux. Paclitaxel belongs to class IV of the biopharmaceutical classification system (Varma et al. 2005).

6.1.3 Marketed Paclitaxel Products

The commercial paclitaxel formulations include Taxol[®], Abraxane[®], Genexol PM[®] and Lipusu[®] (Nehate et al. 2014). The first marketed product of paclitaxel is Taxol[®], which was marketed by Bristol-Myers-Squibb in 1992. Taxol[®] is available in three strengths i.e. 30 mg, 100 mg and 300 mg per vial. Taxol[®] consists of purified Cremophor[®] EL, anhydrous citric acid and dehydrated alcohol. Taxol[®] is indicated as first-line and subsequent therapy of ovarian cancer, for the adjuvant treatment of node-positive breast cancer administered subsequently to standard doxorubicin-containing combination therapy, for the first-line treatment of non-small cell lung cancer along with cisplatin in patients who are not potential candidates for curative surgery and/or radiation therapy and for the second-line treatment of AIDS-related Kaposi's sarcoma. The major side effects of Taxol[®] observed in patients are hypersensitivity reaction, low blood counts, hair loss, myalgias, peripheral neuropathy, mouth sores, nausea, vomiting, diarrhoea, swelling of feet, low blood pressure and darkening of the skin. Taxol[®] injection requires premedication with a steroid to avoid hypersensitivity reaction (Rxlist website 2019).

The main problem associated with Taxol[®] injection is Cremophor[®] EL related toxicity. Cremophor[®] EL is not an inert vehicle and it produces undesirable biological effects. Cremophor[®] EL can cause a severe anaphylactic reaction (Szebeni et al. 1998). Taxol[®] needs to be administered using proprietary IVEX-2 filters. IVEX-2 filters avoid leaching of di-(2-ethylhexyl) phthalate in the product. Leaching of di-(2-ethylhexyl) phthalate in the product from polyvinyl chloride container and administration set has been reported. The leaching was attributed to presence of Cremophor[®] EL and dehydrated alcohol in Taxol[®] formulation (Kim et al. 2005). The literature has cited a number of research publications for the development of delivery systems without using Cremophor[®] EL in order to have safer formulation.

Abraxane[®] is the second commercial product of paclitaxel, which was marketed by Abraxis BioScience in 2005. Abraxane[®] is composed of drug and human serum albumin and has been prepared by high-pressure homogenization method (Ibrahim et al. 2002). Abraxane[®] is Cremophor EL[®]-free formulation and hence does not exhibit hypersensitivity and leaching of plasticizer from polyvinyl chloride. The maximum tolerated dose could be increased from 175 mg/m² to 300 mg/m² with Abraxane[®] as compared to that with Taxol[®] (Gradishar 2006). Lipusu[®] was the first liposome-based injection of paclitaxel, formulated by Luye Pharmaceutical Co. Ltd. and was marketed in China. Lipusu[®] contains paclitaxel, lecithin and cholesterol. Lipusu[®] was effective against breast cancer, ovarian cancer, lung cancer with fewer side effects than Taxol[®].

Genexol-PM[®] is another injectable polymeric micelle based product of paclitaxel, marketed by Samyang Corporation. Genexol-PM[®] is a poly (ethylene glycol)-*b*-poly (lactic acid) block co-polymer based micellar formulation. Genexol-PM[®] does not require steroid premedication and free from the problem of plasticizer leaching from polyvinyl chloride. Genexol-PM[®] can deliver 300 mg paclitaxel dose without additional toxicity (Kim et al. 2004). Genexol-PM[®] was stable at 23 °C for 24 h but exhibited precipitation into large needle-like crystals at 40 °C within 2–4 h (Ron et al. 2008). Genexol-PM[®] was ineffective in cancer patients with multidrug resistance (Fan et al. 2015)

Nanoxel[™] is a micellar paclitaxel formulation composed of a copolymer of *n*-isopropyl acrylamide and *n*-vinyl pyrrolidone having a mean particle size of 80 nm. The intracellular accumulation of paclitaxel in A549 cell was found to be 2.5-fold and 3.3-fold higher in Nanoxel[™] and Abraxane[®]-treated cells respectively as compared to that of Taxol[®]. Nanoxel[™] at 0.7 mg/mL showed significant aggregation, particle-size growth, and crystallization within 4 h at 40 °C. High-pressure liquid chromatography data revealed slightly lower purity of paclitaxel in Nanoxel[™] as compared to both Abraxane[®] and Genexol PM[®]. No drug-related mortality was observed following repeated intravenous administration of Abraxane[®] at dose levels of 5, 15, and 30 mg/kg, while Nanoxel[™] exhibited 100% mortality at 15 and 30 mg/kg dose levels in athymic nude mice (Ron et al. 2008; Madaan et al. 2013; Trieu et al. 2008).

6.1.4 Recent Paclitaxel Products Under Clinical Trials

A number of delivery approaches have been reported in the literature to increase the solubility and enhance the antitumor activity of paclitaxel such as micelles, liposomes, nanoparticles, microparticles, solid dispersions, cyclodextrin-drug complex, implants and prodrug. This chapter discusses approaches to paclitaxel delivery. The emphasis is given on choice of material, type of delivery system and performance. Different delivery systems explored for paclitaxel in the literature are discussed in subsequent sections (Fig. 6.3).

DHP107 is a novel lipid-based mucoadhesive oral paclitaxel formulation composed of an edible lipid and FDA approved emulsifiers. Phase II clinical trial is

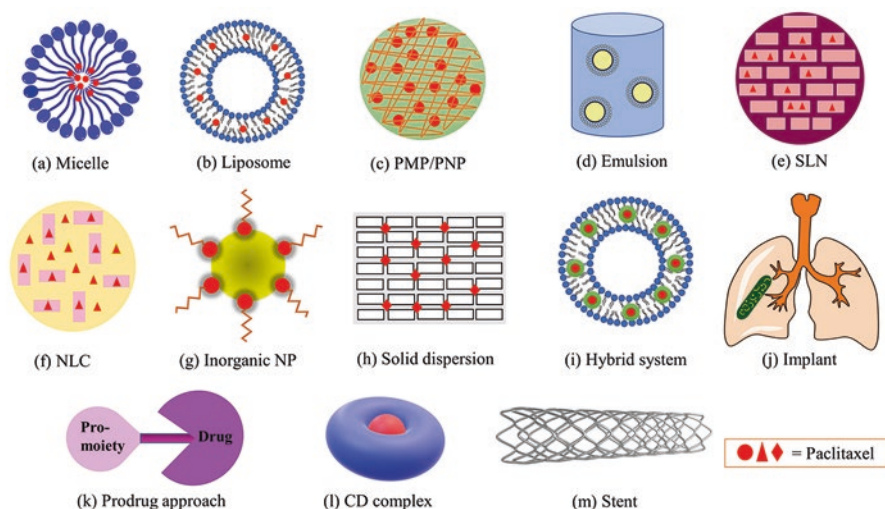


Fig. 6.3 Different delivery systems of paclitaxel (a) Micelles: Self-assembled aggregates of polymers or surfactants which have a distinct polar head and non-polar tail region; (b) Liposomes: Spherical vesicular structures, made up of one or more phospholipid bilayers and an aqueous core; (c) PMP/ PNP: Polymeric microparticles/ Polymeric nanoparticles. These are micron sized or nanosized particles made up of a polymeric matrix in which the drug is dispersed or encapsulated or entrapped; (d) Emulsion: Dispersion of two immiscible liquids where the dispersed phase is thoroughly distributed in a dispersion medium with the help of emulsifiers; (e) SLN: Solid lipid nanoparticles, submicron carriers made up of high melting point lipid (solid lipid) core and coated by aqueous surfactant layer; (f) NLC: Nanostructured lipid carriers, also known as second generation SLN, where the solid lipid core is replaced by a mixture of solid lipid and liquid lipid; (g) Inorganic nanoparticle: Inorganic nanoparticles, the core is made up of nanosized inorganic material while the shell is organic, contains drug and/or polymers; (h) Solid dispersion: Dispersion of a drug into a solid, inert matrix of carriers; (i) Hybrid systems: Combination of more than one systems; (j) Implant: Device containing drug, intended to be implanted inside the body; (k) Prodrug: Inactive form of a drug, which is converted to a pharmacologically active form upon metabolism inside the body; (l) CD complex: Cyclodextrin complex, inclusion complex formed by cyclodextrins with drugs; (m) Stent: Metal mesh tube which is implanted in ducts or vessels of the body e.g. coronary artery. Drug-eluting stents are used to deliver drugs to a specific site for a long time

being conducted for this formulation. The study began on July 25, 2018, and it is expected to be completed by September 2019. The use of the formulation is indicated for metastatic breast cancer (Kang et al. 2018). Another oral formulation of paclitaxel is under phase II clinical trial, named as Oraxol[®]. Oraxol[®] consists of paclitaxel and HM30181A, a P-glycoprotein inhibitor. Oraxol[®] has been found to be well tolerated in patients without any notable hypersensitivity reaction (Lee et al. 2015). The toxicity issues in the existing commercial formulations have led to the development of alternate formulations for paclitaxel.

6.2 Micelle-Based Delivery System

Micelles are nanometre sized structures formed by self-assembly of amphiphilic block copolymers. The hydrophilic part is oriented towards water whereas the hydrophobic portion remains inside the micellar structure (Kwon and Okano 1996). The concentration at which the micelles are formed in water is known as critical micellar concentration. Lower the critical micellar concentration better is the stability of the micelles. The micelles need to be intact for solubilising the hydrophobic drug. Upon ingestion, micelles' structure may be collapsed due to dilution with aqueous fluids resulting in precipitation of drug. The breakdown of micelles can be avoided by the use of amphiphilic copolymers having a low critical micellar concentration (Owen et al. 2012).

Different amphiphilic polymers have been used in the past for preparation of drug-loaded micelles. These polymers include diblock copolymers such as poly (ethylene glycol)-b-poly (lactide), poly (ethylene glycol)-b- poly (lactide-co-glycolide), etc. Triblock copolymers have also been used for micelle preparation such as poly (ethylene glycol)-poly (ϵ -caprolactone-co-L lactide) (Wang et al. 2013), monomethoxy poly (ethylene glycol)- poly (caprolactone)-D- α -tocopheryl polyethylene glycol 1000 succinate (Zhang and Zhang 2015). Chitosan has been modified with hydrophobic moieties to form an amphiphilic polymer. These hydrophobic groups include α -tocopherol succinate (Liang et al. 2016), Pluronic F127 (Xu et al. 2015a, b), N-succinyl palmitoyl group (Yuan et al. 2015), N-octyl N-trimethyl group (Zhang et al. 2016), polycaprolactone (Almeida et al. 2018). Serum albumin has been modified with octyl group to make it amphiphilic for micelle preparation (Liu et al. 2011). The schematic of types of paclitaxel micelles are given (Fig. 6.4).

6.2.1 Simple Micelle-Based Delivery System

Simple micelles are prepared by using an amphiphilic copolymer. The copolymer may be di or triblock copolymer composed of the hydrophilic and hydrophobic component. Hydrophobically modified serum albumin copolymer was synthesized for preparation of paclitaxel micelles. Serum albumin was chosen as it is

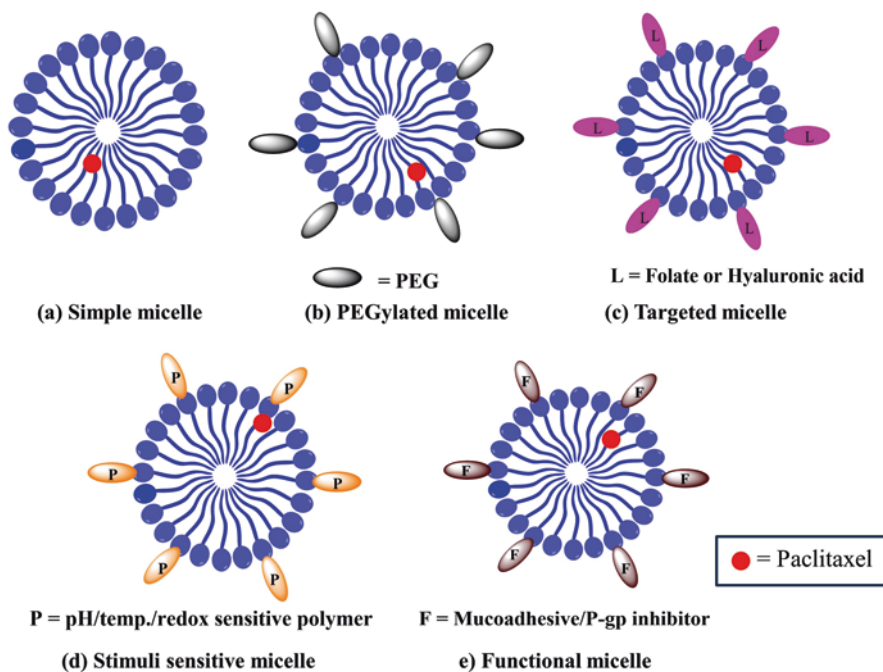


Fig. 6.4 Types of paclitaxel micelles in literature; (a) simple micelle, (b) poly (ethylene glycol) ylated micelle where poly(ethylene glycol) is coated or conjugated to the micelle, (c) targeted micelle; targeting ligands such as folate or hyaluronic acid is conjugated to the micelle, (d) stimuli sensitive micelle; stimuli-responsive i.e. pH/temp/redox-sensitive polymer is conjugated to micelle and (e) functional micelles; functional molecule such as mucoadhesive agent, P-glycoprotein (P-gp) inhibitor or biodegradable polymer is used

endogenously present in the plasma. Serum albumin is biocompatible and nontoxic protein. The reactive primary amino group of albumin was conjugated to octyl chain. The paclitaxel micelles prepared using synthesized octyl conjugated serum albumin exhibited 1.3 times higher drug loading than that of unmodified serum albumin. Octyl group was chosen to enhance interaction between the hydrophobic drug and micelle. *In vitro* cytotoxicity in Hepg2 cells exhibited a higher percentage of cell viability than Taxol[®] indicating better safety profile of octyl modified albumin-based paclitaxel micelles (Gong et al. 2009). Lauryl carbamate modified Inulin was used to prepare paclitaxel micelles. Inulin, a hydrophilic carbohydrate offers the advantage of being an alternate for poly(ethylene glycol)ylation, poly(ethylene glycol)ylation and has been found to exhibit production of anti-poly(ethylene glycol) Immunoglobulin M. Paclitaxel micelles of lauryl carbamate modified Inulin exhibited enhanced anticancer activity in mouse melanoma B16F10 cells at half the dose (Muley et al. 2016).

Polyion complex based micelle composed of cationic Pluronic F127 modified chitosan and anionic sodium cholate was reported for paclitaxel delivery. Sodium cholate, a bile salt was chosen to enhance drug loading in the Pluronic based

micelles. Pluronic block copolymers are approved by USFDA but have the drawback of low drug loading. The synthesized polymer showed higher drug loading and lower critical micelle concentration. These micelles exhibited inhibition of growth of cancer cells in a drug-resistant MCF7 cell line (Ge et al. 2016). In another report, polyion complex based paclitaxel micelle using Pluronic F127 conjugated chitosan with cysteine was investigated. The polyion complex micelles exhibited four times higher drug loading as compared to Pluronic F127 based micelles. The polyion complex micelles exhibited pH-dependent and sustained release upon oral administration (Xu et al. 2015a, b).

Paclitaxel exhibited poor drug loading in poly (ethylene glycol)-b-poly (ϵ -caprolactone). Hence, to increase the drug loading, acyl ester bulky prodrugs of paclitaxel were synthesized. The prodrugs were incorporated into poly (ethylene glycol)-b-poly (ϵ -caprolactone) micelles. The hydrophobic modification of the drug resulted in enhanced solubilization of the prodrug in micelles. These prodrugs exhibited enhancement in drug blood levels as revealed in pharmacokinetics studies in rats. The prodrug micelles not only increased mean residence time and volume of distribution but also sustained the drug release. Chemical modification of the drug resulted in a shift of renal to non-renal clearance of paclitaxel (Forrest et al. 2008).

Paclitaxel micelles prepared using poly (ethylene glycol)-b-poly (lactide) have shown low drug loading. A copolymer of poly (2,4 vinylbenzyloxy)- N, N-diethylnicotinamide) with poly (ethylene glycol) was synthesized and used to prepare paclitaxel micelles. N-N diethylnicotinamide was chosen as a hydrotropic agent. The micelles exhibited 37% by weight drug loading as compared to 27% by weight in poly (ethylene glycol)-b-poly (lactide) micelles. The paclitaxel micelles were stable for 4 weeks at 25 °C whereas there was precipitation of drug in poly (ethylene glycol)-b-poly (lactide) micelles. There was higher antiproliferation of human cancer cells by micelles with synthesized copolymer than poly (ethylene glycol)-b-poly (lactide) micelles (Lee et al. 2007).

6.2.2 Mixed Micelle-Based Delivery System

Mixed micelles utilize two or more polymers to encapsulate the hydrophobic drug in the micelle. The advantages of these over simple micelles include lower critical micelle concentration, higher drug loading and the opportunity to incorporate multiple functionalities in the micellar structure (Attia et al. 2011). Paclitaxel mixed micelles were developed by combining Pluronic P123 with Pluronic F127. The rationale behind such combination relied on co-micellization of these Pluronic grades together during micelle formation. The critical micelle concentration was reduced in mixed micelles as compared to those prepared from Pluronic P123. The mixed micelles reduced half-maximal inhibitory concentration in A549 human lung adenocarcinoma cell lines by 4-fold as compared to Taxol® injection. Mixed micelles exhibited sustained release of paclitaxel. Forty-six percent drug was released after 2 h followed by slow release up to 12 h whereas Taxol® injection

released the drug immediately in an aqueous medium containing sodium salicylate by dialysis method at 37 °C and 100 rpm. The mixed micelles exhibited better stability upon 10 times dilution with phosphate buffer solution and storage for 48 h. Ninety percent drug was retained in mixed micelles whereas 35% of the drug was precipitated in Taxol® injection. The precipitation of the drug was attributed to dissociation of the micelles upon dilution in case of Taxol® injection (Wei et al. 2009).

Sterically stabilized mixed micelles of paclitaxel were developed to increase the drug solubilization with lower critical micelle concentration. It was achieved by incorporation of hydrophobic phosphatidylcholine derivative along with poly (ethylene glycol)-*g*-distearoylphosphatidylethanolamine. The mixed micelles of this graft copolymer exhibited 1000-fold enhancement in paclitaxel solubility. The cytotoxicity study using human breast cancer cell and MCF 7 cell line exhibited comparable cytotoxicity of the mixed micelle with that of 10% paclitaxel solution in dimethyl sulfoxide (Krishnadas et al. 2003). Paclitaxel mixed micelles composed of poly(ethylene glycol-co-lactic acid) and D- α -tocopheryl polyethylene glycol 1000 succinate exhibited higher cellular uptake and effectiveness against multidrug-resistant tumor cells as compared to Genexol PM® (Fan et al. 2015).

Paclitaxel mixed micelles based on Soluplus® and Solutol® HS 15 were prepared for enhancement of drug solubilization. Solutol® HS15 (Murgia et al. 2013) and Soluplus® (Jin et al. 2015) were used in solid dispersions to increase drug solubilization and to prevent drug agglomeration. These mixed micelles exhibited higher plasma concentration in a pharmacokinetic study in Sprague Dawley rats than free paclitaxel. The mixed micelles exhibited higher cytotoxicity than free paclitaxel in MB-231 cell line (Hou et al. 2016). In another study, paclitaxel mixed micelles were prepared by a combination of α -tocopherol polyethylene glycol 1000 succinate and Plasdone® S630. α -tocopherol polyethylene glycol 1000 succinate was chosen for its lower critical micelle concentration of 0.02% w/w and Plasdone® S630® for higher drug solubilization capacity in solid dispersions. The mixed micelles released only 28% drug whereas there was 70% drug release from plain paclitaxel. About 50% drug was released in a sustained manner from mixed micelles upto 50 h. A pharmacokinetic study in Sprague Dawley rats exhibited five times increase in bioavailability of paclitaxel as compared to free paclitaxel. *In vitro* toxicity study in A459 cells revealed enhanced cytotoxicity of mixed micelles as compared to free paclitaxel (Hou et al. 2017).

6.2.3 Stimuli-Responsive Micelle-Based Delivery System

Micelles which can associate or dissociate with respect to change in stimulus are termed as stimuli-responsive micelles. The stimuli such as variation in pH, oxidation-reduction potential, magnetic field, and ultrasound have been used to fabricate stimuli-responsive micelles. pH-sensitive systems are the most popular among these stimuli since there is a variation in pH of fluids present in the milieu of different sites of the gastrointestinal tract, blood, tumor or body organs. The pH is acidic in

the stomach which increases to neutral in the intestine. A pH of 7.4 exists in normal cells whereas it is slightly acidic around tumor cells (Shen et al. 2008). Intracellular and extracellular glutathione concentration varies significantly and hence could be used to trigger an oxidation-reduction reaction (Schafer and Buettner 2001). A pH and oxidation-reduction potential based micelles utilize internal milieu of the human body whereas ultrasound and magnetic field are external stimuli to trigger the release of drug from micelles.

pH-sensitive paclitaxel micelles composed of methoxy poly (ethylene glycol)-b-poly (β -aminoester) were reported. These micelles exhibited 13% and 45% drug release in pH 7.4 and pH 6.0 phosphate buffer solutions respectively after 3 days. The micelles with 16 mg/kg dose exhibited the lowest tumor volume after 10 days of treatment with B16F10 tumor-bearing mice as compared to saline solution (Han et al. 2009).

pH-sensitive paclitaxel micelles using methoxy poly (ethylene glycol)-poly (ϵ -caprolactone)-D- α -tocopheryl polyethylene glycol 1000 succinate were designed. The purpose of use of biodegradable polycaprolactone core was to dissolve the drug in the core whereas polyethylene glycol could bypass reticuloendothelial system uptake. D- α -tocopheryl polyethylene glycol 1000 succinate was chosen to overcome multidrug resistance. These micelles exhibited complete drug release in pH 5.0 whereas only 60% drug was released in pH 7.4 buffer solution after 140 h. The micelles exhibited higher antitumor activity in A549 cells than the free drug. The pharmacokinetic study in Sprague Dawley rats revealed 4-fold higher bioavailability than the free drug (Zhang and Zhang 2015).

N-octyl-N-(2-carboxyl-cyclohexamethenyl) chitosan-based paclitaxel micelles were investigated. High drug loading of 43.25% w/w was obtained in the micelles with a particle size of 145 nm and low critical micellar concentration of 42 μ g/ml. The micelles exhibited pH-sensitive drug release. The pharmacokinetic study in Sprague Dawley mice exhibited longer half-life and a larger volume of distribution than Taxol[®] (Liu et al. 2011).

Polyethylene glycol-fluorenylmethoxycarbonyl-disulfide-farnesyl thiosalicylic acid-based paclitaxel micelles were developed for intracellular delivery. Disulfide group was introduced to impart redox-sensitivity to the system. The micelles formed filamentous micelles with 10-fold lower critical micelle concentration values. The drug loading was found to be 34% w/w in the micelles. The micelles exhibited 74% drug release with 10 mM glutathione in release medium but micelles could release only 40% drug in release medium sans glutathione. The intracellular concentration of glutathione is in the millimolar scale whereas it is in the micromolar level outside the cells (Schafer and Buettner 2001). Pharmacokinetics and biodistribution studies revealed more retention of paclitaxel in the bloodstream with accumulation in tumor (Xu et al. 2015a, b).

Thermosensitive multi-arm star-shaped copolymer-based folate decorated paclitaxel micelles were formulated. The micelles were designed using 4-arm block copolymer consisting of poly (N-isopropylacrylamide-co-acrylamide), poly (ϵ -caprolactone) and folate conjugated methoxy poly (ethylene glycol)/polyethylene glycol. These blocks were chosen for thermosensitive, biodegradable and

biocompatible properties respectively. The micelles exhibited temperature-sensitive drug release. The drug release from these micelles was faster at 40 °C than at 37 °C at the end of 100 h. The rationale was based on the fact that temperature in normal cells is ~37.5 °C whereas 40 °C in tumor environment (Rezaei et al. 2012).

Magnetically responsive paclitaxel micelles were designed. The magnetic material used as superparamagnetic iron oxide nanoparticles which were incorporated in poly (N-isopropylacrylamide-r-acrylamide) conjugated to an arginine-glycine-aspartic acid peptide. These micelles were formulated to have dual targeting. The peptide ligand was selected due to its affinity for $\alpha_v\beta_3$ integrin on cancer cells (Zitzmann et al. 2002) and magnetic force assisted drug release by virtue of iron oxide nanoparticles. The cellular uptake was improved for paclitaxel micelles with peptide in HeLa cells. Incorporation of magnetically responsive material in the micelles exhibited a synergistic effect on cellular uptake in a cell line (Lin et al. 2015).

Paclitaxel micelles based on monomethoxy poly (ethylene glycol)-b-poly (D, L lactide) have increased the maximum tolerated dose to 50 mg/kg from 20 mg/kg for Taxol® in murine B16 melanoma induced female SPF C57 BL/6 mice. This formulation exhibited poor drug internalization (Kim et al. 2001). Howard and coworkers reported local ultrasound-assisted paclitaxel drug internalization from paclitaxel polymeric micelles. Ultrasound enhanced the drug internalization by 20-fold followed by 90% tumor reduction in drug-resistant MCF7/ADmt cell lines (Howard et al. 2006).

6.2.4 Functional Micelle-Based Delivery System

Paclitaxel micelles having specific functionality have been developed in the past. These functionalities include avoidance of multidrug resistance; p-glycoprotein inhibition, biodegradability, mucoadhesive property and the use of carriers with intrinsic anticancer activity. The purpose of functional micelles were to enhance bioavailability, reduce toxicity, and treatment of multidrug-resistant cancer.

P-glycoprotein inhibitors such as brometetradrine (Zhang et al. 2017), N-octyl-N'-phthalyl-O-phosphoryl chitosan derivative (Qu et al. 2019), elacridar (Sarisozen et al. 2012) and Pluronic F127 (Dahmani et al. 2012) were used in compositions of paclitaxel micelles to overcome multidrug resistance. P-glycoprotein causes multidrug resistance by efflux of drug from cells (Gottesman et al. 1996). Various biodegradable polymers such as poly (ethylene oxide)-b-poly (ϵ -caprolactone) (Cai et al. 2007), block copolymers of poly (ethylene glycol) and poly (lactide) (Yang et al. 2009a, b) and poly (ethylene glycol)-poly (L-lactide)-poly {3(S) methyl-morpholine -2,5 dione} (Zhao et al. 2012) were used to prepare biodegradable paclitaxel micelles. Thioglycolic acid-modified octyl glycol chitosan (Huo et al. 2018) and chitosan grafted polycaprolactone (Almeida et al. 2018) were used to prepare mucoadhesive paclitaxel micelles. Excipients having intrinsic anticancer activity such as Rhein (Wang et al. 2019), methoxy poly(ethylene glycol) conjugated octacosanol (Chu et al. 2016), ethylene glycol-b-dendritic polylysine conjugated phenethyl

isothiocyanate (Xiang et al. 2018) and poly (2-ethyl-2 oxazoline) vitamin E succinate and α -tocopherol polyethylene glycol 1000 succinate (Qu et al. 2018) were exploited for preparation of paclitaxel micelles to further substantiate its anticancer activity.

6.2.5 Targeted Micelle-Based Delivery System

Drug delivery to tumor cells can be improved by passive and active targeting of the nanocarriers. Systems that target the systemic circulation can be kept under a passive targeting system. It is a sort of passive process which exploits the natural bio-distribution of the carrier and as a result, it eventually accumulates in certain organs, mainly liver and spleen (Yadav et al. 2019). In passive targeting to the tumor, the drug delivery carriers are exploited for their localization in the tumors by enhanced permeation and retention effects, phagocytosis and/or reticuloendothelial system. Nanocarriers having a size between 100 and 800 nm can accumulate in cancer cells due to leaky vasculature of blood vessels and inadequate lymphatic drainage of cancer cells (Iyer et al. 2006).

Active targeting refers to the attachment of certain components to the drug carrier which can direct the system to the target cells. This is based on molecular recognition phenomenon between ligand and receptor. The ligand possesses high affinity for specific receptor or surface determinant that has been overexpressed in the tumor cells. Overexpression of certain receptors like folate, transferrin, lipoprotein can be exploited as a target for cancer targeting. Certain tumor-associated antigens like melanoma-associated antigen, carcinoembryonic antigen, and other antigens e.g. CD44 are also overexpressed in tumor cells (Thanki et al. 2015). Various peptide-based ligands e.g. albumin, Arg-Gly-Asp peptide; carbohydrate-based ligands e.g. β -galactose; vitamin-based ligands e.g. folate; chimeric proteins and antibodies were used for active targeting. Attachments of these ligands or engineered homing devices or antibodies to drug carrier could facilitate the binding of drug carrier to the target cells. The concentration of these surface modifiers should be optimized in order to avoid reticuloendothelial system uptake or interaction with blood components (Kumar Khanna 2012).

Paclitaxel micelles were reported using mixed micelles composed of N-octyl-N'-trimethyl chitosan, poly (ethylene glycol stearate) and heparin sodium (Zhang et al. 2016), peptide ligand for epidermal growth factor receptor conjugated to poly (ethylene glycol)-distearophosphatidylcholine ethanolamine (Ren et al. 2015). Other systems have used dequalinium (Yao et al. 2011) and prostate carcinoma binding peptide 1 (Chen et al. 2016) for mitochondrial and prostate cancer targeting respectively.

Paclitaxel targeted micelles having dual response were designed wherein any two functionalities like pH sensitivity, biodegradability, active targeting and redox sensitivity have been combined. These micelles include folate conjugated poly (ethyleneimine-pluronic) and Pluronic L121 (Xu et al. 2012), Ala-Pro-Arg-Pro-Gly peptide conjugated poly (lactide-co-glycolide)-b-poly (ethylene glycol) copolymer

(Guo et al. 2015). Other systems include materials such as hyaluronic acid conjugated deoxycholic acid by a redox-sensitive disulfide bond (Li et al. 2015) and E-selectin binding peptide conjugated hyaluronic acid micelles (Han et al. 2017).

6.2.6 Crosslinked Micelle-Based Delivery System

Micelles structure breaks down causing burst release of drug upon dilution in the body. Crosslinking is used to increase the stability of micelles against such breakdown. Crosslinking enables intactness upon dilution of the micelle (O'Reilly et al. 2006). Core crosslinked paclitaxel micelles for improved stability have been reported using micelles composed of poly (ethylene glycol methyl ether acrylate)-*b*-poly (carboxyethyl acrylate) by disulfide crosslinking (Du et al. 2016) and cross-linked di/triblock copolymers of methoxy poly (ethylene glycol) and poly (ϵ -caprolactone) by potassium persulfate (Shuai et al. 2004). The details of various paclitaxel micelles are summarized (Table 6.1).

6.3 Liposomal Delivery System

6.3.1 Simple Liposome-Based Delivery System

Liposomes are spherical vesicular delivery systems composed of phospholipids or other amphiphilic lipids. The advantages of liposomes are bio-compatibility, ease of preparation and applicability for targeted delivery. Liposomes can be used as a drug carrier for both hydrophilic and hydrophobic drugs (Akbarzadeh et al. 2013).

Liposomal paclitaxel formulation composed of soy lecithin and cholesterol were reported. The particle size of liposomes and encapsulation efficiency were found to be 131 ± 30.5 nm and $94.5 \pm 3.2\%$ respectively. *In-vitro* drug release in pH 7.4 phosphate buffer saline was 56% after 96 h. Cytotoxicity study using HeLa cell line exhibited enhanced antitumor efficiency (Nguyen et al. 2017).

6.3.2 Polyethylene Glycolated Liposome-Based Delivery System

Polyethylene glycolation involves coating of poly (ethylene glycol) on liposomes to enhance hydrophilicity and blood circulation time. Liposomes with particle size more than 200 nm are directly taken up by the reticuloendothelial system. The larger particle size of liposomes causes faster elimination of liposomes. The circulation time can be prolonged by poly (ethylene glycol)ylation of liposomes (Sharma and Kumar 2015).

Table 6.1 Paclitaxel delivery system based on micelles

Serial number	System detail	Remarks	Reference
1	P-glycoprotein inhibitor-based micelles		
A	Brometetradine	Brometetradine was co-encapsulated in Solutol HS15 and TPGS mixed micelles. These micelles exhibited superior cytotoxicity and anticancer effect against MCF7/Adr cell line.	Zhang et al. (2016)
B	OPPC (N-octyl-N'-pthalyl-O-phosphoryl chitosan)	OPPC based self-assembled paclitaxel micelles exhibited higher loading than those with unmodified chitosan. These micelles showed higher cellular uptake in Caco-2 cells than Taxol®.	Qu et al. (2019)
C	Elacridar	Elacridar coloaded 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol) -2000] micelles for intracellular delivery by enhanced permeation and retention effect avoided nonspecific distribution of micelles. This led to P-glycoprotein inhibition of only cancer cells. These micelles exhibited higher cytotoxicity in human cancer cell lines.	Sarisozen et al. (2012)
D	Pluronic F127	Paclitaxel mixed micelles composed of Pluronic F127 and low molecular weight all trans-retinoid acid exhibited higher drug loading and lower critical micellar concentration. <i>In situ</i> permeability study through rat intestine exhibited 6-fold enhancement as compared to that with Taxol®.	Dahmani et al. (2012)
2	Targeted micelle-based delivery system		
A	Heparin based system	N-octyl-N-trimethyl chitosan-polyethylene glycol 100 stearate-based paclitaxel micelles showed high drug loading. Heparin sodium coated micelles exhibited higher cellular uptake with longer circulation time in rats.	Zhang et al. (2016)
B	Dual responsive system	pH-responsive and cancer cell recognition programmed mixed micelles composed of (D- α -tocopheryl poly-ethylene glycol 1000 succinate -b-poly(β -aminoester) and aptamer exhibited stability at pH 7.4 but released the drug at tumor pH.	Zhang et al. (2015)
C	Mitochondria-targeted system	Paclitaxel micelles composed of poly (ethylene glycol-2000)-g-distearoylphosphotidylethanol amine, tocopheryl polyethylene glycol succinate with dequalinium had a higher solubility than 1 mg/ml, exhibited delayed-release and enhanced cellular uptake in MCF7/Adr cells than that of Taxol®.	Yao et al. (2011)

Polyethylene glycolated liposomal formulation of paclitaxel composed of soybean phosphatidylcholine and 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine [methoxy (polyethylene glycol)-2000], Cholesterol, Tween 80 and 3-(4, 5-Dimethyliazol-2-yl)-2, 5-diphenyl- tetrazolium bromide was reported. This liposomal paclitaxel formulation resulted in enhancement of solubility by 2000 times as

compared to conventional liposomes. The pharmacokinetic study on Sprague Dawley rats revealed a 3-fold increase in biological half-life in poly(ethylene glycol)ylated liposomal formulation of paclitaxel (Yang et al. 2007).

6.3.3 Targeted Liposomal Delivery System

The targeted delivery system is a strategy of delivering drugs or medications only to its site of action and not to the other cells, tissues or organs. The concentration of medication is higher in particular cells, tissues or organs as compared to others. Targeting systems have the advantages of improving the therapeutic efficacy and reduction of side effects of drugs (Gupta and Sharma 2011). Passive targeting involves targeting of drugs to the systemic circulation of the body. In this method, drug targeting occurs because of the body's natural response to physicochemical characteristics of the drug or drug carrier system. Enhanced permeability and retention effect passively target the drug to the tumor cells (Bazak et al. 2014).

Active targeting involves the use of a ligand that has an affinity for specific receptors which are over-expressed in cancerous organs, tissues, and cells. Transferrin, peptides, antibodies, nucleic acids, and their fragments are used as a ligand for active targeting (Atar et al. 2018).

Targeting of paclitaxel liposomal formulation to the lungs composed of phospholipon 90H and Tween-80 were reported. The particle size of liposomes and entrapment efficiency were found to be $8.166 \pm 0.459 \mu\text{m}$ and $92.2 \pm 2.56\%$ respectively. These liposomes exhibited 60.26% drug release in 24 h. *In vivo* pharmacokinetic study in rabbits revealed a 1.6-fold increase in half-life and the significant decrease in plasma clearance than Taxol®. Liposomes of size higher than $8 \mu\text{m}$ could be the potential carrier for paclitaxel for the treatment of lung cancer (Wei et al. 2014).

Targeting of paclitaxel liposomal formulation to mitochondria composed of triphenyl phosphene, 6-bromohexanoic acid, dicyclohexylcarbodiimide, 4-dimethylamino-pyridine were reported. D- α - tocopheryl poly-ethylene glycol 1000 succinate-triphenylphosphine conjugate was used as the mitochondrial targeting material. The particle size of liposomes and entrapment efficiency were found to be $84.67 \pm 0.61 \text{ nm}$ and $86.27 \pm 3.15\%$ respectively. The liposomes exhibited higher anticancer *in-vitro* activity in human lung cancer A549 cells. The paclitaxel liposomes could enhance the cellular uptake and were selectively accumulated in mitochondria. The increased uptake of the liposomes enhanced the anticancer efficacy (Zhou et al. 2013).

A targeted paclitaxel liposomal formulation composed of dipalmitoyl phosphatidylcholine, dimyristoyl phosphatidylglycerol/monomethoxy, polyethylene glycol 2000, distearoyl phosphatidylethanolamine and folate-poly(ethylene glycol) 3350-distearyl phosphatidylethanolamine was reported. The particle size of liposomes was found to be 97.1 nm. Cytotoxicity study in the human carcinoma cell

line, KB exhibited 4-fold and 2.5-fold lower half maximal inhibitory concentration than non-targeted liposomes and Taxol[®] respectively. The clearance of Taxol[®] was 16.5 times higher than folate receptor-targeted liposomes (Wu et al. 2006).

A targeted liposomal paclitaxel formulation composed of dipalmitoyl-sn-glycero-3-phosphocholine and 1, 2-dioleoyl-3-trimethylammonium-propane, and hyaluronic acid was developed. The particle size of liposomes and encapsulation efficiency were found to be 106.4 ± 3.2 nm and $92.1 \pm 1.7\%$ respectively. *In vitro* drug release in pH 7.4 phosphate buffer saline was 95% in 40 h. *In vivo* antitumor efficacy and biodistribution studies were performed on 4T1 tumour-bearing animal models exhibited higher accumulation of the drug in tumor (Ravar et al. 2016).

6.3.4 Stimuli Sensitive Liposomal Delivery System

Magnetically assisted delivery is a novel approach for delivery of drugs using engineered smart microcarriers which can overcome a number of limitations facing current methods of delivering medicines. The drug is formulated into a pharmaceutically stable formulation which is usually injected through the artery that supplies the target organ or tumor in the presence of an external magnetic field (Koppiseti and Sahiti 2011). Focused ultrasound is a method to increase the permeability of drugs into the blood-brain barrier to promote drug delivery to specific brain regions. It is a potential method of delivery of the drugs into the brain for brain tumors (Burgess et al. 2015).

Focused ultrasound was used to enhance permeation through the blood-brain barrier and blood tumor barrier. 1, 2-dipalmitoyl-sn-glycero-3-phosphocholine, 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine and cholesterol were used to prepare liposomal paclitaxel formulation. Focused ultrasound exposure with a 10 ms pulse length and 1 Hz pulse repetition frequency at 0.64 MPa peak rarefactional pressure was used. *In-vivo* study in rats showed a 3-fold increase in blood drug level from the ultrasound-assisted liposomal formulation as compared to liposomal paclitaxel formulation (Shen et al. 2017). Paclitaxel loaded magneto liposomes composed of 1, 2-dipalmitoyl-sn-glycero-3-phosphocholine and 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-rac-glycerol were reported. The encapsulation efficiency of $83 \pm 3\%$ was obtained. *In-vitro* study under magnetic field on HeLa cell line revealed that 89% of cells were killed (Kulshrestha et al. 2012).

6.3.5 Mucoadhesive Liposomal Delivery System

Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. The mucoadhesive property of a delivery system is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation (Shaikh et al. 2011).

Mucoadhesive liposomes composed of chitosan, thioglycolic acid and Pluronic F127 were used for paclitaxel oral delivery. The particle size of liposomes was found to be 121.4 nm. *In-vivo* study on rats revealed a 3-fold higher bioavailability than non-mucoadhesive liposomes. Enhanced mucoadhesion was observed which increased the retention time of the chitosan, thioglycolic acid and Pluronic F127 containing liposomal paclitaxel formulation (Liu et al. 2018).

6.4 Nanoparticle-Based Delivery System

Nanoparticles can be defined as submicron (10–1000 nm) particles or systems derived from polymers, lipids, and/or inorganic materials. Nanoparticle-based systems can overcome some of the limitations associated with conventional cancer therapy (Xin et al. 2017). The limitations include poor solubility of drugs, low specificity to the tumor cells, inability to accumulate in tumor cells, rapid removal of drugs from the systemic circulation and non-specific targeting. Nanoparticles have the potential to increase bioavailability and enhance the delivery of poorly soluble anticancer drugs like paclitaxel (Tran et al. 2017). Due to small size, high surface to volume ratio, ability to modulate drug release and the possibility of surface modification, nanoparticles lead to enhanced accumulation of drugs in tumor cells. Surface modification, use of internal and external stimuli allows selective targeting of drugs to tumor cells. Nanoparticulate systems are also useful to overcome multidrug resistance facilitated by P-glycoprotein efflux pumps in tumor cells (Shi et al. 2017).

6.4.1 *Single Nanocarrier Based System*

Paclitaxel nanoparticles fabricated using a single polymer have been discussed in this subsection. The carriers can be natural e.g. albumin (Li et al. 2012); semisynthetic e.g. chitosan (Gupta et al. 2017); and synthetic e.g. poly (styrene-co-maleic acid) (Dalela et al. 2015), poly (n-butyl cyanoacrylate) (Huang et al. 2007). Use of biodegradable polymers like poly (lactic-co-glycolic acid) (Le Broc et al. 2013), poly(ϵ -caprolactone) (Zhu et al. 2010), poly(lactide) (Zhang and Feng 2006) were also reported because of their biocompatibility and non-toxicity. Paclitaxel loaded poly (lactic-co-glycolic acid) nanoparticles were formulated using Poloxamer 188 as a stabilizer. Paclitaxel nanoparticles exhibited sustained release of the drug over a period of 4 days. The formulation was safe for intravenous administration. Pharmacokinetic studies in rats have verified longer retention of drug in the systemic circulation. Mean residence time and plasma half-life were increased by 77 and 45-fold respectively as compared to the pure drug (Mittal et al. 2019).

The chitosan-based biocompatible nanoparticulate system was prepared to achieve better delivery of paclitaxel which has shown burst release followed by sustained release of the drug. The half-maximal inhibitory concentration was reduced by 1.6-fold as compared to the pure drug which was attributed to the higher uptake of nanoparticles. Therapeutic efficacy was induced by apoptosis induction. The drug loading was found to be 11.57% (Gupta et al. 2017). Polygeline has been used as a carrier for paclitaxel delivery. Polygeline based paclitaxel nanoparticles were formulated as a reconstitutable lyophilized powder for intravenous administration. The drug loading was found to be 12.04%. It has shown a relative bioavailability of 89.83% as compared to Abraxane® (Xiong et al. 2019).

6.4.2 Multiple Nanocarriers-Based System

It covers the delivery systems of paclitaxel which contain more than one polymer or carriers. Polymers can remain as separate entities as in the case of layer-by-layer based albumin-bound paclitaxel nanoparticles. The nanoparticle was fabricated by alternate deposition of poly(arginine) and poly (ethylene glycol)-block-poly (L-aspartic acid) onto the drug-albumin conjugate. The drug loading capacity was found to be 48% w/w. The protective layers have improved the colloidal stability as well as biodistribution of albumin-bound paclitaxel nanoparticles. Mean residence time and plasma half-life were increased 5 and 4-fold respectively as compared to albumin-drug conjugate. These multilayer conjugates exhibited enhanced cytotoxicity and apoptosis properties (Ruttala et al. 2017).

Two or more polymers can be copolymerized and loaded with paclitaxel to design paclitaxel loaded nanoparticles. Methoxy poly (ethylene glycol)-poly(ϵ -caprolactone) nanoparticles loaded with paclitaxel have shown improved anti-glioblastoma activity than Taxol®. The drug loading was found to be 8.2%. High accumulation of the drug in brain cells was observed. The mean survival time was increased to 28 days which was 20 days in Taxol® treated animals. (Xin et al. 2010). Poly (ethylene glycol)ylated poly(ϵ -caprolactone) based paclitaxel nanoparticles were designed which exhibited similar biodistribution compared to Taxol®. Polyethylene glycol and poly(ϵ -caprolactone) side chains of the nanoparticles could avoid opsonization (Colombo et al. 2015).

Paclitaxel loaded nanoparticles composed of poly(ϵ -caprolactone)-co- α -tocopheryl polyethylene glycol 1000 succinate were formulated. The nanoparticles had 6% drug loading. The nanoparticles exhibited sustained drug release over a period of 144 h in pH 7.4 phosphate buffer solution. The half-maximal inhibitory concentration for the nanoparticles was found to be 7.8-fold lower than Abraxane®. *In vivo* pharmacokinetic study in rats revealed that the half-life was increased by 11 and 1.2-fold as compared to Taxol® and Abraxane® respectively. The formulation could increase the systemic circulation and lower the elimination of drug than its pre-existing marketed formulations (Bernabeu et al. 2014).

6.4.3 Stimuli Sensitive Nanosystem

pH sensitivity can be incorporated into either the corona or core of the nanoparticles. The core-shell type nanoparticles are formulated with pH-dependent solubility and lower critical solution temperature which exhibits drug release at tumor pH (Sutradhar and Amin 2014).

Various polymers have been reported to exhibit pH-responsive release of paclitaxel, such as poly [2-(dimethylamino) ethyl methacrylate-co-methacrylic acid] (Lee et al. 2011), O-carboxymethyl chitosan (Sahu et al. 2011), poly (acrylic acid)-poly(ethylene oxide) (Nguyen et al. 2019), poly(4-vinyl pyridine) (Contreras-Cáceres et al. 2017), poly (lactic acid)-block-poly(ethylenimine) and poly (ethylene glycol)-block-poly (1-aspartic acid sodium salt) (Jin et al. 2018a, b). Chitosan modified poly (lactic-co-glycolic acid) nanoparticles of paclitaxel were designed to overcome the initial burst release of poly (lactic-co-glycolic acid) nanoparticles. The drug loading was found to be 6.42%. Chitosan modified nanoparticles were pH-responsive and have shown faster release in pH 5.5 than at pH 7.4. Enhanced cytotoxicity and cellular uptake in MDA-MB-231 cells were due to chitosan modification (Lu et al. 2019).

Thermoresponsive delivery systems have been explored for paclitaxel where a change in temperature had triggered the release of the drug from the system. A novel thermoresponsive triblock copolymer comprised of methoxy poly (ethylene glycol), poly(octadecanedioic anhydride) and D, L-lactic acid oligomer was developed for paclitaxel delivery. The nanoparticles were formulated as a freeze-dried powder which is suitable for peritumoral or intratumoral injection upon redispersion with water at ambient temperature. The drug loading was found to be 0.90%. Paclitaxel accumulation in tumor cells was enhanced whereas systemic exposure was reduced. Plasma half-life and area under the curve were increased by 4.2 and 1.8-fold respectively as compared to Taxol[®] in the pharmacokinetic study (Liang et al. 2017).

Paclitaxel conjugated recombinant chimeric polypeptide-based nanoparticles have been reported. The nanoparticles self-assemble into spherical nanoparticles of size below 100 nm. The *in vitro* dissolution study of the nanoparticles did not release the drug in pH 7.4 phosphate buffer solution but completely released the drug within 6 h in pH 6.5 carbonate buffer solution. The systemic exposure of paclitaxel was increased by 2-fold as compared to that of Abraxane[®]. The tumor uptake of the nanoparticles was doubled as compared to *that with* Abraxane[®]. Abraxane[®] treated prostate cancer animals could survive less than 60 days, whereas nanoparticle treated animals survived more than 70 days with almost complete tumor reduction (Bhattacharyya et al. 2015).

The reducing environment of tumors serves as a unique internal signal that allows redox-responsive nanoparticles to degrade in tumor cells and release the loaded drug. Rapid drug release can be attributed to the high concentration of glutathione in cancer cells (Guo et al. 2018). Cross-linked polymeric nanocarriers made up of poly (lactic acid) core and glutathione-responsive disulfide cross-linked poly (oligo-ethylene glycol) corona was loaded with paclitaxel. The drug loading

capacity was found to be 20%. *In vitro* release of paclitaxel from the nanoparticles was enhanced in the presence of glutathione in acidic pH. The half-maximal inhibitory concentration showed an 11-fold increase activity in OVCAR-3 cells compared to Taxol[®] which indicated better antitumor efficacy of the nanoparticles (Samarajeewa et al. 2013).

6.4.4 Functional Polymeric Nanoparticles

Multidrug resistance is the major reason for the failure of conventional anticancer therapy. P-glycoprotein mediated drug efflux from cancer cells is one of the important mechanisms of multidrug resistance (Mansoori et al. 2017). Various nanoparticulate systems of paclitaxel have been formulated to overcome this issue. Paclitaxel was loaded in poly [2-(dimethylamino)-ethyl methacrylate-co-methacrylic acid] to obtain water-soluble nanoparticles. These nanoparticles were able to reverse the multidrug resistance in two p-glycoprotein expressing breast cancer cell lines i.e. MCF/ADR, MT3/ADR cell lines compared to pure paclitaxel. This was due to the uptake of nanoparticles by endocytosis, bypassing the P-glycoprotein efflux pump (Lee et al. 2011).

Poly(lactide)-D- α -tocopheryl polyethylene glycol 1000 succinate copolymer-based nanoparticles of paclitaxel were developed, where D- α -tocopheryl polyethylene glycol 1000 succinate acts as a P-glycoprotein inhibitor. The drug loading was found to be 5.2%. These nanoparticles exhibited much higher *in vitro* cytotoxicity in HT-29 cells as compared to Taxol[®] (Zhang and Feng 2006).

P-glycoprotein inhibition potency of tannic acid was used by formulating tannic acid nanoparticles of paclitaxel. Tannic acid has lowered the P-glycoprotein expression; inhibited metastasis, clonogenic formation, proliferation; decreased expression of multidrug-resistant protein; and increased expression of tumor suppressor proteins of MDA-MB-231 breast cancer cells (Chowdhury et al. 2019).

Mucoadhesive polymeric nanoparticles relish localization and prolonged residence at the site of absorption (Boddupalli et al. 2010). Paclitaxel conjugated trimethyl chitosan nanoparticles were developed for oral and intravenous administration of the drug. Intestinal transport of paclitaxel was promoted by the mucoadhesive property of trimethyl chitosan. A pharmacokinetic study in tumor-bearing mice revealed prolong blood retention and improved tumor accumulation of paclitaxel. Further modification of nanoparticles by folic acid has improved the overall antitumor efficacy (He and Yin 2017).

6.4.5 Targeted Polymeric Nanoparticles

Chitosan modified poly (lactic-co-glycolic acid) nanoparticles were loaded with paclitaxel. Chitosan modification produced a positively charged surface which resulted in increased uptake of the nanoparticles into lung cancer cell line A549.

Moreover, a lung-specific biodistribution was achieved as compared to Taxol®. The transient formation of aggregates in plasma increased the size of the nanoparticles upon intravenous administration. Electrical interaction between positively charged nanoparticles and negatively charged tumor vasculature enhanced the accumulation of nanoparticles in lung tumor (Yang et al. 2009a, b).

Various active targeting based polymeric nanoparticles have been reported for paclitaxel. Paclitaxel loaded cationized polyacrylamide nanoparticles engineered with recognition peptide VRPMLQ were designed. The presence of positive charge and the recognition peptide directed the nanoparticles to dysplasia regions in the colon where sialic acid was overexpressed. The uptake of the peptide containing nanoparticles was increased 10-fold as compared to non-peptide nanoparticles (Tiwari et al. 2017). CD44 is a non-kinase transmembrane glycoprotein that is overexpressed in certain cancers like gallbladder cancer, breast cancer and ovarian cancer (Chen et al. 2018). Hyaluronic acid serves as a targeting ligand for overexpressed CD44. Hyaluronic acid decorated serum albumin-based paclitaxel nanoparticles were designed for targeting ovarian cancer cells. The encapsulation efficiency was found to be 90%. The uptake of the nanoparticles was attributed to receptor-mediated endocytosis. A fluorescent dye fluorescein isothiocyanate was labelled to the nanoparticles for *in vitro* imaging of the tumor. The half-maximal inhibitory concentration was decreased by 4.35-fold in hyaluronic acid conjugated paclitaxel as compared to free paclitaxel (Edelman et al. 2019).

Ganipineni and co-workers have compared passive, active, magnetic and hybrid targeting strategies of paclitaxel for glioblastoma treatment. For passive targeting, paclitaxel and superparamagnetic iron oxide loaded poly (lactic-co-glycolic acid) nanoparticles were formulated. Accumulation of nanoparticles in the U87MG tumor model was due to enhanced permeability and retention effect. Active targeting was based on the fact that $\alpha_v\beta_3$ integrin is overexpressed in glioblastoma and Arg-Gly-Asp tripeptide was served as a targeting ligand. So, the surface of the nanoparticles was modified with Arg-Gly-Asp to achieve active targeting. The inherent magnetic property of superparamagnetic iron oxide was explored for magnetic targeting. Hybrid targeting was achieved by adding active and magnetic targeting. The best therapeutic effect was obtained in magnetic targeting followed by the hybrid targeting (Ganipineni et al. 2019). The other polymeric nanocarrier based targeted delivery systems of paclitaxel is given (Table 6.2).

6.4.6 Inorganic Nanoparticle-Based System

Inorganic nanoparticles are developed lately in addition to polymeric or organic nanoparticles. Typically, the inorganic nanoparticles are made up of inorganic core and organic shell (Bayda et al. 2018). The core contains metals like iron oxide, gold, aluminium or non-metals like carbon or silica. The shell protects the core from chemical interactions during circulation and/or acts as a substrate for conjugation with biomolecules, such as antibodies, proteins, and oligonucleotides. Inorganic

Table 6.2 Polymeric nanocarrier based targeted delivery of paclitaxel

Serial number	Systems	Remarks	References
1	Passive targeting based systems		
A	Paclitaxel loaded poly (ethylene glycol)-block poly (trimethylene carbonate – nanoparticle	The nanoparticles exhibited sustained release and slightly higher <i>in vivo</i> antitumor efficacy than Taxol [®] . The uptake of nanoparticles to glioblastoma was enhanced due to passive targeting.	Jiang et al. (2011)
B	Association of poly (ethylene glycol) -paclitaxel with free paclitaxel [poly (ethylene glycol)-paclitaxel/paclitaxel]	<i>In vitro</i> cytotoxicity was more in poly (ethylene glycol)-paclitaxel/paclitaxel than poly (ethylene glycol)-poly(lactide)/paclitaxel. <i>In vivo</i> cellular uptake and antitumor efficacy was more in poly (ethylene glycol)-paclitaxel/paclitaxel than poly (ethylene glycol)-poly(lactide)/paclitaxel and Taxol [®] due to efficient passive targeting.	Lu et al. (2014)
2	Active targeting-based systems		
A	Wheat germ agglutinin conjugated isopropyl myristate incorporated poly(lactide-co-glycolide) nanoparticles	The nanoparticles exhibited stronger <i>in vitro</i> cytotoxicity due to efficient cellular uptake via Wheat germ agglutinin receptor-mediated endocytosis and isopropyl myristate-facilitated release of paclitaxel from the nanoparticles.	Mo and Lim (2005)
B	Poly (vinyl benzyl lactonamide) incorporated paclitaxel loaded poly(lactide-co-glycolide) nanoparticles	Enhanced cellular uptake and cytotoxicity were observed due to receptor-mediated endocytosis of nanoparticles to hepatic cancer cells. Poly (vinyl benzyl lactonamide) carried galactose residues which were served as a ligand.	Wang et al. (2012)
C	Follicle-stimulating hormone β 81–95 peptide conjugated poly (ethylene glycol)-poly(lactide) nanoparticles	Specific paclitaxel uptake by follicle-stimulating hormone receptor expressing ovarian cancer cells. Side effects were reduced as compared to commercial paclitaxel.	Zhang et al. (2013)
D	15F and regulon-peptide modified polyester based nanoparticles	Internalization of nanoparticles was mediated by low-density lipoprotein receptor-1 in the brain. Cellular uptake by glioma cells was improved due to peptide functionalization.	Di Mauro et al. (2018)
E	Alendronate modified paclitaxel-polydopamine nanoparticles	The nanoparticles exhibited specificity towards osteosarcoma cells due to alendronate modification. <i>In vivo</i> antitumor activity was better as compared to Taxol [®] with lesser side effects.	Zhao et al. (2019)

nanoparticles offer good stability and biocompatibility. These can alter the drug release profile and provide the site of attachment for targeting molecules. Additionally, few metallic nanoparticles can also be used for contrast imaging and photodynamic therapy (Núñez et al. 2018).

Paclitaxel was loaded into mesoporous silica nanoparticles of three different pore sizes and was evaluated for *in vitro* and *in vivo* antitumor activity. The *in vitro* release of paclitaxel was dependent on the pore size. Early and late apoptosis was directly proportional to pore size and was boosted as compared to free paclitaxel. Pharmacokinetic parameters were similar to Taxol® (Jia et al. 2013). Paclitaxel was loaded into mesoporous carbon spheres and surface modified by the folate-polyethyleneimine function. The enhanced internalization of nanoparticles by Caco-2 cell lines was due to folate conjugation. The nanoparticles also demonstrated improved oral bioavailability and diminished gastrointestinal toxicity (Wan et al. 2015). Other inorganic nanoparticle-based delivery systems of paclitaxel are given (Table 6.3).

6.4.7 Nanocrystal-Based System

Drug nanocrystals are nanosized, carrier-free, crystalline particles of the drug, usually produced in the form of nanosuspensions and stabilized by surfactants or polymers. Nanocrystals have several advantages over other nanoparticulate systems such as high drug loading capacity, improved solubility, dissolution, stability, and long circulation time. Nanocrystals also enjoy excellent commercialization potentials. So, development of nanocrystals of paclitaxel has gained the interest of researchers in recent years (Lu et al. 2015).

Paclitaxel nanocrystals were prepared using Pluronic F127 as a stabilizer for hyperthermic intraperitoneal chemotherapy of ovarian cancer. The *in vitro* cytotoxicity against human ovarian carcinoma cell line, SKOV-3, was equivalent to Taxol®. The maximum tolerated dose of the nanocrystals was similar to Taxol® however; the rats treated with the nanocrystals recovered faster after hyperthermic intraperitoneal chemotherapy treatment (De Smet et al. 2012). In another study, Pluronic F127 grafted chitosan copolymer was used as a stabilizer for the development of paclitaxel nanocrystals. Enhanced accumulation of paclitaxel in the Caco-2 cell line as a result of P-glycoprotein inhibitory potential of the stabilizer was observed. The nanocrystals have shown 12.6-fold enhanced absorption as compared to Taxol® (Sharma et al. 2015).

Polyethylene glycol stabilized and Arg-Gly-Asp peptide-functionalized paclitaxel nanocrystals were reported. Nanocrystals were coated with polydopamine which gave a site of attachment to polyethylene glycol and Arg-Gly-Asp peptide. Due to surface modification, the uptake and accumulation of nanocrystals were increased in adenocarcinomic pulmonary cells. *In vivo* study in pulmonary tumor-bearing mice resulted in enhanced antitumor efficacy in RGD peptide-functionalized paclitaxel nanocrystals as compared to that with Taxol® (Huang et al. 2019).

Table 6.3 Inorganic nanoparticle-based delivery systems of paclitaxel

Serial number	Systems	Remarks	References
1	Paclitaxel loaded chitosan oligosaccharide stabilized gold nanoparticles	The gold nanoparticles have shown sustained drug release at acidic pH and a strong cytotoxic effect against MDA-MB-231 cells. Gold nanoparticles also have the potential to be used as an optical contrast agent for photoacoustic imaging.	Manivasagan et al. (2016)
2	Poly (ethylene glycol)-carboxyl–poly(ϵ -caprolactone) magnetic nanoparticles	In the presence of a magnetic field, the nanoparticles were targeted to tumor cells. The nanoparticles were less toxic to normal cells and found to be biocompatible.	Li et al. (2017a, b, c)
3	Gadolinium arsenite nanoparticles	Conjugations of arsenic trioxide and paclitaxel have shown a synergistic effect against paclitaxel-resistant HCT 166. Intracellular uptake of paclitaxel by resistant cells was enhanced.	Chen et al. (2017a, b)
4	Pectin conjugated magnetic graphene oxide nanoparticles	The nanoparticles have shown high drug loading capacity i.e. 36% and compatibility. <i>In vitro</i> release was more in endosomal cancer cell medium than normal physiological pH.	Hussien et al. (2018)
5	Hyaluronic acid (HA) functionalized MHANs (mesoporous hollow alumina nanoparticles)	Due to HA modification, MHAN was targeted to liver cancer cells. <i>In vivo</i> cytotoxicity in nude mice was better than pure paclitaxel and non-functionalized MHANs	Gao et al. (2019)

6.5 Lipid-Based Delivery System

Lipid-based systems possess the advantage of incorporation of the hydrophobic drug in amorphous form. It helps to enhance the solubility of the drugs. It also helps improving permeability by providing lipophilicity to the delivery system. Lipid systems can be prepared using solid lipids or a mixture of solid lipids and liquid lipids. The former is referred to as solid lipid nanoparticles and the later one as nanostructured lipid carriers. Solid lipid nanoparticles, as well as nanostructured lipid carriers of paclitaxel, have been formulated. These include simple lipid-based systems, poly (ethylene glycol)ylated lipid-based systems, oral systems, local systems, pulmonary systems, targeted systems and stimuli-responsive systems.

6.5.1 Simple Lipid-Based Delivery System

Simple lipid-based systems of paclitaxel have been prepared using lipid and surfactants. Paclitaxel nanostructured lipid particles were prepared using fluorescein isothiocyanate-octadecylamine using 0.1% Poloxamer 188 aqueous solution by hot melt high-pressure homogenization. The nanoparticles were freeze-dried and were found to have 89 nm size and more than 30 mV zeta potential. The nanoparticles released ~ 80% drug within 48 h but it was about 50% from nanoparticles prepared without octadecylamine. *In vitro* cellular uptake in A549 cells was found to be higher with octadecylamine nanoparticles (Miao et al. 2015).

In another study, paclitaxel solid lipid nanoparticles composed of trilaurin, phosphatidylcholine were prepared using hot homogenization method. The nanoparticles had a size of ~160 nm. These nanoparticles exhibited sustained release in human plasma over 24 h whereas burst release was observed in Taxol® (Xu et al. 2013).

6.5.2 Lipid-Based Oral Drug Delivery System

Glyceryl monostearate based solid lipid nanoparticles of paclitaxel were prepared by emulsification and evaporation method. Wheat germ agglutinin was conjugated to these solid lipid nanoparticles which exhibited higher cytotoxicity than non-conjugated nanoparticles in A549 cell line. The conjugated nanoparticles exhibited a 2-fold increase of area under the plasma curve and mean residence time during *in vivo* pharmacokinetic study in rats as compared to the plain drug (Pooja et al. 2016).

6.5.3 Lipid-Based Topical Drug Delivery System

Paclitaxel loaded solid lipid nanoparticles composed of Carbapol 940, stearic acid, egg lecithin and Pluronic PF 68 were reported for topical delivery. Particle size and pH of the formulation were found to be 78 nm and 5.4 respectively. The gel released 70% drug in 24 h in pH 7.4 phosphate buffer solution. The nanoparticle-based gel showed higher permeability through the dialysis membrane than that of plain drug-loaded gel. *In vivo* study in mice exhibited higher antitumor efficacy (Bharadwaj et al. 2016). Another report for topical delivery of paclitaxel was based on nanostructured lipid carriers composed of glyceryl behenate, capric-caprylic triglycerides mixture with a surfactant cetylpyridinium chloride. The particle size and drug loading were found to be 270–315 nm and 3% respectively. The higher zeta potential of 20 mV was observed. The positive zeta potential helped to increase the permeability of drug through the skin (Tosta et al. 2014).

6.5.4 Lipid-Based Pulmonary Drug Delivery System

Pulmonary lipid nanoparticles are meant for lung cancer treatment. Nanostructure lipid carriers of paclitaxel were designed with a surfactant that can inhibit P-glycoprotein mediated drug efflux. These nanoparticles exhibited sustained release in pH 7.4 phosphate buffer solution. Nanoparticles of Tween 20 exhibited the highest cellular uptake in Caco-2 cell line. *In vivo* studies of nanoparticles exhibited better therapeutic activity and lung deposition (Kaur et al. 2016).

6.5.5 Lipid-Based Targeted Delivery System

Passive and active targeted lipid-based systems were reported for paclitaxel delivery. Positively charged solid lipid nanoparticles of paclitaxel composed of stearylamine, sodium behenate and polyvinyl alcohol were prepared. These nanoparticles exhibited only 1% drug release after 12 h whereas paclitaxel solution released the drug completely in a phosphate buffer solution with 0.1% v/v Tween 80 solution. Cytotoxicity study in hCMEC/D3 cells exhibited better anticancer activity with improved blood-brain barrier permeation (Chirio et al. 2014). Solid lipid nanoparticles of paclitaxel were prepared using tristearin, hydrogenated soy phosphatidylcholine. The surface of the solid lipid nanoparticles was modified with lactoferrin. The size of nanoparticles and zeta potential were found to be 250 nm and 3.7 mV respectively. Cytotoxicity study in BEAS-2B cell line exhibited a 4-fold reduction in half-maximal inhibitory concentration in lactoferrin conjugate nanoparticles as compared to non-conjugated nanoparticles. *In vivo* distribution study in albino rats exhibited 1.6-fold higher uptake of the drug as compared to non-targeted nanoparticles (Pandey et al. 2015).

Folate-conjugated poly (ethylene glycol)-cholesteryl hemisuccinate was used to prepare a paclitaxel targeted delivery system. Paclitaxel nanostructured lipid carrier was prepared using oleic acid and stearic acid from the conjugated polymer. Transmission electron microscopy revealed 100 nm size for these carriers. The bio-distribution study in albino rats exhibited higher deposition of targeted particles in the kidney (Ucar et al. 2017). Paclitaxel solid lipid nanoparticles prepared using conjugated polymer of Pluronic P85, 1, 2 distearoyl-sn-glycero-3-phosphatidylethanolamine and hyaluronic acid by hot homogenization method were developed. *In vitro* drug release study revealed complete drug release from the plain drug but the nanoparticles exhibited sustained release up to 48 h in a phosphate buffer solution with 0.5% w/v Tween 80. The targeted nanoparticles exhibited a 4-fold increase in drug concentration in tumor than from free drug in balb/c mice (Wang et al. 2017).

Paclitaxel brain targeted solid lipid nanoparticles were developed. These were composed of transferrin conjugated polyethylene glycol, oleic acid, Compritol ATO 888 and cholesterol. These were prepared by the solvent evaporation method. The size of the nanoparticles and drug loading were found to be 160 nm and 8.6%

respectively. *In vitro* release study showed that the drug release was in a sustained manner up to 75 h in pH 7.4 phosphate buffer saline. 6-fold reduction of half maximal inhibitory concentration in HL 60 cells was shown by targeted nanoparticles as compared to non-targeted nanoparticles (Dai et al. 2018).

6.5.6 Lipid-Based Stimuli Sensitive Delivery System

Lipid-based stimuli sensitive delivery systems have been utilized for paclitaxel delivery such as pH-sensitive system, magnetically assisted system, enzyme-dependent system and photosensitive system. Arginine lauryl ester-based cationic nanostructured lipid carriers for paclitaxel were developed. The incorporation of arginine was attributed to the pH-sensitive behaviour of the system. These cationic nanocarriers were further coated with bovine serum albumin to increase their blood circulation time by charge masking. The size of these coated carriers was below 100 nm. These carriers exhibited 60–65% drug release at 5.4 pH buffer but released only ~35% drug at physiological pH of 7.4 buffer saline with 0.1% Tween 80. Biodistribution studies in tumor-bearing mice revealed higher retention time and tumor targeting from these carriers as compared to Taxol® injection (Li et al. 2012).

Magnetically assisted paclitaxel solid lipid nanoparticles containing magnetite and glyceryl monostearate were investigated. The melting point reduction from 56 to 43 °C was observed after the formation of solid lipid nanoparticles. Magnetic hyperthermia assisted drug release occurs as a response to altered temperature upon magnetic field change (Moros et al. 2019). The size of these nanoparticles was found to be 277 nm. The nanoparticles released drug faster at 43 °C but only 20% at room temperature. Magnetic hyperthermia-induced more than 75% drug release from these nanoparticles whereas only 10% drug was released from normal nanoparticles (Oliveira et al. 2018).

Enzyme cleavable paclitaxel solid lipid nanoparticles were prepared using soy phosphatidylcholine and glyceryl monostearate. These were fabricated by conjugation of polyethylene glycol-conjugated peptide that is cleaved by a metalloprotease. These nanoparticles exhibited sustained drug release over a period of 200 h in pH 7.4 phosphate buffer with 0.1% Tween 80 at 37 °C. These nanoparticles exhibited higher cytotoxicity in the HT1080 cell line as compared to Taxol®. *In vivo* pharmacokinetic study of these nanoparticles in C57BL/6 N mice after incorporation of a fluorophore, dioctadecyl-3, 3, 3', 3'-tetramethylindodicarbocyanine and 4-chlorobenzenesulfonate salt exhibited 50% fluorescence after 10 h post-injection. The unmodified solid lipid nanoparticles were cleared within 4 h of injection in mice (Zheng et al. 2014).

Photosensitive paclitaxel solid lipid nanoparticles composed of a photosensitive material aluminum 1,8,15,22 tetrakis (phenylthio) 29H, 31H-phthalocyanine soy phosphatidylcholine, Pluronic F68 and ascorbic acid were prepared. These nanoparticles exhibited drug release as a consequence of the breakdown of lipids by

near-infrared light of 730 nm wavelength. The half-maximal inhibitory concentration of these nanoparticles was 20-fold reduced than Taxol® in A549 cells (Meerovich et al. 2019).

6.6 Microparticulate Delivery System

Microparticles are defined as particulate dispersions or solid particles with a size in the range of 1–1000 μm . The drug is entrapped or encapsulated in a micro-particulate matrix. Microparticles are prepared by spray drying, emulsion polymerization, solvent evaporation, and fluidized bed coating. This microencapsulation strategy gives protection of the drug from the environment, stabilization of sensitive drug substances and masking of unpleasant taste. Hence, microparticles can play an essential role for sustained release, controlled release, enhancing bioavailability and reducing side effects of drugs (Madhav and Kala 2011).

6.6.1 Biodegradable Microparticle-Based Delivery System

Biodegradable polymers comprised of monomers linked to one another through functional groups and have unstable links in the backbone. They are degraded into biologically acceptable molecules in the body. Some common examples of biodegradable polymers are poly (glycolic acid), poly (ϵ -caprolactone), poly (lactic-co-glycolic acid), chitin, cellulose and alginic acid (Vroman and Tighzert 2009).

Biodegradable paclitaxel microparticles composed of poly (D, L-lactide) were reported. The particle size of microparticles and encapsulation efficiency were found to be 4.6 μm and 90% respectively. Cytotoxicity study using U251 human glioma cells exhibited a 70% reduction in cell viability after 120 h (Song et al. 2010).

Biodegradable paclitaxel composite microparticles composed of poly (lactic-co-glycolic acid) have been reported. The yield and entrapment efficiency were found to be $73.06 \pm 1.94\%$ and $29.27 \pm 1.09\%$ respectively. Cytotoxicity study revealed that paclitaxel loaded Poly (lactic-co-glycolic acid)-silica microparticles exhibited higher cytotoxicity than those without silica in HeLa cancer cells (Nanaki et al. 2017).

6.6.2 Targeted Microparticles-Based Delivery System

Paclitaxel microparticles composed of Pluronic F-127, Poly (ethylene glycol)-2000 and stearic acid were reported for passive targeting. The particle size of microparticles and encapsulation efficiency were found to be $1.76 \pm 0.37 \mu\text{m}$ and 94.73% respectively. The microparticles exhibited higher cytotoxicity in an *in vitro* study

using SKOC-3 ovarian cancer cells than Taxol® (Han et al. 2019). Paclitaxel loaded microparticles composed of folic acid, chitosan and 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide were used for active targeting. Folic acid-containing microparticles of paclitaxel showed higher cytotoxicity than unmodified microparticles in L929 cells (Wang et al. 2016).

6.6.3 Stimuli Sensitive Microparticles-Based Delivery System

Stimuli are a state of responsiveness to sensory stimulation or excitability. Stimuli sensitive systems deal with the changes in the physiology of the body with respect to the environment changes. These systems are beneficial for the controlled and sustained delivery of the drug in the body (Bhardwaj et al. 2015). Stimuli responsible drug release can be changed in pH, temperature and magnetic field. Magnetically assisted delivery is a novel approach for delivery of drugs using engineered smart microcarriers which overcome a number of limitations facing current methods of delivering medicines. The drug is formulated into a pharmaceutically stable formulation which is usually injected through the artery that supplies the target organ or tumor in the presence of an external magnetic field (Koppiseti and Sahiti 2011).

Thermosensitive paclitaxel microparticles composed of chitosan, poly (lactide-co-glycolide), polyvinyl alcohol were developed. The particle size of microparticles was $6.38 \pm 0.13 \mu\text{m}$. These microparticles showed 63.0% reduction in tumor volume in M-234p BALB/c tumor model in comparison with non-thermosensitive microparticles (Pessoa et al. 2018). Magnetic assisted paclitaxel delivery from microparticles composed of magnetite, poly (lactic-co-glycolic acid) and polyvinyl alcohol was investigated. The particle size of microparticles and drug loading were found to be 0.7 to 5 μm and 38% respectively. *In-vitro* study in MESSA human uterine sarcoma cells showed 5% enhancement in cell killing from magnetic assisted microparticles as compared to Taxol® (Hamoudeh et al. 2008).

6.7 Emulsion-Based Delivery System

Emulsions are liquid biphasic systems in which one phase is dispersed in another immiscible phase. Emulsions are stabilized by the aid of emulsifying agents. This delivery system can be utilized for administration of poorly water-soluble drugs (Goodarzi and Zendeboudi 2019). Microemulsions can be defined as a thermodynamically stable, isotropically clear dispersion of two immiscible liquids. Globule size of microemulsion ranges from 10 to 200 nm. Microemulsions are stabilized by a mixture of surfactants namely, surfactant and co-surfactant (Lawrence and Rees 2000). On the other hand, nanoemulsions are kinetically stable, isotropically clear systems containing two immiscible liquids. The globule size ranges from 50 to 500 nm (Jaiswal et al. 2015). Microemulsions are formed by self-assembly whereas

nanoemulsions are formed by mechanical shear. Emulsions can be administered by oral or parenteral routes.

6.7.1 *Simple Emulsion-Based Delivery System*

Simple emulsions are made up of a single lipid or a blend of lipid or oil, an emulsifying agent and water. Paclitaxel oleate, a prodrug of paclitaxel, was incorporated in a phospholipid-based oil-in-water emulsion. The oil phase was comprised of egg phosphatidylcholine, triolein, dipalmitoyl phosphatidylethanolamine and stabilized by polysorbate 80 and oleyl chloride. Upon intravenous administration of the emulsion in rabbits, improved biodistribution and cytotoxicity was obtained as compared to Taxol[®] (Lundberg et al. 2003).

Two microemulsions of paclitaxel were prepared composed of lecithin, butanol, myvacet oil, water and capmul, myvacet oil, water respectively. Both of the systems were less cytotoxic and less hemolytic as compared to commercial Taxol[®]. A comparatively higher amount of drug i.e. 12 mg paclitaxel per gram of emulsion could be loaded in the microemulsions due to the high solubility of paclitaxel in the oil phase (Nornoo and Chow 2008). The microemulsions have shown the slow and sustained release of the drug as compared to Taxol[®]. *In vivo* pharmacokinetic study in rats after intravenous administration revealed that plasma half-life and biodistribution were improved as compared to Taxol[®] (Nornoo et al. 2008).

Paclitaxel incorporated nanoemulsion of paclitaxel was designed using medium-chain triglyceride as oil phase and Tween 80 as a surfactant. The half-maximal inhibitory concentration of paclitaxel was reduced by 18.82 times in drug-resistant MCF7 cells which indicated that paclitaxel resistance was reversed due to P-glycoprotein inhibition. Tumor volume became 10.06% in microemulsion treated animal models, as compared to paclitaxel solution (Bu et al. 2014).

Tocosol[™] is a tocopherol-based formulation of paclitaxel, manufactured by Bayer Schering Pharma. The product failed in phase III clinical trial. Abu-Fayyad and his co-workers have designed an emulsion-based formulation, similar to Tocoso[™] but substituting the tocopherol with tocoretinol. The shell of the emulsion was made up of polyethylene glycol and tocoretinol. Cytotoxicity of the nanoemulsion was checked on PANC-1 cells and Bx-PC-3 cells. The new system displayed better results than Tocoso[™] along with a reduction in the half-maximal inhibitory concentration value (Abu-Fayyad et al. 2018).

6.7.2 *Emulsion-Based System for Targeted Delivery*

Emulsion-based systems can be passively or actively targeted to tumor cells. A series of lipid nanoemulsion of paclitaxel was prepared by taking medium and long-chain glycerides, oleic acid as oil phase, Tween 80 and polyethylene glycol as a

surfactant. The nanoemulsions have shown stronger cytotoxicity against MCF7 cells. *In vivo* study in mice revealed that the nanoemulsion had improved biodistribution and intratumor accumulation than Taxol®. The improved activity was correlated to enhanced permeability and retention effect (Chen et al. 2017a, b).

Hyaluronic acid serves as a targeting ligand for CD44 overexpressing cancer cells. Hyaluronic acid-coated nanoemulsion, loaded with paclitaxel was prepared for the treatment of ovarian cancer. D, L- α -tocopheryl acetate, soybean oil was taken as oil phase whereas polysorbate 80 was used as a surfactant. The drug loading was found to be 3.75%. Cell affinity studies in SK-OV-3 and OVCAR-3 cells revealed that hyaluronic acid coated nanoemulsion had 10 times higher targeting ability than uncoated nanoemulsion (Kim and Park 2017).

6.7.3 Self Emulsifying Drug Delivery System

Self emulsifying drug delivery systems are made up of a mixture of oil, surfactant, solvents and can be administrated orally by encapsulating in gelatin capsules. After reaching the gastrointestinal tract, these systems form macro or microemulsions. These systems can protect drugs which are prone to enzymatic hydrolysis in the gastrointestinal tract. It results in the enhanced oral bioavailability of poorly soluble drugs (Gursoy et al. 2003).

A series of self-microemulsifying oily formulations were evaluated for their potential for oral delivery of paclitaxel. The self-emulsifying formulations were made up of different concentrations of paclitaxel, D-alpha tocopheryl polyethylene glycol 1000 succinate, tyloxapol, ethanol, docusate sodium and cyclosporin A. *In vivo* study in P-glycoprotein knockout mice and wild type mice revealed that bioavailability of paclitaxel was similar to Taxol® after oral administration of the formulations. Efficacy of the formulations was improved due to the presence of cyclosporin A and a P-glycoprotein inhibitor (Oostendorp et al. 2011).

Paclitaxel loaded self-nanoemulsifying drug delivery system was developed using tocopheryl polyethylene glycol succinate as oil; labrasol as a surfactant; lauroglycol 90 as co-surfactant and ethanol as co-solvent. It showed higher cytotoxicity in MDA-MB-231 cells than Taxol®. Drug release from the self-nano emulsifying system has shown sustained release. Survivin, a member of the inhibitor of apoptosis family, was downregulated by the system due to the presence of tocopheryl polyethylene glycol succinate. Its oral bioavailability was 4-fold higher than Taxol® (Meher et al. 2018).

6.8 Solid Dispersion-Based Delivery System

Solid dispersions are a dispersion of drug in the amorphous polymeric matrix. The purpose of solid dispersions is to enhance drug solubility and to stabilize the drug (Huang and Dai 2014). Paclitaxel solid dispersion composed of hydroxypropyl

β -cyclodextrin, polyvinyl pyrrolidone, α -tocopherol and polyoxyl 40 hydrogenated castor oil prepared by a supercritical antisolvent process which exhibited a 3-fold increase in solubility as compared to Taxol[®]. This solid dispersion exhibited higher tumor growth inhibition as compared to Taxol[®] up to 90 days in female athymic nude mice bearing MDA-MB-231 cancer (Shanmugam et al. 2011). In another study, solid dispersion of paclitaxel referred to as Modrapac001 formulation which was prepared from polyvinyl pyrrolidone K30 and sodium lauryl sulfate. This ternary solid dispersion exhibited a multifold increase in drug dissolution (Moes et al. 2013).

6.9 Cyclodextrin-Based Delivery System

Cyclodextrins are cyclic oligosaccharides of glucose having α -1, 4 glycosidic bonds. It has 6, 7 or 8 units present in α , β and γ derivatives respectively. Cyclodextrins have truncated cone shape wherein the inner cavity is hydrophobic and the outer surface is hydrophilic. Water-insoluble molecules can be incorporated into the hydrophobic cavity of cyclodextrins and they enhance the solubility and/or stability of the molecule. pH-sensitive paclitaxel nanoparticles were prepared using acetylated α -cyclodextrin by oil/water solvent evaporation method. These nanoparticles exhibited faster release i.e. 83% in 8 h in pH 5.0 but slower drug release in pH 7.4 phosphate buffer. The cellular uptake in B16F10 cells exhibited complete cellular uptake within 4 h from pH-sensitive nanoparticles. These nanoparticles exhibited better effectiveness in tumor inhibition *in vivo* in the melanoma-bearing nude mouse model than the plain drug itself (He et al. 2013).

Poly (anhydride) oral nanoparticles containing a complex of paclitaxel in β -cyclodextrin were developed. The drug loading was negligible with the drug per se but it was increased 2 to 4-fold after complexation of the drug in the nanoparticles. These nanoparticles exhibited 83% relative bioavailability with respect to Taxol[®] in rats. Hence, these nanoparticles could be useful for parenteral to oral switch of paclitaxel (Agüeros et al. 2010). In another study, when paclitaxel was incorporated into 2, 6 dimethyl β -cyclodextrin complex, the solubility was increased to 2.3 mM (Hamada et al. 2006).

Poly (acrylic acid)-co- β -cyclodextrin was used to prepare paclitaxel nanoparticles. The nanoparticles exhibited 170 nm size and 100-fold solubility enhancement. The nanoparticles showed sustained release at pH 7.4 phosphate buffer over a period of 120 days. *In vivo* imaging in mice for these nanoparticles revealed their accumulation in the tumor for 144 h due to enhanced permeability and retention effect. *In vivo* antitumor study in H22 tumor-bearing mice exhibited higher antitumor activity and 50 days of survival time than that of Taxol[®] (Yuan et al. 2016).

Folate-conjugated cyclodextrin nanoparticles of paclitaxel were used for targeted delivery to tumor cells. Cytotoxicity study in the 4T cell line exhibited higher cytotoxicity than that of Taxol[®]. The survival rate of these nanoparticles was longer than that of Taxol[®] in 4T cell-bearing mice (Erdoğan et al. 2018).

6.10 Implant-Based Drug Delivery System

Implants are sterile solid masses consisting of a drug made by compression or moulding. These provide a controlled delivery of drug over a period of time at the site of implantation. Implantation can be done under the skin into the subcutaneous tissue called subcutaneous implant. Two types of implants are available such as biodegradable and non-biodegradable implants. Implants are prepared by compression, moulding or extrusion. The advantages are controlled drug delivery with the minimized side effects (Zaki et al. 2012).

6.10.1 Biodegradable Implant

The advantages of biodegradable systems include polymers used in implants are inert and are converted into nontoxic components such as carbon dioxide and water. There is no need for surgical removal of implants after the therapy. The polymers used in biodegradable implants are polylactic acid, poly (lactide-co-glycolide) and chitosan (Rajgor et al. 2011).

Biodegradable implants of paclitaxel composed of poly (ϵ -caprolactone), polyethylene glycol 6000 were reported. The drug loading was found to be 93%. *In vitro* study showed 79% drug release after 30 days in pH 7.4 phosphate buffer saline (Hiremath et al. 2013). Biodegradable chitosan-based film implants of paclitaxel composed of chitosan, lysozyme, Tween 80 and Poloxamer 407 were reported. The drug loading and *in vitro* release in pH 7.4 phosphate buffer saline after 6 h were 31% and 10% respectively. *In vivo* study using Swiss mice revealed that the implant was biodegradable as it lost the integrity and identity after 50 days (Dhanikula and Panchagnula 2004). Biodegradable microfiber implants of paclitaxel composed of poly (D, L lactide-co-glycolide) were investigated. The drug loading and encapsulation efficiency were found to be 8.92% and 98% respectively. *In vitro* release study showed 16% drug release after 9 days in pH 7.4 phosphate buffer saline (Ranganath and Wang 2008).

Biodegradable stent coating to paclitaxel implants composed of poly (lactic-co-glycolic acid) and poly (vinyl alcohol)-graft-poly (lactic-co-glycolic acid) were reported. The drug loading was found to be 10%. *In vitro* release study showed 64% drug release after 48 days in pH 7.4 phosphate buffer saline (Westedt et al. 2006).

6.10.2 Non-biodegradable Implant

Non-biodegradable implants are used to administer medications. It is useful for patients who need treatment for chronic diseases. These implants need to be removed surgically once the medication has been released. These implants are not designed to be metabolized by the body. These implants start to work immediately upon

insertion and can continue releasing drug doses in a controlled manner over the years. The polymers used in non-biodegradable implants are poly (methyl methacrylate), thermoplastic polyurethane and poly (ethylene vinyl acetate (Stewart et al. 2018).

Non-biodegradable stent implants of paclitaxel composed of poly (methyl methacrylate), 316 L stainless steel stents; poly (n-butyl methacrylate) and poly (ethylene-co-vinyl acetate) were reported. *In vitro* study showed 60% drug release after 14 days in pH 7.4 phosphate buffer solution (Shaulov et al. 2009). In another study, non-biodegradable stent implants of paclitaxel composed of 316 L stainless steel stents, N-(2-carboxyethyl) pyrrole and butyl ester of N-(2-carboxyethyl) pyrrole were reported. *In vitro* study showed 50% drug release after 30 days in pH 7.4 phosphate buffer solution (Okner et al. 2009).

6.10.3 Site-Specific Implant-Based Delivery System

Targeting to a particular organ or site is a smart approach for delivery of biologically active agents. It enhances the therapeutic efficacy of the drugs and reduces the drug concentration in non-target organs or sites. It can be very useful for the delivery of anticancer drugs to a particular site (Himri and Guaadaoui 2018).

Urinary tract tumor-specific implant of paclitaxel composed of poly(ϵ -caprolactone) resin PCL 787, alginate sodium salt, and gelatin were reported. *In vitro* release study exhibited complete drug release after 72 h in pH 5.5 artificial urine solution. *In-vitro* study in T24 cell line revealed the half-maximal inhibitory concentration of 7.3 ng/ml after 72 h. The tumor growth inhibition from paclitaxel implant was 75% in T24 cells (Barros et al. 2016).

Ovarian tumor-specific implant of paclitaxel composed of chitosan, phosphatidylcholine and 3-(4, 5- dimethyl-2-thiazolyl)-2, 5-diphenyl-[2H]-tetrazolium bromide) was reported. *In-vitro* study in SKOV-3 cells showed half-maximal inhibitory concentration of 0.211 $\mu\text{m}/\text{mL}$ of these paclitaxel implant (Ho et al. 2005).

The tracheal tumor-specific implant of paclitaxel composed of Carbopol 974P, ethylene-vinyl acetate was reported. Carbapol 974P was chosen for mucoadhesive effect in the trachea. *In vitro* release study showed 77% drug release after 85 days in pH 7.8 phosphate buffer solution with 0.5% sodium dodecyl sulfate (Jin et al. 2018a, b).

6.10.4 Stimuli Sensitive Implant

Stimuli sensitive paclitaxel implants composed of poly (D, L lactide-co-glycolide), polyethylene glycol and Tween 80 were reported. The irradiation was performed using Cobalt 60 isotope to enhance the drug release. *In vitro* study showed 10% drug release after 6 h in pH 7.2 phosphate buffer solution (Wang et al. 2003).

6.10.5 *In-Situ Forming Implants*

In-situ implants are a potential alternative strategy to preformed implants and they avoid surgery. They are injected as a low viscous solution and transform in the body to a gel or solid depot due to phase separation or lowered solubility (Kempe and Mäder 2012). The *in-situ* forming implant of paclitaxel composed of polyethylene glycol, trimethylene carbonate and glycolide was reported. *In vivo* study of this implant in the mouse flank model exhibited higher antitumor efficacy than that of Taxol® (Olbrich et al. 2012). *In situ* forming injectable paclitaxel implant composed of n-butyl-2-cyanoacrylate and ethyl oleate was reported. It was based on the sol-gel transition. *In vitro* drug release in pH 7.4 sodium salicylate solution exhibited 25% from the implant versus 91% from Taxol® after 6 days. Fifty percent of the implant was degraded in female ICR mice after 8 weeks and hence it was biodegradable. The tumor inhibition in mice bearing human MDA-MB-231 was 80% whereas it was 44% in Taxol® treated mice (Wu et al. 2017).

6.11 Prodrug-Based Delivery System

The prodrug is defined as an inactive form of a drug, which is converted to a pharmacologically active form upon metabolism inside the body. Various prodrugs of paclitaxel have been designed in order to alter its physicochemical properties to make it suitable for delivery systems.

6.11.1 *Small Molecule-Based Prodrug Delivery System*

Small molecules such as malic acid, squalene and silicate-based prodrugs of paclitaxel have been developed in the past. The hydrophilic prodrug of paclitaxel was synthesized by incorporation of dihydroxyl derivative using solketal chloroformate. The prodrug exhibited pH-sensitive hydrolysis at the acidic condition. The prodrug exhibited 50 times higher water solubility than the unmodified drug. The prodrug exhibited a 2.5-fold higher maximum tolerable dose as compared to the unmodified drug in Balb/c mice (Niethammer et al. 2001). Silicate ester prodrugs of paclitaxel were synthesized and loaded into poly (ethylene glycol)-b-poly(lactide-co-glycolide) nanoparticles by using flash nanoprecipitation method. The drug loading was found to be 74%. The silicate ester was sensitive to acidic condition leading to hydrolysis followed by drug release. These prodrugs exhibited a 10-fold reduction in half-maximal inhibitory concentration in the cell lines (Han et al. 2015).

The lipidic prodrug of paclitaxel was prepared with lipophilic squalenoyl derivative to increase its lipid affinity. The prodrug was further converted into

multilamellar vesicles using 1,2-dimyristoyl-sn-glycero-3-phosphocholine. The prodrug could enhance the loading of the drug into vesicles (Sarpietro et al. 2012).

6.11.2 Peptide-Based Prodrug Delivery System

Peptides such as octreotide and Ac-Cys-Arg-Gly-Asp-Arg-NH₂ (Papas et al. 2007) have been used to prepare paclitaxel prodrugs. Octreotide based paclitaxel prodrug was prepared to increase the hydrophilicity of the drug that resulted in 20,000 times solubility enhancement in water than an unmodified drug. The prodrug exhibited sustained drug release over a period of 168 h and faster drug release in acidic pH. *In vitro* cytotoxicity study in NCI-H446 cells revealed 2.6-fold lower half maximal inhibitory concentration for the octreotide prodrug as compared to the unmodified drug. *In vivo* antitumor growth inhibition study in NCI-H446 xenograft model exhibited 1.22 times higher antitumor effect of peptide prodrug than that of Taxol® (Huo et al. 2015).

6.11.3 Polymer-Based Prodrug Delivery System

The drug is attached to the polymer chemically either directly or via a spacer. The nature of the polymer and spacer determines the site of release of the drug from the prodrug and its release kinetics (Ringsdorf 1975). The molecular weight of the polymer should be up to 40,000 Da to aid the filtration by kidneys (Hoste et al. 2004). Poly-(γ -L-glutamyl glutamine) conjugate of paclitaxel was developed which showed a 3-fold reduction of tumor growth in NCI-H460 human lung cancer cells than Abraxane® (Feng et al. 2010). Oligo (lactide)₈-paclitaxel prodrug composed of poly (ethylene glycol)-b-poly (D, L lactic acid) was reported. Paclitaxel loaded into poly (ethylene glycol)-b-poly (lactic acid) exhibited the issue of stability and faster elimination from the body. *In vitro* cytotoxicity study in 4T1-Luc breast cancer cells for the drug-loaded synthesized polymer exhibited lower half maximal inhibitory concentration than the plain drug (Tam et al. 2019).

6.11.4 Targeted Prodrug Delivery System

The targeted prodrug of paclitaxel composed of folic acid, distearoyl phosphatidylcholine, triolein cholesteryl oleate and polyethylene glycol was reported. *In vitro* study showed 10% drug release after 24 h in pH 7.4 phosphate buffer solution. *In-vitro* study in KB, M109 and CHO cell line revealed higher cytotoxicity compared to Taxol®. *In vivo* antitumor efficacy in Balb/c mice revealed that folic acid

conjugated with paclitaxel containing cholesteryl oleate exhibited higher antitumor efficacy compared to Taxol® (Stevens et al. 2004).

The targeted prodrug of paclitaxel composed of hyaluronic acid, diphenylphosphinic chloride, adipic acid dihydrazide and succinic anhydride was synthesized. *In vitro* study in H22 cell line revealed higher cytotoxicity compared to paclitaxel alone. *In vivo* antitumor study in H22 tumor-bearing mice revealed a 4-fold decrease in tumor growth compared to paclitaxel alone (Xu et al. 2015a, b).

Arg-Gly-Asp peptide-based targeting of paclitaxel prodrug composed of poly (lactic-co-glycolic acid), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, Soybean lecithin and 3, 3'-dithiodipropionic acid was prepared. *In vivo* antitumor study in lung tumor-bearing mice revealed peptide modified paclitaxel had higher antitumor efficacy compared to free paclitaxel (Wang et al. 2018).

6.11.5 Stimuli-Sensitive Prodrug Delivery System

Prodrug based pH-sensitive paclitaxel micelles prepared using poly (ethylene glycol), 2-hydroxyethyl vinyl ether and acryloyl chloride was reported. The drug loading capacity was found to be 60.3%. *In vitro* study in HeLa and MDA-MB-231 cells exhibited higher antitumor activity in poly (ethylene glycol) conjugated paclitaxel compared to paclitaxel alone (Huang et al. 2018).

The photosensitive prodrug of paclitaxel composed of folic acid and polyethylene glycol was reported. The prodrug of paclitaxel was activated by the far-red light. *In vitro* study in SKOV-3 cells exhibited folic acid conjugated and photosensitive prodrug of paclitaxel with polyethylene glycol exhibited more cytotoxicity than non-conjugated paclitaxel (Thapa et al. 2017).

The redox-sensitive prodrug of paclitaxel composed of methoxy polyethylene glycol amine, N-hydroxysuccinimide, 4-dimethylaminopyridine and 3, 3'-dithiodipropionic acid was reported. These polymeric paclitaxel conjugates were structurally confirmed by ¹H NMR and exhibited an approximately 23,000-fold increase in water solubility over parent paclitaxel. *In vivo* studies on NCI-H466 tumor-bearing nude mice exhibited that redox-sensitive prodrug of paclitaxel conjugates possessed superior tumor targeting ability and antitumor activity compared to Taxol® (Yin et al. 2015).

6.12 Hybrid Delivery System

Liposomes, micelles, polymeric nanoparticles, and lipid-based nanoparticles are some of the most explored delivery systems for paclitaxel. Each of these systems exhibit some inherent problems. Difficulties allied to these systems can be minimized by combining two or more of these systems which can be defined as a hybrid drug delivery system.

Bao and co-workers have developed such a hybrid system by combining gold nanoparticles and liposomes. A thiol-terminated polyethylene glycol-paclitaxel derivative was covalently attached on the surface of gold nanoparticles followed by the incorporation of the conjugate in the phospholipid bilayer region of the liposomes. Due to this, the drug loading was increased to 50.4%. *In vitro* study exhibited 50% drug release in 7.4 pH phosphate buffer solutions. The hybrid system exhibited prolonged circulation of the drug and increased accumulation in the liver as compared to Taxol[®]. Improved pharmacokinetic properties of the system were attributed to the protective shell of the liposomes (Bao et al. 2014).

In another study, hybrid liposomes were prepared by incorporating paclitaxel loaded polyionic micelles. The micelles were made up of positively charged Pluronic F127- poly (ethyleneimine) copolymer and negatively charged sodium cholate whereas the liposomes were composed of phospholipid. The drug loading of the final system was found to be 5.45%. It was able to sustain the release of paclitaxel. Cellular uptake of the system by multidrug-resistant breast cancer cells was significantly higher which can be attributed to the P-glycoprotein inhibitory potential of Pluronic F127. Formation of liposome not only allowed intestinal absorption of paclitaxel but also stabilized the drug from gastric degradation. The absolute oral bioavailability of paclitaxel in hybrid liposomes was found to be 37.91% (Li et al. 2017a, b, c).

Silica coated liposomes of paclitaxel were developed by Ingle and co-workers, named as liposils. Stability study of 6 months revealed that the liposils were more stable than corresponding liposomes. *In vitro* release study showed silica coating was able to retard the drug release from the liposils. The liposils also exhibited *in vivo* release of paclitaxel over a longer duration than corresponding liposomes and Taxol[®]. Biodistribution study in B16F10 cells revealed that accumulation of liposils and liposomes was significantly higher in the tumor cells as compared to that of Taxol[®] (Ingle et al. 2018).

6.13 Miscellaneous Delivery System

Miscellaneous drug delivery systems for paclitaxel based on dendrimer, exosomes, dry powder inhalations, and hydrogels are discussed in this subsection.

6.13.1 Dendrimer-Based Delivery System

Dendrimer-based paclitaxel delivery composed of methoxy polyethylene glycol-succinimidyl carboxymethyl ester, N-ethyl diisopropylamine, poly (amidoamine), α -tocopheryl succinate and polyethylene glycol was reported. The diameter and entrapment efficiency were found to be 31.19 ± 0.07 nm and $78.33 \pm 2.81\%$ respectively. *In vitro* study showed 63.97% drug release after 36 h in pH 7.4 phosphate

buffer saline. *In vitro* cytotoxicity study in B16F10 and MDA MB231 cells demonstrated that the paclitaxel loaded methoxy polyethylene glycol-succinimidyl carboxymethyl ester, N-ethyl diisopropylamine, poly (amidoamine), α -tocopheryl succinate and polyethylene glycol exhibited higher cytotoxicity compared to free paclitaxel (Bhatt et al. 2019).

Dendrimer-based paclitaxel delivery composed of azido-cyanine 5.5, N, N-diisopropylethylamine, and N, N, N', N'-tetramethyl – (1H-benzotriazol-1-yl) uranium hexafluorophosphate was reported. The diameter and drug content were found to be 74 nm and 20.9% respectively. *In vitro* cytotoxicity study in 4T1, 3T3 and C2C12 exhibited higher cytotoxicity than paclitaxel injection (Li et al. 2017a, b, c).

6.13.2 Dry Powder Inhalation-Based Drug Delivery

Dry powder inhalation formulation based on paclitaxel micelles composed of folic acid, polyethylene glycol and dextran was reported. The particle size and entrapment efficiency of the micelles were found to be 57 ± 2 nm and $99 \pm 2\%$ respectively. *In vitro* release study from the micelles showed 70% drug release after 24 h in pH 5.0 phosphate buffer. *In-vitro* study of the micelles in M109-HiFR cell line revealed 2-fold reduction of the half-maximal inhibitory concentration as compared to that of Taxol[®]. The formulation exhibited a fine particle fraction upto 50% with good redispersibility in physiological buffer (Rosière et al. 2016).

6.13.3 Exosomes

Exosomes of paclitaxel isolated from raw milk of Jersey cows were reported. The particle size and loading efficiency were found to be 108 nm and 8% respectively. *In vitro* study showed 90% drug release after 48 h in pH 5.0 fed-state simulated-gastric fluid. *In vivo* antitumor efficacy of exosomes of paclitaxel using athymic nude mice bearing subcutaneous lung cancer A549 xenografts exhibited higher cytotoxicity compared to paclitaxel alone (Agrawal et al. 2017).

6.13.4 Hydrogel-Based Delivery System

Thermosensitive hydrogel formulation of paclitaxel composed of chitosan, β -glycero phosphate and sodium dodecyl sulfate. *In vitro* release study showed 92% drug release after 30 days in pH 7.4 phosphate buffer saline. *In vivo* antitumor efficacy of hydrogel formulation of paclitaxel in EMT-6 tumors implanted subcutaneously on Balb/c mice exhibited 4-fold higher efficacy than Taxol[®] (Ruel-Gariépy et al. 2004).

Self-assembled paclitaxel hydrogel of composed of folic acid, hydroxyl benzo-triazole, alkaline phosphatase and 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetra-zolium bromide was reported. The hydrodynamic diameter and zeta potential were found to be 137.3 ± 15.2 nm and 43.8 ± 3.2 mV respectively. *In vitro* study in HepG2 cells exhibited higher cytotoxicity compared to free paclitaxel. *In vivo* anti-tumor study in nude mouse model exhibited enhanced anticancer efficacy compared to free paclitaxel. *In vivo* real-time imaging further demonstrated that the hydrogel preferentially accumulated in tumor site (Shu et al. 2017).

6.14 Conclusion

Poor solubility and permeability of Paclitaxel have compelled formulation scientists to commercialize it as injectable products such as Taxol[®], Genexol PM[®], and Abraxane[®]. Newer delivery systems like micelles, nanoparticles, liposomes, lipid systems that can overcome the issues associated with the commercial products of paclitaxel have been discussed. Some of these systems have utilized specific materials to impart stimuli sensitivity, targeting or functionality. The highest solubility enhancement has been shown by prodrugs, mixed micelles, cyclodextrin complexes and solid dispersions for paclitaxel. Drug loading could be increased in implants, nanoparticles, emulsions and lipid systems of paclitaxel. Implant and cyclodextrin complexes of paclitaxel exhibited sustained release characteristics for a prolonged period of time. The half-maximal inhibitory concentration of paclitaxel was reduced substantially in the case of micelles, emulsions, nanoparticles. Enhancement in oral bioavailability was found to be best in nanoparticles. More efficient tumor growth inhibition was found in cases of emulsion, liposome, prodrug and nanoparticulate delivery system as compared to that with Taxol[®]. Non-invasive oral systems of paclitaxel such as DHP107 and Oraxol[®] are under clinical evaluation.

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