



Paclitaxel Nanoparticles - An Approach to Improve the Bioavailability

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Accepted on: 03-05-2014; Finalized on: 30-06-2014.

ABSTRACT

Numerous investigations have shown that both tissue and cell distribution profiles of anticancer drugs can be controlled by their entrapment in submicronic colloidal systems (nanoparticles). The rationale behind this approach is to increase antitumor efficacy, while reducing systemic side-effects. Over the past three decades, taxanes represent one of the most important new classes of drugs approved in oncology. Paclitaxel (PTX), the prototype of this class, is an anti-cancer drug approved for the treatment of breast and ovarian cancer. However, notwithstanding a suitable premedication, present-day chemotherapy employing a commercial preparation of PTX (Taxol®) is associated with serious side effects and hypersensitivity reactions. For the past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Generally, both *in vivo* mice tumor models and human clinical trials demonstrated that PTX nanoparticulate formulations significantly increase a maximum tolerated dose (MTD) of PTX which outperform that for Taxol®. Moreover, certain types of nanoparticles showed some interesting capacity to reverse MDR resistance, which is a major problem in chemotherapy. The purpose of this review is to present the physicochemical properties and pharmacokinetic characteristics of paclitaxel, then to cover nanoparticulate formulation attempts designed to overcome its bioavailability limitations.

Keywords: Bioavailability, cancer, drug delivery, nanoparticles, Paclitaxel, targeting.

INTRODUCTION

Localized delivery of chemotherapeutic agents has long been the aim of clinical cancer therapy to limit the indiscriminate activity of many anti-cancer drugs on rapidly dividing cells, including normal tissues. The ideal delivery system is envisioned to selectively and efficiently transport the anticancer drug to the target organ/cells. It will not only minimize the side effects associated with inappropriate drug distribution, but will also enhance therapeutic efficacy by localizing the drug concentration and reduce therapeutic cost by requiring a smaller drug dose.

Taxanes are complexes of diterpenoid natural products and semisynthetic analogs. Presently, these drugs belong to prominent anticancer agents used for combined chemotherapy.¹ Paclitaxel (Fig. 1) (PTX, the chemical name is 5 β ,20-epoxy-1,2 α ,4,7 β ,10 β ,13 α - hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine), the prototype of this class, derived from the bark of the Pacific yew tree *Taxus brevifolia*.² It has been shown to exhibit such a significant activity against various solid tumors, including ovarian, breast, nonsmall cell lung cancer, head and neck carcinomas etc. that paclitaxel was hailed by National Cancer Institute as the most significant advance in chemotherapy of the 20 years.³ The taxanes exert their cytotoxic effect by arresting mitosis through microtubule stabilization, resulting in cellular apoptosis.² However, significant toxicities, such as myelosuppression and

peripheral neuropathy, limit the effectiveness of paclitaxel-based treatment regimens.³⁻¹¹

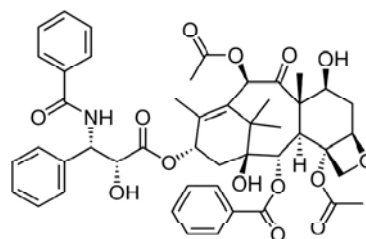


Figure 1: Structural formula of Paclitaxel molecule

Physicochemical and Pharmacokinetic properties of paclitaxel

Paclitaxel is white to off-white crystalline powder. It is highly lipophilic, insoluble in water and melts at around 216–217 °C. Its disappearance from plasma is found to be biphasic.⁴ The initial rapid decline represents distribution to the central compartment and elimination of the drug and the later phase is due in part, to the efflux of the drug from the peripheral compartment.⁵ Generally accepted dose is 200–250 mg m⁻² and is given as 3 and 24 h infusion. Pharmacokinetics of paclitaxel shows wide variability. Terminal half-life was found to be in the range of 1.3–8.6 h (mean 5 h)⁶ and the steady-state volume of distribution was found to be ~87.1 m⁻². The drug undergoes an extensive P-450 mediated hepatic metabolism and less than 10% drug in the unchanged form is excreted in the urine. Most of the drug is eliminated in feces. More than 90% of the drug binds

rapidly and extensively to plasma proteins.^{7,8} The highest concentration of the paclitaxel following a 6-h infusion in rats was found to be in lung, liver, kidney and spleen and was essentially excluded from brain and testes.⁹

Solubility

Paclitaxel is poorly soluble in an aqueous medium, but can be dissolved in organic solvents. Its solutions can be prepared in a millimolar concentration in a variety of alcohols, such as methanol, ethanol, tertiary-butanol as well as in DMSO. Non-aqueous solubility is found to be ~46 mM in ethanol, ~20 mM in methylene chloride or acetonitrile, ~14 mM in isopropanol.¹⁰ Numbers of reports have been published on the solubility of paclitaxel and acceptable value of aqueous solubility is 0.6 mM.^{11,12} Moreover, paclitaxel lacks functional groups that are ionisable in a pharmaceutically useful range and therefore manipulation in pH does not enhance its solubility. Furthermore, common approaches to improve solubility like addition of charged complexing agents or by producing alternate salts of the drug are not feasible in the case of paclitaxel.¹³

Neoplastic tissues may be divided into three subcompartments: vascular, interstitial and cellular. The vascularization of tumors is heterogeneous, showing regions of necrosis or hemorrhages as well as regions which are densely vascularized in order to sustain an adequate supply of nutrients and oxygen for rapid tumor growth (angiogenesis).¹⁴ Tumor blood vessels present several abnormalities in comparison with normal physiological vessels, often including a relatively high proportion of proliferating endothelial cells, an increased tortuosity, a deficiency in pericytes and an aberrant basement membrane formation.^{15,16} Resulting enhanced permeability of tumor vasculature is thought to be regulated by various mediators, such as vascular endothelium growth factor (VEGF), bradykinin, nitric oxide, prostaglandins and matrix metalloproteinases.¹⁷

Macromolecular transport pathways across tumor vessels have been shown to occur via open gaps (interendothelial junctions and transendothelial channels), vesicular vacuolar organelles (VVO) and fenestrations.¹⁸ It remains, however, controversial as to which pathways are predominantly responsible for tumor hyperpermeability and macromolecular transvascular transport. Regardless of the transport mechanism, the pore cutoff size of several tumor models has been reported ranging between 380 and 780 nm.^{18,19} In vivo fluorescence microscopy has even permitted direct measurement of the extravasation of sterically stabilized liposomes into solid tumor tissue (neuroblastoma C-1300), suggesting that the cutoff size of the pores lies around 400 nm.²⁰ The tumor interstitial compartment is predominantly composed of a collagen and elastic fiber network.²¹ Interdispersed within this cross-linked structure are the interstitial fluid and macromolecular constituents (hyaluronate and proteoglycans), which form a hydrophilic gel.²¹ The interstitium, unlike most normal

tissues, is also characterized by a high interstitial pressure leading to an outward convective interstitial fluid flow, as well as the absence of an anatomically well-defined functioning lymphatic network.^{21,22} Hence, the transport of an anticancer drug in the interstitium will be governed by physiological (i.e. pressure) and physicochemical (i.e. composition, structure, charge) properties of the interstitium and by the physicochemical properties of the molecule (size, configuration, charge, hydrophobicity) itself.²¹ Thus, to deliver therapeutic agents to tumor cells in vivo, one must overcome the following problems: (i) drug resistance at the tumor level due to physiological barriers (non cellular based mechanisms), (ii) drug resistance at the cellular level (cellular mechanisms), and (iii) distribution, biotransformation and clearance of anticancer drugs in the body. In chemotherapy, clinical drug resistance may be defined either as a lack of tumor size reduction or as the occurrence of clinical relapse after an initial positive response to anti-tumor treatment.²³

First, non-cellular drug resistance mechanisms could be due to poorly vascularized tumor regions which can effectively reduce drug access to the tumor and thus protect cancerous cells from cytotoxicity. The acidic environment in tumors can also confer a resistance mechanism against basic drugs. These compounds would be ionized, preventing their diffusion across cellular membrane. High interstitial pressure and low microvascular pressure may also retard or impede extravasation of molecules.²⁴ Then, the resistance of tumors to therapeutic intervention may be due to cellular mechanisms, which are categorized in term of alterations in the biochemistry of malignant cells. They comprise altered activity of specific enzyme systems (for example topoisomerase activity), altered apoptosis regulation, or transport based mechanisms, like P-glycoprotein efflux system, responsible for the multi-drug resistance (MDR), or the multi-drug resistance associated protein (MRP).^{23,24} Finally, anticancer drugs generally feature large volumes of distribution. As cancer fighting drugs are toxic to both tumor and normal cells, the efficacy of chemotherapy is often limited by important side-effects.

A strategy could be to associate antitumor drugs with colloidal nanoparticles, with the aim to overcome non-cellular and cellular based mechanisms of resistance and to increase selectivity of drugs towards cancer cells while reducing their toxicity towards normal tissues.

Nanoparticles may be defined as being submicronic (<1 μm) colloidal systems generally, but not necessarily, made of polymers (biodegradable or not). If designed appropriately, nanoparticles may act as a drug vehicle able to target tumor tissues or cells, to a certain extent, while protecting the drug from premature inactivation during its transport. Indeed, at the tumor level, the accumulation mechanism of intravenously injected nanoparticles relies on a passive diffusion or convection across the leaky, hyperpermeable tumor vasculature.²⁵



The uptake can also result from a specific recognition in case of ligand decorated nanoparticles ('active targeting').²⁶

Hence, as the clearance via lymphatics is generally seriously compromised in neoplastic tissues, there will be an additional retention of the colloidal particles (or macromolecules with a molecular weight above 50 kDa) in the tumor interstitium. This particular concept denominated 'enhanced permeability and retention effect' (EPR) results in an important intratumoral drug accumulation which is even higher than this observed in plasma and other tissues.²⁷⁻²⁹ Furthermore, a controlled release of the drug content inside of the tumoral interstitium may be achieved by controlling the nanoparticulate structure: polymers used and the way by which the drug is associated with the carrier (adsorption or encapsulation).

This paper will review how nanoparticles loaded with Paclitaxel successfully increase drug concentration in cancer tissues, enhancing antitumor efficacy. Moreover, nanoparticles may also act at the cellular level. They can be endocytosed / phagocytosed by cells, with a resulting cell internalization of the encapsulated drug. Certain types of nanoparticles were also found to be able to overcome MDR resistance, which is due to the presence of the P-glycoprotein efflux system localized at the cancerous cell membrane.

Nanoparticles

Nowadays, targeted drug delivery systems (TDDSs) have been extensively exploited to improve the therapeutic efficiency and reduce severe side effects of anticancer drugs. Nanoparticles are prospective platform for drug delivery, due to its advantages including small size, acceptable biocompatibility, high drug encapsulation efficiency especially for hydrophobic drugs, controlled drug release manner, high cellular internalization efficiency, desired pharmacokinetics, and long circulation half-life.

A nanocarrier drug-delivery system was developed based on micelles formed by a linear PEGylated two-arm oligomer of cholic acids in aqueous solution. The loading capacity of the nanocarrier for PTX (PTX) was found to be extremely high (12.0 mg/mL), which is equivalent to 37.5% (w/w) of the total mass of the micelle. PTX release profile from the micelles was found to be burst-free and sustained over a period of seven days. PTX-loaded nanocarriers demonstrated superior anti-tumor efficacy compared to Taxol[®] at equivalent PTX dose in ovarian cancer xenograft model.³⁰

Functionalized nanoparticles

Folic acid pegylated TiO₂ nanoparticles when used as drug carriers have the ability to target cancer cells and also capable of evading the reticuloendothelial system. PEGylated nanocarriers evade the reticuloendothelial system (RES). Folic acid (FA) is used as the ligand to target

folate receptors, which are found abundant in cancer cells. The study on the loading of anticancer drug paclitaxel revealed that the titanium dioxide nanocarrier possessed a considerably higher adsorption capability. The *in vitro* release profile of paclitaxel from FA-PEG-TiO₂ nanoparticles was characterized by an initial fast release followed by a sustained release phase.³¹

Surface-functionalized poly(D, L-lactide-co-glycolide) (PLGA) nanoparticles loaded with paclitaxel were resulted in a 5-fold increase in apparent permeability (P_{app}) across Caco-2 cells. Functionalization of nanoparticles with folic acid further increased the transport (8-fold higher transport compared to free paclitaxel).³²

A functional drug carrier comprised of folic acid modified lipid-shell and polymer-core nanoparticles (FLPNPs) including poly(D,L-lactide-co-glycolide) (PLGA) core, PEGylated octadecyl-quaternized lysine modified chitosan (PEG-OQLCS) as lipid-shell, folic acid as targeting ligand and cholesterol was prepared as shown in figure 2 and evaluated for targeted delivery of paclitaxel (PTX). PTX loaded FLPNPs showed a significantly higher cytotoxicity than the commercial PTX formulation (Taxol). The intravenous administration of PTX encapsulated FLPNPs led to tumor regression and improvement of animal survival in a murine model, compared with that observed with Taxol and biodistribution study showed that PTX concentration in tumor for PTX encapsulated FLPNPs was higher than other PTX formulations. Our data indicate that PTX loaded FLPNPs are a promising nanosized drug formulation for cancer therapy.

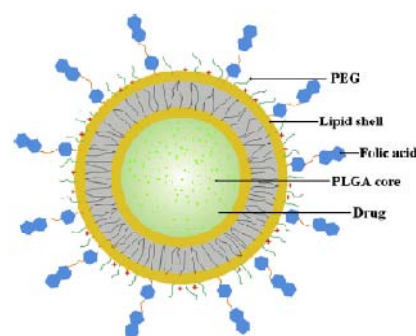


Figure 2: Schematic illustration of drug-loaded folic acid targeted nanoparticles of mixed lipid-shell and PLGA core (FLPNPs).

Intravesical paclitaxel gelatin nanoparticles showed low systemic absorption, and favorable bladder tissue/tumor targeting and retention properties with pharmacologically active concentrations retained in tumors for at least 1 week when tested in dogs. Constant drug release from paclitaxel gelatin nanoparticles overcome the problem of drug dilution by newly produced urine and the sustained drug levels in tumors may decrease treatment frequency.³³

pH-Sensitive poly(*N,N*-dimethylaminoethyl methacrylate (DMAEMA)/2-hydroxyethyl methacrylate (HEMA))

nanoparticles can be actively triggered by small, physiological changes in pH (within 0.2–0.6 pH units). Paclitaxel release was limited to 9% of the payload at pH 7.4 after a 2-h incubation at 37 °C. After adjusting to pH 6.8, 25% of the payload was released within 2 h.³⁴

Zabaleta et al., have developed pegylated nanoparticles with mucopenetrating properties in order to conduct paclitaxel onto the surface of the enterocyte. The pharmacokinetic study in mice has shown that these nanoparticles were capable to offer therapeutic plasma levels of paclitaxel up to 72 hours. In addition, the oral relative bioavailability of paclitaxel when loaded in nanoparticles pegylated with poly(ethylene glycol) 2000 (PEG) was found to be 85%. In a subcutaneous model of tumour in mice, these pegylated nanoparticles administered orally every 3 days have demonstrated a similar efficacy than Taxol (®) administered intravenously every day during 9 days. All of these results suggested that these pegylated nanoparticles were capable to cross the mucus layer of the gut and, then, reach the surface of the enterocytes. The PEG molecules would facilitate the adhesion of nanoparticles to this epithelial surface, minimise the pre-systemic metabolism of paclitaxel and, thus, promote its absorption.³⁵

Pegylated poly(anhydride) nanoparticles were also developed by Zabaleta et al., as carriers for the oral delivery of paclitaxel (PTX). The loading of PTX in pegylated nanoparticles increased between 3 and 7 times the intestinal permeability of paclitaxel through the jejunum compared with the commercial formulation Taxol. The permeability of PTX was significantly higher for PTX-NP2(PEG-2000) and PTX-NP6(PEG-6000) than for PTX-NP10(PEG-10000). When PTX-NP2 and PTX-NP6 were administered to rats by the oral route, sustained and therapeutic plasma levels of paclitaxel for at least 48 h were observed. The relative oral bioavailability of paclitaxel delivered in nanoparticles was calculated to be 70% for PTX-NP2, 40% for PTX-NP6 and 16% in case of PTX-NP10. All of these observations would be related with both the bioadhesive properties of these carriers and the inhibitory effect of PEG on the activity of both P-gp and P450 cytochrome.³⁶

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PTX-loaded MPEG-PTMC nanoparticles significantly enhanced the anti-glioblastoma activity of PTX.³⁸

A lectin-conjugated isopropyl myristate (IPM)-incorporated PLGA nanoparticle system (NP) for the local delivery of paclitaxel to the lungs was prepared. In vitro paclitaxel release profile was not affected by WGA but initial drug release was enhanced by adding IPM into the formulation. The WIT-NP showed a burst-release of about 32% of the paclitaxel load within the first 5 h followed by a slow zero-order release of another 7% of the drug load in the next 115 h. Compared with the clinical paclitaxel formulation, paclitaxel-loaded nanoparticles without IPM or WGA, or paclitaxel-loaded nanoparticles with only IPM or WGA, the WIT-NP had superior in vitro cytotoxicity against A549 and H1299 cells. IC50 for WIT-NP after 5 and 24 h incubation with A549 cells were not significantly different (15.5 and 15 µM, respectively) whereas the clinical formulation was not cytotoxic after 5 h but had IC50 of 14 µM after 24 h incubation. WIT-NP exhibited stronger cell-killing effect because of more efficient cellular uptake via WGA-receptor-mediated endocytosis and IPM-facilitated release of paclitaxel from the NPs.³⁹

Active targeting of nanoparticles

Cyclic RGD peptide-decorated polymeric micellar-like nanoparticles (MNP) based on PEGylated poly(trimethylene carbonate) (PEG-PTMC) were prepared for active targeting to integrin-rich cancer cells. An amphiphilic diblock copolymer, α-carboxyl poly(ethylene glycol)-poly(trimethylene carbonate) (HOOC-PEG-PTMC), was synthesized by ring-opening polymerization. The c(RGDyK) ligand, a cyclic RGD peptide that can bind to the integrin proteins predominantly expressed on the surface of tumor cells with high affinity and specificity, was conjugated to the NHS-Activated PEG terminus of the copolymer. Cellular uptake of c(RGDyK)-MNP/PTX was found to be higher than that of MNP/PTX due to the integrin protein-mediated endocytosis effect. In vitro cytotoxicity, cell apoptosis and cell cycle arrest studies also revealed that c(RGDyK)-MNP/PTX was more potent than those of MNP/PTX and Taxol. Pharmacokinetic study in rats demonstrated that the polymeric micellar nanoparticles significantly enhanced the bioavailability of PTX than Taxol.⁴⁰

For active targeted therapy, pac-MNPs were functionalized with lectin glycoprotein which resulted in higher cellular uptake and lower IC(50) value suggesting the efficacy of targeted delivery of paclitaxel. Both pac-MNPs and lectin conjugated pac-MNPs have a prolonged circulation time in serum suggesting increased bioavailability and therapeutics index of paclitaxel *in vivo*.⁴¹

PEG-coated biodegradable polycyanoacrylate nanoparticles (PEG-nanoparticles) conjugated to



transferrin, showed the average encapsulation efficiency of ATN was $93.4 \pm 3.6\%$ with particle size (101.4 ± 7.2 nm) and zeta-potential (-13.6 ± 1.1 mV). The paclitaxel loaded ATN exhibited a low burst effect with about only 16.2% drug release within the first phase. Subsequently, paclitaxel release profiles displayed a sustained release phase. The amount of cumulated paclitaxel release over 30 days was 81.6%. The distribution profiles of ATN in S-180 solid tumor-bearing mice after intravenous administration showed the tumor accumulation of paclitaxel increase with time, and the paclitaxel concentration in tumor was about 4.8 and 2.1 times higher than those from paclitaxel injection and PEG-nanoparticles at 6 h after intravenous injection.⁴²

Long circulating nanoparticles

Polymeric nanoparticles have long been sought after as carriers for systemic and targeted drug delivery. The ability of these particles to circulate in the bloodstream for a prolonged period of time is often a prerequisite for successful targeted delivery. To achieve this, paclitaxel loaded chitosan and polyethylene glycol coated PLGA (PLGA-CS-PEG) nanoparticles were formulated and characterized that could efficiently encapsulate hydrophobic drugs, and also evade the phagocytic uptake by reducing opsonization by blood proteins, hence increasing the bioavailability of the drug. PLGA-CS-PEG nanoparticles showed dramatic prolongation in blood circulation, as well as reduced macrophage uptake, with only a small amount of the nanoparticles sequestered in the liver, when compared to PLGA-CS and PLGA nanoparticles. Superior anti-proliferative effect and cell cycle inhibition was observed in case of PLGA-CS nanoparticles and PLGA-CS-PEG nanoparticles over PLGA nanoparticles and native paclitaxel, which may be due to higher cellular uptake resulting in greater antiproliferative activity of nanoparticles.⁴³

Glycoprotein non-metastatic melanoma protein B (GPNMB) overexpressed by glioblastoma cells, was actively targeted using GPNMB conjugated Pac-MNPs in U-87 cells. As blood brain barrier (BBB) is the primary impediment in the treatment of glioblastoma, therefore, the biodistribution and brain uptake of Pac-MNPs in rats was evaluated. The bioavailability of Pac-MNPs illustrated a prolonged blood circulation *in vivo*, which demonstrated the presence of significant amounts of drug in rat brain tissues as compared to native paclitaxel.⁴⁴

Lipid based nanoparticles

Lipid-based liquid crystalline nanoparticles (LCNPs) have attracted growing interest as a new drug nanocarrier system for improving bioavailability for both hydrophilic and hydrophobic drugs.

Self-assembled LCNPs based on soy phosphatidyl choline and glycerol dioleate, were prepared using poly(ethylene glycol)-grafted 1,2-distearoyl-sn-glycero-3-phosphatidylethanolamine (DSPE-PEG) as the dispersing

agent to load Paclitaxel (PTX). PTX-loaded DSPE-PEG-LCNPs exhibited a biphasic drug sustained release pattern with a relatively fast release at the initial stage and a sustained release afterwards. PTX-loaded DSPE-PEG-LCNPs presented higher AUC ($410.942 \pm 72.522 \mu\text{g/Lh}$) when compared with commercial product Taxol ($212.670 \pm 41.396 \mu\text{g/Lh}$).⁴⁵

Solid lipid nanoparticles (SLNs) have the potential of in improving the oral bioavailability of paclitaxel. Paclitaxel-loaded SLNs (PTX-SLNs) were prepared by modified solvent injection method using stearylamine as lipid, soya lecithin and poloxamer 188 as emulsifiers. The drug entrapment efficiency was found to be $75.42 \pm 1.5\%$ with a loading capacity of $31.5 \pm 2.1\%$ (w/w). After oral administration of the PTX-SLNs, drug exposure in plasma and tissues was ten- and twofold higher, respectively, when compared with free paclitaxel solution. PTX-SLNs produced a high mean C (max) (10, 274 ng/ml) compared with that of free paclitaxel solution (3,087 ng/ml).⁴⁶

Polymeric nanoparticles

The poly(D, L-lactide-co-glycolide) (PLGA) nanoparticles containing paclitaxel, etanidazole and paclitaxel & etanidazole were prepared by o/w and w/o/w emulsification-solvent evaporation method. Co-culture of the two tumor cell lines with drug-loaded nanoparticles demonstrated that released drug effectively sensitized hypoxic tumor cells to radiation. The radiosensitization of paclitaxel & etanidazole nanoparticles was more significant than that of single drug-loaded nanoparticles.⁴⁷

Paclitaxel-incorporated polysaccharide nanoparticles made with modified pullulan showed initial drug burst release until 2 days and then the drug was continuously released over 1 week. The nanoparticles showed lower antitumor activity *in vitro* against HCT116 human colon carcinoma cells than that of paclitaxel itself, indicating the sustained release properties of nanoparticles. An *in vivo* study using HCT116 human colon carcinoma-bearing mice showed that paclitaxel incorporated PA nanoparticles reduced tumor growth more than that of paclitaxel itself.⁴⁸

PTX-loaded PEGylated PLGA-based nanoparticles showed the higher incorporation efficiency of PTX. The release behavior of PTX exhibited a biphasic pattern characterized by an initial burst release followed by a slower and continuous release. The *in vitro* anti-tumoral activity was assessed using the Human Cervix Carcinoma cells (HeLa) by the MTT test and was compared to the commercial formulation Taxol[®] and to Cremophor[®] EL. When exposed to 25 $\mu\text{g/ml}$ of PTX, the cell viability was lower for PTX-loaded nanoparticles than for Taxol[®] (IC_{50} 5.5 vs 15.5 $\mu\text{g/ml}$). PTX-loaded nanoparticles showed greater tumor growth inhibition effect *in vivo* on TLT tumor, compared with Taxol.⁴⁹

Poly (D,L-lactide-co-glycolide) (PLGA) nanoparticles (NPs) showed the drug encapsulation efficiency ranging from 34.8 ± 1.6 to $62.6 \pm 7.9\%$. Paclitaxel was released from the



nanoparticles in a biphasic profile with a fast release rate in the first 3 days followed by a slow first-order release. A higher or comparable cytotoxicity against glioma C6 cells was found for the drug formulated in the PLGA NPs in comparison with the free drug Taxol[®].⁵⁰

In another study a polymeric drug delivery system for paclitaxel, intended to be intravenously administered, capable of improving the therapeutic index of the drug and devoid of the adverse effects of Cremophor[®] EL was developed. The release behaviour of paclitaxel from the developed Nps exhibited a biphasic pattern characterised by an initial fast release during the first 24 h, followed by a slower and continuous release. Exposure of human small cell lung cancer cell line NCI-H69 cells to 25 µg/ml Taxol[®] resulted in a steep decrease in cell viability indicating strong enhancement of the cytotoxic effect of the drug as compared to Taxol[®].⁵¹

Rice-like polymeric nanoparticles (NPs) composed of a new redox-responsive polymer, poly(ethylene glycol)-*b*-poly(lactic acid) (MPEG-SS-PLA), were prepared to carry paclitaxel (PTX) for glutathione (GSH)-regulated drug delivery. The NPs released almost 90% PTX within 96 h when GSH presented at intracellular concentrations, whereas only a very small PTX amount was released at plasma GSH levels.⁵²

Vitamin E TPGS-emulsified Poly(D, L-lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) exhibited a biphasic in vitro drug release profile with an initial burst followed by a sustained release. In vitro HT-29 cell viability experiment demonstrated that the drug formulated in the NPs was 5.64, 5.36, 2.68, and 1.45 times more effective than that formulated in the Taxol[®] formulation after 24, 48, 72, 96 h treatment, respectively at 0.25 µg /mL drug concentration. The area-under-the-curve (AUC) for 48 h for Vitamin E TPGS emulsified PLGA NP formulation of paclitaxel were found 3.0 times larger than that for the Taxol[®] formulation. The sustainable therapeutic time, at which the drug concentration drops below the minimum effective value, for the NP formulation could be 1.67 times longer than that for the Taxol[®] formulation.⁵³

Paclitaxel-loaded chitosan oligosaccharide (CSO) nanoparticles showed the drug entrapment efficiency increase from 83.68% to 92.30%, and the paclitaxel release rate was slowed.⁵⁴

Cyclodextrin nanoparticles

Paclitaxel is a potent anticancer agent with limited bioavailability due to side-effects associated with solubilizer used in its commercial formulation and the tendency of the drug to precipitate in aqueous media. Amphiphilic cyclodextrin nanoparticles emerged as promising alternative formulations for injectable paclitaxel administration with low toxicity and equivalent efficacy. In this study, paclitaxel was encapsulated in amphiphilic cyclodextrin nanoparticles. Safety of blank nanoparticles was compared against commercial vehicle cremophor:ethanol (50:50 v/v) by hemolysis and

cytotoxicity experiments. Data revealed that nanoparticles caused significantly less hemolysis. A vast difference between the cytotoxicity of nanoparticles and cremophor:ethanol mixture was observed. Recrystallization of paclitaxel, very typical in diluted aqueous solutions of the drug, did not take place when the drug is bound to cyclodextrin nanoparticles. Cyclodextrin nanoparticle caused a slightly higher anticancer effect than cremophor:ethanol vehicle.⁵⁵ Second-generation derivatives of methyl-β-cyclodextrin, especially MaRAMEB, monoamino randomly methylated β-cyclodextrin enhanced taxol permeability across Caco-2 cells with less toxicity and similar effectiveness as (RAMEB) randomly methylated β-cyclodextrin (RAMEB).⁵⁶

Incorporating cyclodextrins in poly(anhydride) nanoparticles, results in improvement of their bioadhesive capability, the loading of lipophilic drugs and the significant effect on efflux membrane proteins and cytochrome P450.⁵⁷

Paclitaxel (PTX) was encapsulated as a complex with cyclodextrins in poly(anhydride) nanoparticles (NP) using three different cyclodextrins β-cyclodextrin (CD), 2-hydroxypropyl-β-cyclodextrin (HPCD) and 6-monodeoxy-6-monoamino-β-cyclodextrin (NHCD). For PTX-CD NP and PTX-HPCD NP, these sustained levels of the anticancer drug were found to be between 27 and 33-fold higher than the reported value of drug activity whereas the relative oral bioavailability of paclitaxel was calculated to be higher than 80%. These facts would be directly related with a synergistic effect obtained by the combination of the bioadhesive properties of poly(anhydride) nanoparticles and the inhibitory effect of cyclodextrins on the activity of P-glycoprotein and cytochrome P450.⁵⁸

Albumin-bound paclitaxel nanoparticles

Nanoparticle technology is used to bind paclitaxel to human albumin (nanoparticle albumin-bound paclitaxel; *nab*-paclitaxel; Abraxane[®]) ensures solubility of the taxane without the use of solvents and minimizes the risk of hypersensitivity reactions without premedication. Nab-Paclitaxel targets tumors, enhances tumor penetration by the novel mechanism of albumin receptor-mediated (gp60) endothelial transcytosis, and avoids the use of surfactants and solvents such as Cremophor and Tween. nab-Paclitaxel minimizes the toxicities associated with Cremophor and eliminates the need for premedication for hypersensitivity reactions caused by Cremophor. The homogeneous colloidal suspension created allows rapid dispersal of unbound drug and linear pharmacokinetics. Albumin-mediated transport of paclitaxel across the endothelium facilitates uptake of drug, and a degree of tumour selectivity is achieved by the albumin-binding propensity of SPARC (Secreted Protein Acidic Rich in Cysteine), a substance expressed on and around many breast tumours. Clinical trials in first- and second-line MBC show that *nab*-paclitaxel is both more effective than solvent-based taxanes and associated with less severe neutropenia. Sensory neuropathy occurs but improves



rapidly when compared with that caused by conventional taxanes. A clinical development programme is investigating *nab*-paclitaxel in the adjuvant and neoadjuvant settings. The low incidence of neutropenia makes *nab*-paclitaxel a good candidate for combination with other cytotoxics.⁵⁹

In nonclinical studies, *nab*-paclitaxel achieved higher intratumoral concentrations compared with solvent-based paclitaxel and increased the bioavailability of paclitaxel by eliminating the entrapment of paclitaxel in the plasma. Compared with solvent-based paclitaxel, at equitoxic doses, the *nab*-paclitaxel produced more complete regressions, longer time to recurrence, longer doubling times, and prolonged survival. *nab*-Paclitaxel has been shown to have superior efficacy compared with solvent-based paclitaxel without the need for premedication in clinical trials of patients with advanced solid tumors. *nab*-Paclitaxel has been effective in patients for whom previous chemotherapy has not been helpful. *nab* Technology has the potential to be applied to other insoluble drugs.⁶⁰

Nab-paclitaxel was also found to be tolerable in this cohort of refractory ovarian cancer patients previously treated with paclitaxel.⁶¹

Nab-paclitaxel has considerable activity and moderate toxicity in the treatment of drug resistant, metastatic and recurrent cervix cancer.⁶²

A study was done to evaluate the efficacy and safety of nanoparticle albumin-bound paclitaxel as a rescue regimen in the treatment of patients with advanced non-small-cell lung cancer. Weekly-administered albumin-bound paclitaxel seems to be an effective and safe regimen for elderly patients with stage IV non-small-cell lung cancer who were refractory to conventional therapy.⁶³

CONCLUSION

The foregoing show that nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. PX is one of the most effective anticancer drugs ever developed whose clinical applications are limited by poor water solubility and P-gp-mediated efflux. It is active against a broad range of cancers. Since nano-delivery systems could have the potential to enhance PX solubility, improve PX pharmacokinetic profiles in vivo, decrease its side effects, passively or actively target to tumor sites due to the enhanced permeability and retention (EPR) effect and the use of targeting ligands, respectively, nanotechnology is a very active research area. Therefore, various types of paclitaxel nano-delivery systems have been developed as discussed in this review. To date, the PX albumin-bound NPs (Abraxane®) have been approved by the FDA for the treatment of metastatic breast cancer and NSCLC, and there are a number of novel PX NP formulations in clinical trials. Some of them have demonstrated certain

advantages in terms of toxicity, such as lower incidence of hypersensitivity reactions, myelosuppression, etc. However, whether these novel formulations may improve survival is largely unknown.

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Source of Support: Nil, Conflict of Interest: None.

