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Review Article

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A comparative study on the physicochemical properties of polymer and albumin based paclitaxel

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ABSTRACT

Taxanes are highly active chemotherapeutic agents in the treatment of early-stage and metastatic breast cancer. Taxanes signify an important class of antitumor agents which have proven to be fundamental in the treatment of advanced and early-stage breast cancer, but the clinical advances of taxanes have been limited by their highly hydrophobic molecular status. Novel formulations have been developed to improve effectiveness and decrease toxicity associated with these cytotoxic agents. To overcome the poor water solubility of Taxanes , lipid-based solvents have been used as a vehicle, and new systemic formulations have been developed, mostly for paclitaxel, which are Cremophor-free and increase the circulation time of the drug. ABI-007 is a novel, albumin-bound, 130-nm particle formulation of paclitaxel, free from any kind of solvent apart from this, technological parameters such as polymer concentration and polymer composition have significant influences on characterization of nanoparticles. These parameters lead to variations in particle size and surface charge of nanoparticles which are very important parameters on their transmembranal passage and tissue targeting properties. The encapsulation of paclitaxel in biodegradable and non-toxic nanodelivery systems can protect the drug from degradation during circulation and in-turn protect the body from toxic side effects of the drug thereby lowering its toxicity, increasing its circulation half-life, exhibiting improved pharmacokinetic profiles, and demonstrating better patient compliance. In this review we two types of developed paclitaxel nano-delivery systems such as polymer based and albumin based will be compared for the best choice of drug delivery system of nanoparticels.

Key words: Paclitaxel, Taxanes, Polymer based, Albumin based.

INTRODUCTION

Paclitaxel is an anti-cancer chemotherapy drug. Paclitaxel is classified as a "plant alkaloid," a "taxane" and an "antimicrotubule agent." The Paclitaxel compound is extracted from the Pacific yew tree Taxus brevifolia with antineoplastic activity. Paclitaxel is a crystalline powder which is white to off-white in appearance. Its empirical formula is C47H51NO14 and is known to have a molecular weight of 853.9 units. It is highly lipophilic thus highly insoluble in water. Its melting point is around 216-217°C. Paclitaxel binds to tubulin and inhibits the disassembly of microtubules, thereby resulting in the inhibition of cell division. Two major side-effects of paclitaxel therapy are frequent hypersensitivity reactions and neuropathy [1]. Standard paclitaxel contains Cremophor EL as a solvent, thus requiring premedication with high doses of antihistamines and corticosteroids, as well as prolonged infusion times. Since nano-delivery systems could have the potential to be free of Cremophor EL and ethanol, to enhance Paclitaxel solubility, improved pharmacokinetic profiles in vivo and to decrease its side effects , various types of Paclitaxel nano-delivery systems have been developed such as such as polymeric nanoparticles, lipid-based formulations, polymer conjugates, inorganic nanoparticles, carbon nanotubes, nanocrystals, and cyclodextrin nanoparticles. To date, the Paclitaxel albumin-bound Nano particles (Abraxane®) have been approved by the FDA for the treatment of metastatic breast cancer and NSCLC [2] and there are a number of novel Paclitaxel nanoparticels formulations in

clinical trials. This review we have made an attempt to compare two important formulations of Nanopaclitaxel one is polymer based and another one is albumin based.

1. Advantages of Nanoparticle-Based Paclitaxel Delivery Systems

The engineering, characterization, synthesis, and use of materials and devices of 100 nanometers or less is called nanotechnology [3]. The appliance of nanotechnology to medicine, designated as nanomedicine has greatly accelerated the diagnosis, imaging and treatment of many diseases. In cancer medicine, nanotechnology has become a potential application for the development of nanoparticles as drug delivery systems. As an effective chemotherapeutic agent, Paclitaxel has been formulated in various nano-delivery systems which have several advantages over the standard-of-care therapy. The various types of the paclitaxel were formulated to get the improvements in the properties

1. The aqueous solubility of paclitaxel can be greatly enhanced when it is conjugated with water-soluble polymers, or encapsulated into lipid-based NPs.
2. They are small in size (several to several hundred nanometers in diameter), which enables the preferential delivery of Paclitaxel into the tumor site due to the enhanced permeability and retention (EPR) effect.
3. They can escape the recognition of reticuloendothelial system (RES) in healthy tissues and therefore reduce the side effects of the drug. As a consequence, higher maximum tolerated doses (MTD) of NPs are realized [4]
4. Fourth, the pharmacokinetic profiles of the drug from NPs are improved and decrease the side effects of the drug [5].

2. Common Nanoparticles Used in Cancer Medicine

Nanotechnology showed a new path to the development of diverse organic and inorganic drug carriers, known as nanoparticle. Source materials include phospholipids, lactic acid, chitosan, dextran, polyethylene glycol (PEG), cholesterol, carbon, silica, and some metals [3,6,7,8,9,10]. Accordingly the nanopaclitaxel includes Polymeric nanoparticels, Albumin Nanoparticles, Lipid-Based Nanoparticles, Micro- and Nano-Emulsions, Inorganic Nanoparticles, Carbon Nanotubes (CNTs), Nanocrystals, Cyclodextrin (CD) Nanoparticles, Nanogel, ANG 1005. Though the pharmacists and researches understood the impact of nanomedicine in cancer therapy, in practice the commonly used nanoparticels are albumin based and polymer based . So let us have a comparative analysis of these two nano paclitaxel.

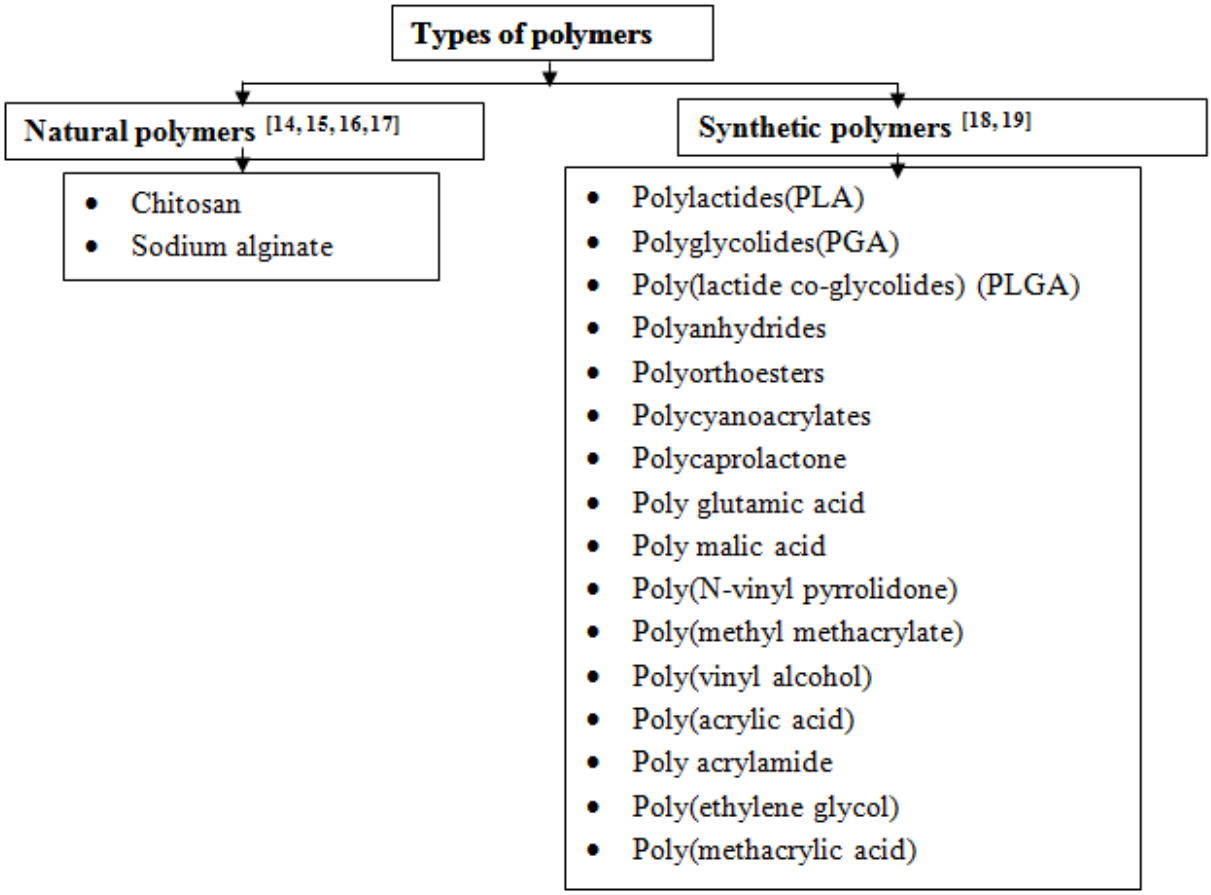
2.1. Polymeric nanoparticles:

The polymers which have been employed for drug delivery must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable [11].The desirable physical properties of the polymers concerned with the drug delivery are elasticity, insulating ability, physical strength and transparency, hydrophilicity , toughness and lack of swelling, suspension capabilities

2.1.1Significance of polymeric nanoparticles [12, 13]

- Improves the stability of any volatile pharmaceutical agents
- Easy fabrication of large quantities
- Varity of methods available
- Improvement in the efficiency of the drugs.
- Delivers a higher concentration of pharmaceutical agent to a desired location.

The most commonly used are classified as shown in fig.1



2.2. Methods of preparation of Polymer based Nanoparticles

The polymeric nanoparticles (PNPs) are prepared from biocompatible and biodegradable polymers in size between 10-1000 nm where the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation nanoparticles, nanospheres or nanocapsules can be obtained. The methods of preparation must be adopted depending upon the on the particular application. The properties of the nanoparticels must be optimized according to the applications. Dispersion of drug in preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA), poly (D, L-glycolide) (PLG), poly (D, L-lactide-co-glycolide) (PLGA) and poly (cyanoacrylate) (PCA). These can be accomplished by different methods described below [20].

- Solvent evaporation
- Nanoprecipitation
- Emulsification/solvent diffusion
- Salting out
- Dialysis
- Supercritical fluid technology (SCF)

Methods for preparation of nanoparticles from polymerization of monomers

- Emulsion
- Mini emulsion
- Micro emulsion
- Interfacial polymerization
- Controlled/Living radical polymerization(C/LRP)

2.3. Improved Physicochemical and Pharmacokinetic properties of polymer based nanoparticles:

Over the past few decades, there has been considerable interest in developing biodegradable nanoparticles as effective drug delivery devices various polymers have been used in drug delivery research as they can effectively deliver the drug to the target site and thus increase the therapeutic benefit while minimizing side effect [21]. Studies

show that polyethylene glycom (PEG) on nanoparticle surfaces prevents opsonization by complement and other serum factors. PEG molecules with brush-like and intermediate configurations reduce phagocytosis and complement activation, whereas surfaces comprised of PEG with mushroom-like structures are potent complement activators and favoured phagocytosis [22]. Prolonged circulation can help to achieve a better effect for targeted (specific ligand-modified) drugs and drug carriers, allowing more time for their interaction with the target because of the increased number of passages through it with the blood. Chemical modification of pharmaceutical nanocarriers with PEG is the approach most frequently used to impart in-vivo longevity to drug carriers [23]. The mechanisms by which PEG prevents opsonization include shielding of the surface charge, increased surface hydrophilicity, enhanced repulsive interaction between polymer-coated nanocarriers and blood components, and the formation of the polymeric layer over the particle surface, which is impermeable for large molecules of opsonins even at relatively low polymer concentrations [24]

As a protecting polymer, PEG provides a very attractive combination of properties and excellent solubility in aqueous solutions, high flexibility of its polymer chain, very low toxicity, immunogenicity and antigenicity, lack of accumulation in RES cells, and minimal influence on specific biological properties of modified pharmaceuticals [25].

The polymer based nanopaclitaxel is showing improved pharmacokinetic profiles of the drug , for example, increasing the half-life and tumour accumulation of paclitaxel also the surface of paclitaxel a nanoparticle system can be functionalized with active ligands for targeting purpose, which in-turn will further increase the tumor uptake and decrease the side effects of the drug [26-30]. Yadav et al synthesized N-isopropylacrylamide/ vinyl pyrrolidone (NIPAAm/VP) nanoparticles by radical polymerization and conducted Physico- chemical characterization of the polymeric nanoparticles dynamic light scattering, transmission electron microscopy, scanning electron microscopy and nuclear magnetic resonance. They assessed the drug release using a spectrophotometer and proved drug loaded nanoparticles were associated with increased viability of MCF-7 and B16F0 cells in comparison to free paclitaxel [31]. Paclitaxel encapsulated PLGA nanoparticels showed enhanced in vitro cytotoxicity as compared to free Paclitaxel in various cancer cell lines, such as glioma C6 cells [32], L. Mu et. al conclude that vitamin TPGS has advantages either as emulsifier or as matrix material blended with PLGA for the manufacture of nanoparticles for controlled release of paclitaxel [33]. Fonseca et al demonstrated that the in vitro anti-tumoral activity of Ptx-PLGA-Nanaoparticles on human small cell lung cancer cell line (NCI-H69 SCLC) is more compared to the in vitro anti-tumoral activity of the commercial formulation Taxol and also the incorporatio n of Ptx in nanoparticles strongly enhances the cytotoxic effect of the drug as compared to Taxol [34]

Paclitaxel loaded PEGylated PLGA-based nanoparticels were prepared by Danhier et al and it was proved that the tumour growth inhibition effect in vivo on TLT tumor of theses nanoparticels is greater, compared with Taxol. [35]. Kim et al prepared chitosan-coated Poly (D,L-lactide-co-glycolide) (PLGA) nanoparticels and slowed the in vitro drug release rate and significantly changed the zeta potential from negative (-30.1+/-0.6 mV) to positive (26+/-1.2 mV) and also the drug release rate from chitosancoated nanoparticles was slightly slower than that of the uncoated nanoparticles. [36]. Chakravarthi et al. [37]demonstrated that the A 4-10 fold increase in cellular association of paclitaxel was observed when chitosan was adsorbed or conjugated to the PLGA particles. Chitosan-conjugated PLGA microparticles were most cytotoxic with an IC(50) value of 0.77 μM and also chitosan-PLGA microparticles adhered to the surface of 4T1 cells. Bhardwaj et al [38] formulated poly(lactide-co-glycolide) (PLGA) nanoparticles using a quaternary ammonium salt didodecyl dimethylammonium bromide (DMAB) and the MTT and LDH assays showed the surfactant to be safe to in vitro cell cultures at concentrations <33 microM. PLGA nanoparticles prepared using this stabilizer were also found to be non-toxic to cell lines . A comparative study was done on a series of polymers to PVA in a 2(2) full factorial design [39]. The influence of the concentration of PVA and the polymers tested on particle size and zeta potential value and found that the Zeta potential values were usually slightly negative. Poly (vinyl alcohol) (PVA) is the most commonly used emulsifier. Other emulsifiers were also applied in PLGA NPs. For example, when d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) was utilized in PX-loaded PLGA NPs as the surfactant emulsifier, the PLGA/TPGS NPs could achieve drug encapsulation efficiency of 100% [40], and enhanced cellular uptake and cytotoxicity [41] compared to that of PVA-emulsified PLGA NPs. The TPGS-emulsified. Fully biodegradable synthetic polymers have been available since many years, such as poly (lactic acids) (PLA). Among all biopolymers, PLA was extensively studied in medical implants, suture, and drug delivery systems since 1980s due to its biodegradability.

A paclitaxel/MPEG-PLA block copolymer conjugate was prepared [42] and the antitumor activity of the conjugate against human liver cancer H7402 cells was evaluated by MTT method. The results showed that paclitaxel can be released from the conjugate without losing cytotoxicity. paclitaxel-loaded polylactide (PLA)-polyethylene glycol (stealth) nanoparticles [43] and showed that the nanoparticles are internalized by MCF-7 breast cancer cells within 1 h. Preliminary biodistribution studies also show nanoparticle accumulation in tumor xenograft model. The nanoparticles are suitable for the controlled delivery of bioactive agents. Paclitaxel–polylactide (Ptxl–PLA)

conjugate nanoparticles (NCs)[44] found to be able to effectively target prostate-specific membrane antigen in a cell-specific manner. Paclitaxel-loaded copolymer poly(lactide)–d-*α*-tocopheryl polyethylene glycol 1000 succinate (PLA–TPGS) nanoparticles [45] were prepared and the characteristics such as surface morphology, size distribution, zeta potential, solubility and apoptosis were investigated *in vitro and proved that* spherical nanoparticles were negatively charged with a zeta potential of about −18 mV with the size around 44 nm and a narrow size distribution and are universal cancer chemotherapeutic agent. Functional polylactide-g-paclitaxel–poly(ethylene glycol), a novel graft polymer–drug conjugate (GPDC) with paclitaxel (PTXL) as the divalent agent to bridge between the degradable polylactide (PLA)-based backbone and hydrophilic poly(ethylene glycol) (PEG) side chains[46] were prepared and the DLS analysis proved that GPDC molecules assembled in water to form nanoparticles with sizes of 8–40 nm, A system of novel nanoparticles of star-shaped cholic acid-core polylactide-D-α-tocopheryl polyethylene glycol 1000 succinate (CA-PLA-TPGS) block copolymer was developed for paclitaxel delivery for breast cancer treatment[47] and characterized in terms of size, surface charge, surface morphology, drug encapsulation efficiency, and in vitro drug release and showed that the CA-PLA-TPGS nanoparticles have higher antitumor efficacy than the PLA-TPGS nanoparticles and PLGA nanoparticles in vitro and in vivo. Paclitaxel-loaded poly(ethylene glycol)-b-poly(l-lactide (LA)) (PEG-PLA) micelles were [48] prepared and the the antitumor activity of the paclitaxel-loaded micelles against human liver cancer H7402 cells was evaluated by 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) method and proved that Both the paclitaxel-loaded micelles showed comparable anticancer efficacy with the free drug.

3. Albumin based nano paclitaxel:

Protein-bound paclitaxel is an injectable formulation of paclitaxel, a mitotic inhibitor drug used in the treatment of breast cancer, lung cancer and pancreatic cancer[49-51]. In this formulation, paclitaxel is bonded to albumin as a delivery vehicle [52]. It is sometimes called **nab-paclitaxel**. It is manufactured and sold in the United States by Abraxis BioScience under the trade name **Abraxane** where it is designated as an orphan drug as first-line treatment, in combination with gemcitabine, for the orphan disease "metastatic adenocarcinoma of the pancreas"[53]. Albumin is a protein that can be obtained from a variety of sources, including egg white (ovalbumin), bovine serum albumin (BSA), and human serum albumin (HSA). Albumin is a major soluble protein of the circulating system and involved in the maintenance of osmotic pressure and binding and transport of nutrients to the cells. Many drugs and endogenous molecules are known to bind to albumin. Albumin serves as a depot and transporter protein [54]. Albumin is widely used in the preparation of nanospheres and nanocapsules [55]. These albumin nanocarriers are biodegradable, easy to prepare, and have well-defined sizes and reactive functional groups (thiol, amino, and carboxyl) on their surface that can be used for ligand binding and other surface modifications. Drug release from albumin nanoparticles can be achieved naturally by protease digestion.

3.1.Various methods of producing Albumin based paclitaxel [56]:

- Cross linking in w/o emulsion (for the preparation of BSA & HAS)
- Phase separation in aqueous medium (for the preparation of BSA)
- simple coacervation technique (for the preparation of BSA)
- Desolvation Method (for the preparation of paclitaxel-loaded biodegradable bovine serum albumin nanoparticles

3.2.Improved Characteristics of albumin based paclitaxel

Nanoparticle albumin-bound paclitaxel (*nab*™-paclitaxel; ABI-007; Abraxane®) is a novel CrEL-free formulation of paclitaxel. This formulation is prepared by high-pressure homogenization of paclitaxel in the presence of serum albumin, resulting in a nanoparticle colloidal suspension.[57] The albumin concentration is 3-4%, which is similar to the albumin concentration in the blood.[58] The human albumin-stabilized paclitaxel particles have an average size of approximately 130 nm, which allows intravenous infusion without the risk of capillary blockage.[59]*Nab*-paclitaxel can be reconstituted in normal saline at concentrations of 2-10 mg/ml compared with 0.3-1.2 mg/ml for CrEL-paclitaxel; therefore, the volume and infusion time are reduced.[57] The *nab*-paclitaxel formulation provides several practical advantages over CrEL-paclitaxel: premedications for hypersensitivity reactions are not required, the infusion time is shorter (30 min for *nab*-paclitaxel vs 3 h for CrEL-paclitaxel) and conventional infusion equipment may safely be used since there is no danger of leaching plasticizers from infusion bags or tubing.

ABI-007 , albumin-bound, nanoparticle paclitaxel [60] was developed to retain the therapeutic benefits of paclitaxel and reported that the the maximum tolerated dose of ABI-007 was higher than that reported for Taxol for both an every-3-weeks regimen and the response rates were significantly higher for ABI-007 than for Taxol. ab-paclitaxel (Abraxane) [61] and found to show very fast dissolution in plasma, high tumor/plasma ratio, and dose-proportional PK, and showed IG-001 is a superior alternative to Taxol and despite a lack of serum albumin in its formulation, IG-001 takes full advantage of its ability to rapidly deliver paclitaxel to the targeted tissue via an album in mediated transport

In is proved that, in vitro, the non-crosslinked particles could rapidly disintegrate and the crosslinked was stable and the the pharmacokinetics of both formulations was different especially at early time and the non-crosslinked particles were cleared rapidly [62]. After non-crosslinked particle treatment paclitaxel had a tendency to accumulate into heart and kidney and following therapy with the crosslinked particles, paclitaxel was liable to be delivered into lung, spleen and liver. The delivery efficiency of paclitaxel into tumor following the non-crosslinked particle treatment was greater than that of the crosslinked ($p < 0.05$), thus resulting in a considerably improved antineoplastic activity

The study on nab-paclitaxel showed that it causes more rapid and deeper tissue penetration and slower elimination of paclitaxel compared with solvent based paclitaxel. Less-frequent neutropenia with nab-paclitaxel can be explained by the rapid decline of paclitaxel concentrations below the threshold of 720 ng/mL in circulation [63]. Tumor-homing peptides to target abraxane was prepared [64] and showed that nanoparticles can be effectively targeted into extravascular tumor tissue and that targeting can enhance the activity of a therapeutic nanoparticle.

In addition to human albumin, Zhao et al. [65] prepared PX-loaded bovine serum albumin (BSA) NPs using a desolvation method, and subsequently coated NPs by folic acid for targeting. The folate-decorated NPs exhibited high stability and desired surface properties which specifically targeted to human prostate cancer PC3 cells. In another study, a novel octyl-modified bovine serum albumin (OSA) was synthesized to improve the lipophilicity of albumin and facilitate to form PX-loaded core-shell nanomicelles. The OSA NPs had smaller particle size, higher drug entrapment efficiency, and greater stability compared to unmodified NPs [66].

DISCUSSION AND CONCLUSION

Paclitaxel is effective against a wide range of cancers that are inflexible to conventional therapy. Developing a suitable carrier system for this drug has proved to be a challenge due to the physicochemical characteristics of the drug, and although widely used, the commercially available solution dosage form of paclitaxel remains far from ideal due to toxicities resulting from the vehicle.

Various drug delivery carriers have been used to improve the efficacy and reduce side effects of cancer therapy. Among these carriers, small biodegradable and biocompatible nanoparticles (<100 nm) have received the most attention. For systemic delivery of anticancer drugs, it is generally accepted that small particles (<500 nm) can avoid the reticuloendothelial system (RES), resulting in a longer circulation time [67].

The development of nanoparticle drug delivery systems is expected to have a major impact on the treatment of cancers and other life-threatening diseases. Protein and polymers from natural sources are promising materials for constructing the nanocarrier systems. Of the various proteins for drug delivery applications, gelatin and albumin are most widely used. The commercial success of albumin-based nanoparticles has created a great interest in other proteins. By rationally designing protein nanoparticles based on their behaviors in the tumor microenvironment and based on cancer cell biology, improved efficacy and safety of cancer therapy can be achieved. Although the application of protein nanoparticles for cancer therapy has already produced some exciting results and holds even greater promise in the future,

Despite being clinically very active, paclitaxel is associated with many serious side effects which often preclude the prolonged use in patients. A number of these side effects have been associated with the vehicles used for the formulation: the cremophor EL (CrEL-polyethoxylated castor oil) [68] for paclitaxel that alters their pharmacokinetic profiles. Paclitaxel-loaded nanoparticles show drastically enhanced cytotoxicity compared to pure paclitaxel and Polymer-paclitaxel conjugates are expected to prolong their plasma half-life and to have high tumor accumulation due to their slow excretion from kidney and the enhanced permeation and retention effects, respectively. Li et al. [69] reported that PG-PTX prolonged over 100 times in plasma compared with that of Taxol, and tumor accumulation of PG-PTX was five times higher than that of Taxol. Similar trends were observed with PGG-PTX [33]. PK showed 23 times extended duration of PGG-PTX than that of Taxol, and tumor accumulation of PGG-PTX was seven times higher than that of Taxol [70]. On the basis of the results of PK and tumor accumulation, the findings of prolonged PK and enhanced tumor accumulation of polymer-paclitaxel conjugates could have important efficacy of antitumor activity. However, none of the polymer based paclitaxel conjugate have as yet been approved by the U.S. Food and Drug Administration. Here we focus this review on specific clinically relevant anticancer polymer paclitaxel therapeutics. This review might shed light on designing and the improves pharmacokinetics of various polymer based and albumin based nanoparticles which can give a better idea for the researchers to go for the preparation of such nanopaclitaxel and lead to be a new and better polymer paclitaxel therapeutics for potential anticancer applications in the clinical applications.

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