Polymeric Nanoparticles for Anti-Cancer Treatment- A Review of its Mechanisms

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ABSTRACT:

Nanoscale drug delivery system is one of the best methods because they are capable to enhance the drug accumulation at the site of action, decrease in off-target effects and help to increase the drug delivery in the cancer. The utilization of the drug is better as compared to the other methods. In these days, polymers are being extensively used to increase the bioavailability of drug molecules and to deliver the drug at specific site. Polymers are attached with drugs are administered in the body, so the leading aim of localized drug delivery to the tumor cell by a controlled release of drugs over a long time period. The polymeric nanoparticles have high anti-tumor activity to wipe out the cancer but very minimum toxicity to the other normal cells. In this review we discussed about method of preparation of nanoparticle like Single or double-emulsion-solvent evaporation method, Nanoprecipitation, Emulsification solvent diffusion [ESD] method, Dialysis, Supercritical fluid technique (SCF). Mechanism of action of polymeric nanoparticles made up of PEG, PLGA, HPMA, CHITOSAN, PLA, PCL on cancer cells.

KEYWORDS: Polymeric nanoparticles, polymers, cancer, mechanism of action.

INTRODUCTION:

Nanotechnology is frequently used in every field like fiber, agriculture, electronics, forensic science, science and medical field. For improving bioavailability, solubility and retention time, biodegradable nanoparticles are frequently used. The nanoparticles loaded with drugs are very helpful to reduce the risk of toxicity of drugs and reduce the economic burden to the patient. Nanoencapsulation of medical drugs (nanomedicines) help to increase the drug efficacy, tolerability and therapeutic index of the corresponding drug. The nanomedicines have many advantages like protection of the loaded drug from premature degradation and interaction with the biological environment. Nanomedicines are also reported to possess enhanced absorption in selected tissue, improvement of intracellular penetration, bioavailability and retention time[1].

Many diseases related bioactive/drugs molecules are encapsulated to improve bioactivity, bioavailability and controlled delivery. Nanomedicines are also useful and compatible of the dreadful diseases like AIDS, malaria, diabetes, cancer, prion diseases tuberculosis in testing these are taking different trial phase and some of them are commercialized. Nanomedicines formulations are depending upon choice of suitable polymeric system for high encapsulation efficacy and improvement of bioavailability and retention time. The encapsulation processes with polymeric nanoparticles are better and advanced as compare to the other nanoparticle systems. This drug Nano formulations containing are better as compare to the traditional medicine with respect to control release and targeted delivery. These targeting capabilities of the drug molecules are increased by architecting careful changes in particle size, surface modification and hydrophobicity. The particle size and size distribution are helpful to determine the interaction with cell membrane, and their capacity to cross the physiological drug barrier[2]. For the cellular interaction of nanoparticles, surface charge is very important so according to target we have to modify the charge, because oppositely charged particles interact with the cell membrane. If the surface on the nanoparticles are occupied with cationic charges, they may help to promote the interaction of the nanoparticles with the cells. For delivery in the target site, the nanoparticle is requiring enhanced systemic circulation in the body. For increasing the

circulation time in the blood, the surface of prevailing nanoparticles is modified with another molecules. Coating of hydrophilic polymers creates a cover on the drug surface and will repel plasma proteins interaction. The drug release can be slow down by the application of the polymers with high molecular weight[3]. By careful design of this delivery system the target and route of administration related problems may be solved for the new class of active molecules.

ADVANTAGES:

The advantages of using nanoparticles as a drug delivery system are:

1. The release of the drug can be altered and delivered at the site of action by which the distribution of the drug in other parts of the body deducted and hence, the therapeutic efficacy can be increased and reduction in side effect can be achieved.
2. The decreased toxicity and occurrence of adverse drug reaction.
3. The utilization of the drug is better as compared to the conventional drug delivery systems.
4. By the help of magnetic guidance the site-specific targeting can be achieved[4].

METHODS OF PREPRATION OF POLYMERIC NANOPARTICLES:

Single or double-emulsion-solvent evaporation method:

Single or double-emulsion-solvent evaporation method is the best method for preparing the PLGA nanoparticles. In the single emulsion process involves an oil-in-water (o/w) emulsification, and in double-emulsion process we use water-in-oil-in-water (w/o/w) technique. For the water-soluble drugs like peptides, proteins, vaccines (w/o/w) method is best suited and give a proper result, whereas the oil in water (o/w) method is preferred for water insoluble drugs such as steroids. In few cases, solid/oil/water (s/o/s) technique is used with PLGA based microspheres, especially on those cases in which high drug loading of large water-soluble peptides[5].

Nanoprecipitation method:

Nanoparticles formation is an instantaneous process and the whole process is carried out in one step. In this process, we require two solvents that are miscible with each other[6]. Ideally, polymer and drug both must be dissolved in the first part of system (the solvent) but not in the second part of system (the non-solvent), Nanoprecipitation is formed, when polymeric solution is mixed to the non-solvent and the process is very fast[7].

Emulsification solvent diffusion (ESD) method:

In this method, the solvent and water are mixed together until the thermodynamic equilibrium is achieved and mixing is done until it reaches the room temperature. The organic solution containing polymer and the drug is properly emulsified in an aqueous surfactant solution by the help of high-speed homogenizer during continuous stirring the water is added in the oil in water emulsion system, after this causing phase transformation and solvent diffusion occurs in the internal phase, and leads to the formation of colloidal nanoparticles. At the end, the remaining solvent is removed by the help of evaporation method or vacuum steam distillation method[8].

Dialysis method:

Dialysis is an effective and very simplest method for create and developed a small size and narrowly distributed nanoparticles identical to the Nanoprecipitation. The polymer is fully dissolved in organic solvent and insert in a dialysis tube. The dialysis performed as a non-solvent miscible with a good organic solvent[9]. The good organic solvent is removed by the non-solvent and in resulting the polymer solubility is loss and ensue the formation of polymer aggregates. Nanoparticles of homogeneous suspension are possessed after the displacing the organic solvent with other non-solvent[10].

Supercritical fluid technique (SCF):

Supercritical fluid technology is a very much interesting and effective technique for the small particle production fends off most of the traditional methods. The supercritical fluid method is frequently used because in this method we use more environmentally friendly solvents and has the potential to produce nanoparticles with high purity and no residual solvent[11]. Two processes have been developed for the manufacturing of nanoparticles using supercritical fluid. First one is the rapid expansion of supercritical solution (RESS) and second one is rapid expansion of a supercritical solution into a liquid solvent (RESOLV) but one of the main and important limitation of the RESS is the use of very low concentration and very low molecular weight PLAs. The limitation of this method is that it is very hard to control particle quality like, morphology and size[12].

Mechanism of action of polymeric -nanoparticles on cancer cells:

In these days, polymers are being extensively used to increase the bioavailability of drug molecules and to deliver the drug at specific site. Polymer/s are attached with drug/s are administered in the body, so the leading aim of localized drug delivery to the tumor cell by a controlled release of drug/s over a long time period. Firstly, enter the systemic circulation, and the polymer slowly releases the attached drug with significant release at the tumor site, and consequently, therapeutic level of anticancer drug is, maintained for the longer time period, making the extraordinarily suitable treatment and compliant for patient. Making the therapy more reliable and compliant by preferable release of anti-cancer drug to the tumor cell and reduce the systemic adverse effect. The extended circulation time is most favorable for drugs those help to show short plasma half-life and rapid clearance. The polymer drug conjugates, micelles, dendrimers and other type of polymeric drug forms are having separate individual structures and are diverse to the other drug –delivery system that hardly entangle the drug in them or solubilize it and extend the drugs into the biological system without build any chemical attachment or bonding with the drug. Linear polymers are the best and most widely used ones for conjugation with the biologically active molecules. Moreover, there are numerous conveniences for modifying the polymeric structure as well as its molecular weight and change into desired qualities. PEG, PLGA, HPMA and other are extensively researched and utilized for their enhancement effect on properties of drugs[13].

The polymeric nanoparticles have high anti-tumor activity to wipe out the cancer with very minimum toxicity to the other normal cells. Incorporate an ibuprofen-based amphiphilic diblock copolymer (POEG-b-PVBIBU) by the reversible addition transmission polymerization of the drug-based vinyl monomer. The diblock copolymer have a capacity to self-assemble into the prodrug nanomicelles and loaded anti-cancer drugs with very high capacity to self-assemble into prodrug nanomicelles and load anti-cancer drugs with very high capacity for example, paclitaxel, doxorubicin. The drug containing polymeric micelles and these polymeric micelles have more good capacity to inhibit the tumor growth then free DOX.

By using TDAPEI, achieved RNA tinkering for cancer therapy, a synthetic derivative of the low molecular weight polythylenimine (PEI) as a very best and very effective carrier of plasmid DNA convert VEGF ShRNA. Polymer where the connection between labeled and stranded PEI and 2, 5 thiophenedicarboxaldehyde [TDA] is connected to imine bonds. In VIVO antitumor effectiveness and gene silencing, the Nanocomplex has demonstrated an efficient and strong impact comparable to PEI as carrier but greater biocompatibility.

NPs have an essentially successful potential to treat cancer. For example, given cerium oxide NPs have carried out strong anti-cancer activities that are commonly attributable to CNPs redox action, whereas the other research documented non-redox mechanisms. From the redox transition, the radiosensitizing impact of CNPs on human keratinocytes is auto sufficient. Mechanisms have been suggested that include particle dissolution with discharge of ce4 + atoms, or differential settlement of catalase vs. superoxide dismutase mimetic behavior with H2o2 build-up, just partly describe these interesting results[14].

PLGA:

The polyester PLGA is the combination of polylactic acid (PLA) and polyglycolic acid (PGA) copolymer. In terms of design and efficiency it is the strongest established biomaterial suitable for drug delivery. Poly lactic acid comprises an asymmetric α-carbon usually defined in classical stereochemical terms as the D or L type and occasionally as the R and S type, respectively. The polymer PLA's enantiomeric forms are D-lactic acid (PDLA) poly and L-lactic acid (PLLA) poly. PLGA is usually an acronym for poly D, L-lactic-co-glycolic acid in which the sources of D- and L-lactic acid are in similar proportion. The PLGA are less hydrophilic, retain less water and degrade more gradually afterwards. PLGA shall be able to produce the payload for the expected therapeutic impact with sufficient extent of biodistribution and concentration. The basic properties include structure, geometry and location, must also integrate vehicle deterioration and clearance mechanisms as well as compatibility with active pharmaceutical ingredients (API).

PLGA's biodistribution and pharmacokinetics adopt a dose independent profile. In addition, previous researches show that both blood clearance and mononuclear phagocyte (MPS) uptake could be based on the dosage and structure of PLGA carrier systems. Formulation of PLGA, such as nanoparticles, easily accumulates in the liver, bone marrow, lymph nodes, spleen and peritoneal macrophages. The PLGA carriers 'degradation is fast on the initial stage (around 30 percent) and gradually slows to be cleaned in the lung by respiration. Studies have examined the role of surface modification in overcoming these limitations, indicating that integration of surface modifying agents will substantially improve the half-life of blood circulation[15].

PLGA nanoparticles are appropriate for using this so-called passive targeting technique, such as high stability and tunable sustained blood circulation time. This passive targeting strategy was introduced to chemotherapy-based PLGA-based nanoparticles. such as doxorubicin (DOX), PTX, cisplatin, and curcumin (CUR) to enhance antitumor activity, improve stability and prolong circulation time of the drug by protect it from the blood components. Phagocytic absorption represents the time of blood circulation inverse relationship for actively targeted nanoparticles possess stealth properties can resist phagocytic uptake and thus circulate in the blood longer. In addition, the encapsulation of anticancer drugs in biocompatible polymers and the passive delivery to the tumor site decreased drug side effects substantially. In line with such a, cisplatin-encapsulated nanoparticles also did not cause major changes in body weight and blood urea nitrogen plasma levels in tumor-bearing mice (while the free drug resulted in a rise in both parameters) suggesting decreased adverse effects for PLGA nanoparticles compared to the free drug. Therefore, the encapsulation of antitumor drugs via PLGA nanoparticles increases the potency of antitumor, and also significantly reduces adverse effects in the body.

Nanoparticles are capable to bind with the receptors or antigens on tumor cells, tumor microenvironment, or tumor vasculature in order to improve the specificity to the target site and to encourage cellular uptake. Biotin, folic acid, antibodies and peptides are ligands widely used during PLGA nanoparticles. However successful targeting can also cause adverse effects: due to increased opsonization and recognition by the MPS, circulation time is most often shortened after surface modification. These details motivated researchers to build nanoparticles that target receptors in various tumor cell differentiation states that are overexpressed. For example, functionalized hyaluronic acid nanoparticles bind to the CD44 receptor, which would be over-expressed in both the stem cells of breast cancer and typical cancer cells. Despite combined care tumor cells proliferated after removal of the medication in case of treatment with PLGA nanoparticles loaded with only one of the drugs.

PLGA nanoparticles, their surface modification plays a significant role in strategic selection, biocompatibility and the half-life of the blood. In particular, this latter can be improved by combining PLGA with other polymers such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), and d-α-tocopheryl PEG 1000 succinate (TPGS). Surface alteration through, for example, PEGylation (PEGylation) improves formulation hydrophilicity resulting in stealth particles with increased blood circulation time and enhanced pharmacokinetics by preventing opsonization and mononuclear phagocyte system uptake. However, for the same reasons, target cell absorption (which may be mandatory depending on the treatment) may also be decreased and the targeting capabilities of these particles are extremely dependent on the specific chemical composition of the surface. Synthesized CUR-loaded PLGA nanoparticles with and without PEGylation via a single emulsion solvent-evaporation technique and compared both formulations with a free drug, showing that PEGylation may boost the pharmacokinetic properties of the product and PLGA particles. The biological half-life of the CUR after per administration for PEGylated PLGA nanoparticle formulations was also improved compared to non-PEGylated formulations, and the bioavailability of the loaded CUR could be increased[16].

PLA:

PLA was widely used in the production of drugs because of their biodegradable and flexible mechanical properties. They can be engineered and synthesized with various molecular weights and L: G ratios for individual applications at low cost with high reproducibility. For enhancing the oral bioavailability of poorly water-soluble drugs, PLA nanoparticles were suggested. After oral administration, Nano-particles are believed to be absorbed from the gastrointestinal tract. Low water-soluble drugs with sufficient oral bioavailability are challenging to convert into acceptable dosage forms. Particles loaded with a poorly soluble drug that increases the rate of dissolution of drugs dramatically. The intestine has a unique system for consuming particles with a size of 100 nm and displays a much stronger absorption than larger particles[17]. PLA-based micro- and Nano-particles have shown particular promise in improving protection from plasma enzymes, alternative routes of administration (e.g., nasal, oral, pulmonary, and mucosal), and prolonged gene delivery efficacy[18]. One of the main delivery systems for just the small interference RNA (siRNA) system is cationic PEG–PLA nanoparticles. Systemic delivery of small interfering polo-like kinase 1 (siPlk1) by PEG–PLA nanoparticles significantly decreased the tumor growth in a murine xenograft model of MDA-MB-435s (cancer cells). It was shown that siRNA encapsulated in PEG – PLA nanoparticles entered the cells effectively, resulting in a remarkable gene-specific knockdown in the heart of adult zebra fish. For either the incorporation of genes, PLA-based nanoparticles containing polythylenimine (PEI) were used on their surfaces. Also used in the co-delivery of supercoiled minicrcle (mc) DNA vectors and Dox was PEO–PLA–PEI. Such Nano carriers have the benefit of non-fouling oxazolines for biological stability, PLA for Dox encapsulation

hydrophobicity and bioreductive PEI for gene complication. The dual delivery of mcDNA-Dox to the cell line B16F10 (Mus musculus skin melanoma; ATCC ® CRL-6475TM)-Luciferase tumor-bearing mice resulted in reduced tumor size and viability of cancer cells. Dual or multi-drug delivery systems have recently shown huge potential for cancer and gene therapy in the drug delivery field.

The flexibility is one of the benefits of using PLA for making nanoparticles. Physical properties, such as size and shape, and chemical properties, including molecular weight can be easily managed to achieve appropriate pharmacokinetic and biodegradable properties. Use Nano-particles, vaccines have been extremely successful in preventing many infectious diseases. AIDS, hepatitis B, anthrax, SARS, and MERS are the subject of new vaccines. Most research teams work on developing single-shot vaccines based on Nano-particle based on PLA materials. HIV Gag antigens (p24)-coated PLA nanoparticles obtained from HIV-1 monocyte-derived dendritic cells (MDDCs) induced MDDC maturation and enhanced proliferation of HIV-specific CD8 + T-cells compared to p24 alone. For the encapsulation of the hepatitis B surface antigen (HBsAg) as an oral vaccine delivery system, PEG - PLA - PEG block copolymer Nano-particles were evaluated. HBsAg encapsulated copolymer and PLA nanoparticles were used for adjutancy during oral administration in the production of immune enhancement. PEG - PLA - PEG copolymer nanoparticles, along with mucosal (sIgA) and cellular immune response (TH1), display successful levels of humoral immunity. Analysis of the relationship between PLA - PEG particle size and transportation effectiveness around the nasal mucosal, tetanus toxoid was encapsulated in PLA - PEG particles of varying sizes (200nm, 1.5μm, 5μm, and 10μm) prepared using the double-emulsion solvent evaporation technique. The nasal bioavailability of tetanus toxoid encapsulated into 200nm nanoparticles was higher than into larger particles. PLA- PEG Nano-particles and aluminum phosphate have been used as a potential adjuvant system using tetanus toxoid. The efficiency of encapsulation in PLA - PEG nanoparticles was improved to nearly 90% compared to 55% in a traditional vaccine. PLA-PEG-aluminum (Al) and PLA-Al reported 80% and 50% survival rates, respectively, even at 180 days, compared to 30% of standard tetanus vaccine survival rates. In PLA micro-and nanoparticles, cyclosporine A (CyA) showed improved bioavailability and sustained release kinetics during extended periods of time. Albumin release from PLA micro-particles in vitro was sustained for 1 month after mixing the particles with PEG. PEG - PLA nanoparticles loaded with insulin provided a continuous release for more than 2 months. As PEG molecular weight or PEG content expanded the drug concentration by the burst release. Insulin-loaded PLA-based particles had much more precise and selective release under high pH conditions, which could improve the bloodstream effect of insulin (pH 7.4). Cancer chemotherapy is one of the broad areas of drug delivery. Particles treated with paclitaxel have significantly increased the potency of anti-tumor compared to free drugs. Paclitaxel-loaded Nano-particles from PLA - PEG - PLA showed a sustained release of paclitaxel within one month. Analysis of in vitro cytotoxicity in cancer cell lines reported strong cytotoxicity of PLA - PEG nanoparticles compared to free paclitaxel. The loaded PEG-PLA nanoparticles with Gemcitabine hydrochloride (GEM) had zero-order release profiles. The particles improved the antitumor impact on various cancer cell lines relative to the free drug and showed a significant improvement in cell interaction. The loaded PEG - PLA Nano-particles with Gemcitabine hydrochloride (GEM) had zero-order release profiles. The particles improved the antitumor impact on various cancer cell lines relative to the free drug and showed a significant improvement in cell interaction. For in vivo particle anticancer operation, two xenograft murine models of human solid tumors have been used. GEM - PEG - PLA nanoparticles substantially inhibited tumor growth and enhanced the rate of survival of mice compared to free drug[19]. Docetaxel and tamoxifen were effective breast cancer medications. If both medications are mixed, there is an antagonistic problem as they have different metabolisms. TPGS-PLA primed docetaxel and tamoxifen show a significant decrease in drug antagonism in the cell line of MCF7[20].

PCL:

PCL (poly - caprolactone) is destroyed by hydrolysis of its ester associations in physiological environments (such as in the human body) and has thus gained significant attention for use in drug delivery. Due to its slower degradation than polylactide, it is extremely important for the preparation of long-term implantable devices. The delivery of therapeutic molecules exclusively or preferentially to the target site at the appropriate dose for a fixed duration is really necessary for an effective drug delivery system[21]. Due to its slow rate of degradation, PCL is a preferred polymer particularly used as a long-term drug delivery carrier. Another benefit of PCL is its compatibility with a broad range of drugs that, due to its hydrophobic nature, provide homogeneous distribution of particularly lipophilic drugs in the carrier matrix[22]. While metallic and ceramic drug carrier systems operate, polymeric systems have become much more important due to their flexibility. As a blood-brain barrier, Nano will cross biological barriers. It is therefore used for delivery of several medications such as; a) Cisplatin hydrophilic drugs, Doxycycline, Tetracycline. B) hydrophobic (Curcumin, Dexamethasone, Paclitaxel, Ketoprofen, Cannabinoid, etc.) and c)

amphiphilic (Amiodarone). Hydrophilic drugs appear to move in the direction of both the interface and remain adsorbed on the surface. PCL degradation rate can be adapted to the requirements of specific applications by preparing its copolymers, composites and mixtures[23]. Biocompatibility and efficacy tests on PCL-based materials were performed in vitro and in vivo, and many PCL-based drug delivery devices were authorized by the FDA. Many tumor cells have an acidic environment that motivates the development of pH-sensitive drug delivery systems, thereby reducing the toxic side effect of anticancer drugs. Qi et al. prepared pH-responsive micelles (approximately 100 nm) from a PEG and PCL diblock copolymer connected to a pH-sensitive hydrazine (Hyd) bond using solvent evaporation method and loaded with Paclitaxel (PTX), an anti-cancer drug. These copolymer micelles involving biodegradable and pH sensitive hydrazone were highly toxic to HepG2 cells. In some other study, micelles prepared by membrane dialysis were loaded into guar gum grafted poly(π-caprolactone) (GG-g-PCL). Approximately 18 percent of the drug loaded into micelles (approx. 75-162 nm), w/w. Micelles showed the first initial rupture release followed by a continuous release over a 10-68 h period[24].

PCL is biodegradable but also more stable compared to polylactides because it has fewer frequent ester bonds per monomer, so it takes more time for PCL chain fragments to be enzymatically hydrolysed in the body. Degradation relies, in addition to many other considerations, on the molecular weight, form, residual monomer content, autocatalysis. In overall, complete degradation of PCL in a constantly changing interstitial fluid takes 2-3 years in the biological media[25].

Chitosan:

Chitosan is a natural polysaccharide that is non-toxic, biocompatible, biodegradable, and processed from chitin by deacetylation. Increased bio distribution, improved precision and sensitivity, and decreased pharmacological toxicity are obtained by combining chitosan with nanoparticles, making them ideal polymer platforms for the development of new drug release systems for pharmacology and therapy. Chitosan nanoparticles (CNPs) might be administered via non-invasive routes such as oral, nasal, pulmonary and ocular routes. However, CNPs have been proposed as non-viral gene therapy vectors and also have demonstrated their adjuvant role in vaccines. CNPs are also used in the delivery of chemotherapy drugs through combining them with monoclonal antibodies in some specific cancer patients with such a reduction of drug side effects[26].

CNP can be an adjuvant candidate which is safe and effective for therapeutic vaccines. Experimental results have shown that CNP has a strong potential to increase cellular and humoral immune responses, resulting in a respectful response to Th1/Th2.

CNP and its toxicity for the supported immune response against ovalbumin (OVA) in mice[27]. For OVA alone or with OVA diluted in saline containing Quil A, chitosan, or CNP, the mice were subcutaneously immunized. No cell death or adverse effects were caused by CNP. We found that CNP increased significantly the serum OVA-specific antibody titers IgG, IgG1, IgG2a, and IgG2b and splenocyte proliferation induced through Con A, LPS, and OVA relative to OVA and chitosan classes. CNP significantly increased NK cell activity destroying activities. CNP also significantly facilitated the development of Th1 (IL-2 and IFN-π) but also Th2 (IL-10) cytokines or upregulated the expression of IL-2, IFN-π and IL-10 cytokines in immunized mice splenocytes compared to OVA and chitosan groups. a significant increase in humoral both cellular immunities in immunized mice, which avoided E infection. Coli and survived whereas the control mice displayed clear infection signs and lesions. Our findings showed which CpGCNP inoculation significantly increased the amount of IgG, IgM, and IgA in the immunized mice sera. Raised numbers of white blood cells and lymphocytes and high IL-2, IL-4 and IL-6 levels have also been observed in CpG-CNP mice. It indicates that CpG-CNP can be used as an important adjuvant to enhance porcine immunoprotection and tolerance to infectious diseases. The interaction mechanism between chitosan and fat is not well known and has not yet been clinically proven to become an effective substitute to help lose weight during the diet or maintain one's weight[28].

PEG:

PEG, as a synthetic biodegradable scaffold, shows good biocompatibility and low immunogenicity, and is non-toxic. PEG is soluble in water, as well as in other organic solvents. PEG prevents the development of vacuoles and scars, and it does not build up in the body. PEG prevents degeneration of nerve fibres, reduces inflammatory response, protects the nervous membrane, reduces cell death, protects mitochondria, accelerates the development of electroneurographic signals and can be used as a sealant for wounded axon membranes. PEG hydrogels can be used as soft polymers as drug carriers whose size, structure and function can be managed to have a differential effect on

in vivo biological properties. Electron beam lithography and ultraviolet optical lithography were used to thoroughly monitor the size and shape of hydrogels, effectively generating manageable size and nanostructure PEG hydrogels[29].

In the early stage of Spinal Cord Injury (SCI), PEG was shown to reduce the inflammatory reaction and effectively prevent nerve fiber degeneration indicated that the application of PEG in the acute phase of SCI would inhibit the development of vacuoles and wounds, effectively inhibit nerve fiber degeneration and establish a good microenvironment for nerve fiber regeneration. PEG's role in blocking nerve fiber degeneration may be attributed to its ability to preserve the integrity of cells, minimize antigen release and mitigate inflammatory response. After extreme SCI, PEG hydrogels can quickly restore the nerve conduction, promote axon myelination and enhance sensory and motor functions. The implantation of PEG hydrogels into the cavity may provide an attachment or a new route for continuous astrocyte migration that migrates to the empty region, prevents cell aggregation, and inhibits the formation of scars. Upon resection of a chronic SCI scar, Estrada and group had inserted an immunologically inert PEG600 material into the scar region; their findings showed that long-range axonal regeneration in the scar region was conducive to the migration of beneficial cells (Schwann cells, endothelial cells and astrocytes) and elongation (astrocytes), facilitating neurological recovery[30].

Through securing cell membranes and mitochondria, PEG decreases cell apoptosis and eliminates free radicals, and prevents lipid peroxidation. PEG inserted at the injury site substantially reverses the damage-induced changes in the permeability of the cell membrane. PEG implantation in pigs at the site of the fully transected spinal cord facilitates the regeneration of the spinal cord and is conducive to the restoration of function of the spinal cord. Luo et al. had reported that PEG decreases caspase-3 activity significantly after SCI by restoring damaged cell membranes and decreasing programmed cell death. PEG's association with mitochondria enhances mitochondrial activity, decreases cytochrome c release, and then prevents cell apoptosis. The application of PEG aqueous solution in the subarachnoid space reduces the cavity and facilitates restoration of function in dogs, and its local application preserves nerve membranes and accelerates the development of electroneurographic signals[31].

HPMA:

As a water-soluble material, pHPMA is purified primarily by renal excretion from the body. Conjugating a drug to the backbone of HPMA polymer increases the solubility and stability of the drug, enhancing its half-life in blood circulation. It was observed that the conjugate accumulates in tumor tissue at far higher concentrations when the Mw of an HPMA conjugate is above renal threshold (~50 kDa) than in normal tissue/organs. Maeda described this phenomenon as the enhanced effect of permeability and retention (EPR) caused by the leaky walls of the tumor's unstable growing vasculature and less developed lymphatic drainage system. HPMA was used to develop doxorubicin containing conjugates and was the first synthetic polymer-anti-cancer drug conjugate to be put to clinical trials in 1994. Nevertheless, the researchers stressed in the rational design of polymeric conjugates after an initial period of lousy patch and succeeded in the good clearing of phase II clinical trials. Some of the researchers also produced and tested drug-HPMA conjugates across different types of cancer[32]. a conjugate of HPMA-copolymer/9-Aminocamptothecin (9-AC) against an orthotopic colorectal cancer model with an applied spacer. For the research, nude mice with HT29 cancer cells subcutaneously induced were used. Significant tumor suppressive function was found in the treated group of HT29 xenografts. Compared to free-drug treatment, systemic toxicity during oral administration has been high. Significant differences were observed in the tumor size of treated and untreated categories. The study revealed that 9- AC was released slowly in the colon and that the drug lasted in the colon for about 24 hours making the delivery site specific[33]. Williams et al. have brought development to the technique. Using a graft-from method, they used RAFT technique for covalent and site-specific HPMA polymer attachment to 7-ethyl-10- hydroxycamptothecin (SN-38). The corresponding conjugates showed excellent water solubility and stability. The conjugate's cytotoxic activity was similar with that of the parent drug. The conjugates derived from RAFT demonstrated specificity for invitro tumor cells. Peng and Kopecek established a conjugate of HPMA-doxorubicin that was further connected to iRGD, a peptide penetrating cell. This whole system was responsive to MMP2 enzyme. A tetra-peptide spacer that is lysosomally cleavable used to allow the conjugate for tumor penetration. The concentration of drugs in DU-145 cancer cells contained in conjugate layers was comparatively higher than drug retention in control groups. The cytotoxicity results show that at stage G2/M, the conjugate results in a higher cell cycle detention. The cytotoxicity planted against cancer cells by the formulated conjugate was more prominent than the effect of a pure drug or a mixture of a simple drug peptide. Likewise, in 3D multicellularDU-145 cancer cells, it also displayed full cell penetration efficiency. These results indicate increased nano-conjugate penetration and aggregation into tumor cell mass, which is due to iRGD's covalent attachment to the conjugate via enzyme-sensitive bonds[34].

CONCLUSION:

Polymeric nanoparticles are capable of improving the bioavailability, solubility, retention time and capable to reduce the risk of toxicity and this nanotechnology helps to increase the drug efficacy, tolerability and the therapeutic index of corresponding drug. Nanomedicines have capacity to enhance the absorption in the selected tissue, improvement of intracellular penetration, bioavailability and retention time. Nanomedicines are also capable to the deadfall diseases like cancer. Polymers are attached with drugs and administered in the body, so the leading aim of localized drug delivery to the tumor cells by a controlled release of drug over a long time period. The polymeric nanoparticles have high anti-tumor activity to wipe out the cancer cell but minimum toxicity to the other normal cells.

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