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Review Article

POLYLACTIDE-CO-GLYCOLIDE NANOPARTICLES THERAPEUTIC BENEFITS IN CANCER

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ABSTRACT
Anticancer therapy majorly hindered by drug low water solubility, poor drug permeability, and high efflux of drug from cells. Nanotechnology is severing as an important tool to overcome these problems of cancer drug therapy. Nanomaterials have been used to enhance drug delivery at targeted site with less toxicity to healthy cells. Biodegradable polyester, polylactide-co-glycolide is approved for use for humans. Review is focusing on recent developments concerning polylactide-co-glycolide nanoparticles prepared for cancer treatment. We have reviewed, methods used for the preparation and characterization of polylactide-co-glycolide nanoparticles and their applications in the delivery of a number of active agents. Polylactide-co-glycolide nanoparticles have provided the necessary momentum for promising future use of these agents in cancer treatment, with higher efficacy and fewer side effects.
KEYWORDS: PLGA, Biodegradable polymers, Nanoparticles, Cancer

INTRODUCTION

Developments in nanotechnology have been enabled new research strategies in enhancing the drug delivery developments. There has been notable development happing in nanoparticles as an efficient drug dosage form and carriers.[1] Nanoscale drug delivery systems have shown the ability to encapsulate a variety of therapeutic agents, such as small molecules (hydrophilicand/or hydrophobic), peptide protein-based drugs, and nucleic acids.

Polymeric nanoparticles provide significant flexibility in design because different polymers from synthetic or natural sources can be used. Polymeric nanoparticles may represent the most effective nanocarriers for targeted drug delivery. Some common polymers used for nanoparticle formation include polylactide-co-glycolide (PLGA), polylactic acid, dextran, and chitosan. Biodegradable polymers are typically degraded into oligomers and individual monomers, which are metabolized and removed from the body via normal pathways.[2,3] PLGA is one of the most commonly used degradable polymers. PLGA synthesis has shorter reaction times and higher monomer conversion rates.

PLGA has generated tremendous interest due to its excellent biocompatibility, biodegradability, and mechanical strength.[4] PLGA biodegradation is an important step because it determines the rate and mechanism of the release of therapeutic agents. Therapeutic agent release from nanoparticles have been shown to be biphasic, in beginning, by diffusion through the polymer matrix and later, bydiffusion and degradation of the polymer matrix.5 Biodegradation of PLGA copolymers are by hydrolytic cleavage of the ester linkage to lactic and glycolic acid. These metabolitesdegraded via the Krebs cycle and eliminated from the body.[6]

PLGA polymers have been extensively used for pharmaceutical and biomedical applications. It has become important ingredient of various polymeric devices, such as microspheres, microcapsules, nanoparticles, pellets, implants, and films. PLGA can be formulated easily into various drug delivery systems. Some of the formulations of PLGA are now approved by the Food and Drug Administration for human.[6, 7, 8]

Preparation Methods of PLGA nanoparticles

In the preparation of polymeric nanoparticle different methods are used such as reverse salting-out, nanoprecipitation, emulsification solvent evaporation and diffusion method.

Emulsification solvent evaporation method

This method is most frequently used for nanoparticles preparation. In first step, drug and polymer needs to dissolve in a water-immiscible volatile solvent, such as chloroform, thereafter, it is emulsified in stabilizer containing aqueous solution. Emulsification is carried-out in a high-energy shearing source such as ultrasonic device or homogenizer. The volatile organic phase is evaporated in vaccum or reduced pressure, which results into formation of fine nanoparticles. The nanoparticles are collected by high speed ultracentrifuge and washed with distilled water and lyophilized for the better storage. This method is useful for lipophillic drugs. However, for hydrophilic drugs, double-emulsion technique is used. In this method, aqueous drug is mixed with organic polymer with vigorous stirring.[1, 10-13]

Emulsification solvent diffusion method

In this method, partly water soluble solvent is used for the emulsification. Polymer is added with vigorous stirring in the stabilizer containing aqueous solution. Which is resulted into formation of oil-in-water emulsion, it is then diluted by using pure water. This dilution is resulted into dispersion of droplets by diffusion from the droplets and precipitation of polymers.[8, 14,15]

Emulsification reverse salting-out method

This emulsification technique is carried-out by addition of polymer and drug into water-miscible solvent, such as acetone. Thereafter, above preparation has been vigorous mixed with aqueous solution containing salting-out agents, such as calcium chloride, magnesium chloride and colloidal stabilizer, such as polyvinyl pyrrolide. This oil-in-water emulsion is diluted in pure water, which causes diffusion of acetone in the aqueous phase and subsequently formation of nanoparticles. At the same time, dilution leads to sudden decrease in the salt concentration from continuous phase of emulsion and pushes the polymer solvent out of emulsion

droplets. The excess of the solvent and salting-out agent are removed by cross-flow filtration.[1, 8, 16, 17]

Nanoprecipitation method

This method is useful for lipophillic drugs nanoparticles preparation. The ingredients are used in this method, polymer, polymer solvent, and nonsolvent of the polymer. The solvent should have few characteristics, such as organic in nature, miscible with water and easy evaporation. Most commonly used solvent for nanoprecipitation is acetone. The drug, polymer and lipophillic surfactant are mixed together and then dissolved in water miscible solvent, such as ethanol or acetone. This miture is poured or injected in stabilizer containing aqueous solution under magnetic stirring. Nanoparticles formation takes place by solvent diffusion and solvent is removed by reduced pressure or vaccume.[6, 8, 18-21]

PLGA NANOPARTICLES FOR DRUG DELIVERY TO TUMORS

According to World Health Organization, millions of people are died and suffering from cancer. Thus, cancer treatment is big concerned and health burden world-wide. Different strategies are being used for cancer diagnosis, treatment and prevention. However, there is a need of effective cancer treatment. Available cancer therapies are associated with less specificity, adverse effects, and toxicities. The conventional drug formulation, such as tablets, capsules, and intravenous injections are in routine use but due to non-specificity and less availability of active drug at target site make these formulations less effective. There is need of drug formulation, which can specifically release the drug at target site of cancer and cause maximum damage to tumor. Nanoparticles have advantage over conventional drug delivery system, such as nanoparticles can pass through small blood capillaries, and more drug availability at target site.[22] Recent development in the anti-cancer drugs is as discussed in detail.

Paclitaxel

Paclitaxel is useful drug against different types of cancer. However, due to poor cell penetration, paclitaxel cannot exert its full effect. Paclitaxel loaded PLGA nanoparticles have markedly increased anticancer effect. Increased paclitaxel loaded PLGA nanoparticles accumulation and retention was observed in MCF7 and MCF7TR-tumor bearing mice.[23] Paclitaxel loaded PLGA nanoparticles has increased efficacy in different types of cancers such as lung cancer[24], C6 glioma[25], HeLa cells[26] and Retinoblastoma cells.[27] Vitamin E-TPGS emulsified PLGA nanoparticles have shown improved bioavailability of paclitaxel in vitro and in vivo studies.[28] Conventional formulation of paclitaxel cannot cross blood brain barrier but paclitaxel loaded glutathione-coated PLGA nanoparticles could serve as a better therapy for brain cancer.[29]

Cisplatin

Cisplatin loaded PLGA nanoparticles were more effective in delaying tumor growth and survival of HT29 tumor bearing mice than conventional cisplatin delivery system.[30] Cisplatin loaded PLGA nanoparticles were serve as more effective against prostate cancer[31], osteosarcoma[32] and ovarian cancer.[33]

Doxorubicin

Doxorubicin nanoparticles of acid-ended PLGA showed pH-dependent release in MDA-MB-231 breast cancer cell line.[34] Doxorubicin loaded PLGA nanoparticles has improved efficacy and selectivity in carcinoma treatment, such as breast cancer[35], lung cancer[36] and uterine cancer[37]. Doxorubicin loaded PLGA polyethylene glycol nanoparticles has improved pharmacokinetics and cytotoxicity in lung cancer.[36] Synergistic effect was observed on tumor growth inhibition when nanoparticles loaded with doxorubicin and paclitaxel.[38]

Vincristine

Vincristine and Verapamil dual agent loaded PLGA nanoparticles showed enhanced cytotoxicity in multidrug resistance cancer than conventional formulation.[39] Dextran sulfate-PLGA hybrid nanoparticles have enhanced oral bioavailability and increase uptake in MCF/ADR cells.[40]

Curcumin

Curcumin loaded PLGA nanoparticles has improved adjuvant effect in prostate cancer.[41] These nanoparticles have shown selective and better inhibition effect on metastatic cancer growth than traditional formulation.[42] Curcumin loaded PLGA nanoparticles enhanced chemo/radio-sensitization in ovarian cancer cells.[43] These nanoparticles have improved efficacy in different cancer, such as metastatic breast cancer[44] and human neuroblastoma SK-N-SH cells.[45] Curcumin pharmacokinetic profile has been improved and able to cross blood brain barrier.[46]

CONCLUSION

Nanoparticles have tremendous potential in futuristic anti-cancer drug therapy over conventional drugs delivery system. Biodegradable polymer, PLGA is an ideal for the preparation of nanoparticles because of its biocompatibility and biodegradability properties. Drug loaded PLGA nanoparticles can effectively target tumor through passive targeting and retention by appropriate ligand. Thereby, drug loaded PLGA nanoparticles can achieve more efficacy at target site and less toxicity to healthy tissues. However, drug loaded PLGA nanoparticles delivery system will need more research and studies on pharmacokinetics and pharmacodynamics.

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