Review Article

Poly (Lactic Acid) Nanoparticles: A Promising Hope to Overcome the Cancers

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Abstract

Nanoparticles are used mainly for the transmission of the therapeutic molecules (like drugs, proteins, or DNA) to the organ/tissue of human body. Polymeric nanoparticles are mostly applied for therapeutic effectiveness in cancer therapy. The micro environment of tumor tissues in vessels can assist nanoparticles in achieving their anticipated accumulation. Poly (lactic acid) (PLA) is a novel green polymer with natural sources (like sweet potato and sugar cane). PLA is a linear aliphatic which has great sustainability, renewability and compostability. PLA has popper mechanical, thermal and barrier properties. This biomaterial is thermoplastic polyester with biocompatibility, non-toxicity and biodegradability. Various forms of PLA nanoparticles are synthetized for biomedical applications like cancer treatments and wound healing process. This review article introduces the various structures of polylactic acid nanoparticles used to deliver anticancer drugs. Furthermore, the investigational approaches that are considered for using PLA nanoparticles in treatment of different types of cancers will be reported briefly.

Keywords: Poly (Lactic Acid), Polymeric Nanoparticle, Cancer Treatment, Drug Deliver, Gene Delivery, Tumor Cell

Introduction

Cancer is the main reason for death in industrialized countries (1, 2). Now, the conservative therapeutic methods for the treatment of cancer are surgery, radiotherapy, and chemotherapy (3, 4). Chemotherapy, which is presently extensively applied, offers high toxicity as chemotherapeutic agents impose injury to healthy cells (5-7),), thereby controlling the therapeutic effectiveness (8-10). Consequently, the chief objective of nanomedicine in the treatment of oncological illnesses is to selectively carry the drug just to cancer cells (11-13) so as to advance its efficiency and decrease its

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toxicity(14, 15). Up to now, numerous chemotherapeutic drugs like doxorubicin (DOX), curcumin (CUR), paclitaxel (PTX) and camptothecin (CPT) have been combined with nanoparticles in several kinds of cancer(16-19). For healing the neoplastic pathologies, drug delivery arbitrated via nanoparticles could include passive targeting or active targeting (20-23).

Passive targeting includes the release of the drug by developing the distinguishing vascularization of the tumor tissue (24-26) that lets the passageway of the molecules over convection or passive diffusion in the interstitial space and the cells themselves (26-28). Especially, the improved infusion and retaining influence is oppressed, a procedure found in furthermost cancers disturbing humans (29-31). While situations, for instance an inflammatory-state or hypoxia are existent(32, 33), the endothelial lining of blood vessels converts further permeability, permitting the passageway of molecules that accrue in the interstitial space(2, 3, 21, 34). Active targeting is definite with the satisfactory functionalization of the nanoparticles via fixing on the surface of particular antibodies, proteins and peptides (23, 35-37). Generally the ligand is selected based on the kind of receptor (38-41), that is evenly over expressed in tumor cells (2, 7, 28).

By means of merging chemo therapeutics, a synergistic influence can be attained(15, 30, 42). Combination therapy delivered with nanoparticles, makes cancer cells further predisposed to the delivered therapeutic agents(4, 31, 43, 44).

Poly (Lactic Acid)

Numerous polymers (natural and synthetic) are applied for producing nanoparticles (27, 45, 46); between the presently maximum active materials, some biobased polymers, like poly (lactic acid) (PLA) can be named (20, 34, 47, 48). PLA molecules are composed of simple monomers which certainly exist in the human body (49, 50), so simply defecated without remaining toxic (51-54).

PLA nanoparticle has attracted the most attention as a useful nanostructure in cancer treatment because this biomaterial has some benefits over other materials used in this field as follows (55-57):

- PLA nanoparticles have nice biological communications with the host cells in the human body.
- PLA degradation rate equals the healing time of damaged human body tissues.
- PLA degrades to monomeric units of lactic acid as a natural intermediary in carbohydrate absorption.

PLA is a biobased, bioresource, bioactive, biodegradable, bioabsorbable and biocompatible material (58-61). It has a chemical structure like linear aliphatic polyesters and is made up of Lactic acid (2-hydroxypropionic acid, CH3–CHOHCOOH)(62-65).

This biomaterial is used alone or in combination with other polymers to produce nanoparticles. These nanoparticles have been used as carriers of drugs or genes in the treatment of various diseases such as cancers.

In the following, the different studies and researches based on PLA nanoparticles in cancer treatment field will be highlighted and stated in detail.

PLA nanoparticles for Breast cancer treatment

In 2020, poly(lactide-co-glycolic acid) (PLGA) nanoparticles were manufactured for delivering Dox(doxorubicin) molecules into MCF-7 cancer cells. PLGA nanoparticles presented a burst of Doxrelease in the first hour. The initial burst was followed by a continuous release of the drug until 24 hours. Free Dox lead to a modest reduction of tumor growth, with the tumor volume and weight following treatment ~78% and 55%, correspondingly. Drug-loaded PLGA nanoparticles reduced the tumors from the first size of 26 ± 2 mm3 to 23 ± 2 mm3 after treatment(66). In another work in 2020, PLGA/Honokiol nanoparticles were used for breast cancer treatment. These nanoparticles have a diameter size of 140-250 nm, the zeta potential of -10 to -8 mv and encapsulation efficiency of 70-90%.

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The in vivo anti-tumor activity in mice-bearing tumors after treatment with these nanoparticles showed that the normal tumor size was about 266.89 ± 115.69 mm3 and the proportion of tumor growth inhibition (% TGI) was around 80.85%. Also, the tumor weight decreased from 2.2 to 0.2 gr after this treatment. PLGA/Honokiol nanoparticles can successfully inhibit the in vitro cell growth of breast cancer cells by 80.2% and 58.1% compared to 35% and 31% with PLGA nanoparticles in the case of MCF-7 and EAC breast cancer cells, correspondingly(67).

PLGA nanoparticles coated with chitosan were manufactured by Alshehri et al., as the delivery system for thymoquinone drugs. These nanoparticles presented particle size, polydispersibility index (PDI), and encapsulation efficiency(%EE) in the range between 126.03–196.71 nm, 0.118–0.205, and 62.75%–92.17%. The release profiles of thymoquinone from these nanoparticles revealed a biphasic release, first a significantly rapid release in 4 hours after that, a sustained release up to 24 hours occurred. The rapid release in the initial 4 hours could be because of the faster dissolution of drug molecules adsorbed on the nanoparticles' surface. The sustained release after 4 hours to 24 hours was owing to the thymoquinone encapsulated in the internal core of the polymeric matrix, which was released gradually by slow diffusion. Antioxidant assays of PLGA/Thymoquinone/Chitosan nanoparticles displayed a maximum activity of 96.24% 6.78%, whereas PLGA/Thymoquinone nanoparticles and pure thymoquinone represented 81.58%±5.78% and 69.26%±4.84%, correspondingly. Cytotoxicity analysis of PLGA/Thymoquinone/Chitosan nanoparticles against MDA-MB-231 cancer cells showed that cell viability decreased from 83% to 75% after 48 hours. Also, the cytotoxicity analysis of PLGA/Thymoquinone/Chitosan nanoparticles against MCF-7 cancer cells revealed that cell viability decreased from 96% to 93% after 48 hours(68). In a novel work in 2019 (69), researchers have explored nanoparticles manufactured from the poly ethylenimine (PEI) associated with PLA/poly(ethylene glycol)(PEG)/PLA polymer for effectual DNA encapsulation and DNA delivery. The PLA/PEG/PLA/PEI/DNA nanoparticles were used for gene delivery into MCF-7 breast cancer cells. The mean particle size of nanoparticles was 305.97± 10.74 nm. The efficiency of DNA encapsulation was about 93.72% for these nanoparticles. in vitro release of plasmid DNA from nanoparticles displayed that DNA releasing at first bursts(78% in 1 day), and then occurred gradually(up to 88% in 28 days). Toxicity evaluations of these nanoparticles presented almost no cytotoxicity (cell viability was greater than 83%) in MCF-7 cells. The fluorescence microscopy image exhibited a green emission in some MCF-7 cells treated with nanoparticles. These consequences prove the capability of the nanoparticles to transfer and intracellular release of DNA into the MCF-7 cells. The transfection efficiency of these nanoparticles was 43.08% (69).

Kong et al. (70) stated a novel approach (chemo-photothermal system) to fight against breast cancer. The researchers synthetized poly(ε-caprolactone-ran-lactide) nanoparticles (70). These nanoparticles were used for the delivery of docetaxel (DTX) drug molecules. The results showed that the average size of docetaxel-loaded nanoparticles was 103.4±3.3 nm. The in vitro cytotoxicity examines by MTT presented that DTX loaded nanoparticles together with NIR laser irradiation (chemo-photothermal therapy) could meaningfully inhibit breast cancer cells (MCF-7 cells) proliferation compared with all other groups. The anti-tumor efficacy of this treatment on the nude mice bearing MCF-7 xenograft showed that the tumor volume was decreased from 180 mm3 to 0 after 14 days(70). ß—sitosterol(β—Sit) is nutritional phytosterol having established anticancer action against a board of cancers(71). In a different work, PLGA and copolymers of PEG-block-PLA were applied for encapsulating β—Sit in nanoparticles. Their cellular uptake and anti-proliferative activity were assessed against MCF-7 and MDA-MB-231 human breast cancer cells by means of flow cytometry and MTT assays, correspondingly. In vitro ß—sitosterol

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release displayed an initial burst release, subsequently a sustained release for 408 hours. Flow cytometry examination designated that β—Sit/PLGA nanoparticles were efficiently taken up by the cells in contrast to β—Sit/PEG/PLA nanoparticles. β—Sit/PLGA nanoparticles were, therefore, chosen to assess anti-proliferative activity. Cell viability was reserved by up to 80% in a concentration range of 6.64–53.08 µg/mL compared to the untreated cells. The outcomes proved that encapsulation of ß—sitosterol into PLGA nanoparticles is a capable approach for developing its anticancer action against breast cancer cells(18).

Hoang et al.,(72) stated that PLA/PEG/PLA nanoparticles can display the possibility as an anticancer agent for metastatic breast cancer. These nanoparticles were used for delivery of DOX drug. There was burst release influence in DOX releasing in the first hour, subsequently a comparatively sustained and slow release till 12 hours. The cytotoxicity of nanoparticles was evaluated with CCK-8 viability assay against MDA-MB-231 cell line. Both PLA/PEG/PLA/DOX and PLA/PEG/PLA nanoparticles obviously presented cancer cells growth inhibition. The PLA/PEG/PLA/DOX nanoparticles displayed significantly greater cytotoxicity with two- to five fold reduction in IC50 compared with PLA/PEG/PLA nanoparticles.

Methotrexate (MTX) with chemical formulation of $C_{20}H_{22}N_8O_5$ is a chemotherapy medicine for treating cancer and autoimmune diseases. Massadeh et al.,(73) manufactured the protein-coated PLA/PEG/PLA/methotrexate nanoparticles for breast cancer treatment. The mean particle size of these nanoparticles was about 170±1.1 nm. The entrapment efficiency was 47.8% and the highest loading capacity was 0.77%. in vitro, drug release assays displayed some degree of burst result in the initial 5 hours (about 73%), and the MTX was then released gradually above 72 hours (about 98%), which makes these nanoparticles candidates for sustained release designs. The outcomes displayed that these nanoparticles have the noteworthy potential for application in breast anti-cancer therapies instead of IV treatments(73).

In a different study, Yang et al.,(74) synthetized the PLA/PEG nanoparticles for delivering siRNA to Her2+ and Her2- breast tumor cells. in vivo evaluations in a murine model with Her2+ and Her2− xeno-grafts after treating with these nanoparticles showed that at a dose of 20 µg per injection the tumor growth will be inhibited(74).

PLA nanoparticles for prostate cancer treatment

The prostate gland is an organ that surrounds the urethra of males at the base of the bladder, comprising a muscular portion, which controls the release of urine, and a glandular portion, which secretes an alkaline fluid that makes up part of the semen and enhances the motility and fertility of sperm(75).

Gene expression of PLA/(poly(d,l-lactide-co-glycolide)) nanoparticles encapsulating plasmid DNA was determined in PC-3 prostate cancer cells. The nanoparticles with different DNA content (1.7, 1.8, 1.9 and 2.9 mg/100 mg nanoparticles) were synthetized. in vitro release of DNA from nanoparticles reached 1700 ng that after 7 days. Transfection of nanoparticles in PC-3 cells reached 0.23 pg/mg cell protein after 3 days(76).

PLA nanoparticles for Glioma treatment

Glioma is a kind of tumor that starts in the glial cells of the brain or the spine. Gliomas include around 30% of all brain tumors and central nervous system tumors, and 80% of all malignant brain tumors(77, 78).

In a study by Muniswamy et al.(3) in 2019, prepared PLGA/doxorubicin nanoparticles. The PLGA degraded in the pH ~ 4.5–5.5 in cancer cells and released the doxorubicin molecules. Also, the structure was capable of penetrating the blood/brain/barrier and blood/tumor/barrier. Cell assays using U-87 MG glioblastoma cells presented a 5.5-fold increase in tumor cell death because of enhancement of the expression levels of the caspase-3 gene which referees Cellular apoptosis(3, 79).

Athawale et al,(80) manufactured PLA/temozolomide nanoparticles for treating glioma. Categorization of the PLA nanoparticles indicated

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that 60% of temozolomide was entrapped to the nanoparticles. A biphasic release shape of temozolomide was displayed from these nanoparticles considered by a first fast release of 30% drug throughout the first 2 hours. Afterward, a leisurely and continuous release occurred at very slow rates for a period of 7 days. MTT assay for PLA/temozolomide nanoparticles was evaluated on the U-87 MG cell line. The results showed that after 96 hours, the cell viability decreased from 250 to 105 µg/ml(80).

Also, Gao et al in 2013 synthetized peptide functionalized PLA/PEG nanoparticles as a potential delivery system for paclitaxel medicine for glioma treatment. in vitro release research displayed that in the first 6 hours, a burst release was attained. Twenty four hours later, the release rate was delayed. At the end of 96 hours, the cumulative release of paclitaxel from nanoparticles was 74.83 ± 2.68%(79, 81).

In an innovative work, methotrexate and paclitaxel were co-loaded into PLGA nanoparticles coated with polyvinyl alcohol and Poloxamer188. The mean size of these nanoparticles was around 212 nm, with a zeta potential of approximately -15.7 mV. Encapsulation efficiency and drug loading were determined to be 72% and 4% for methotrexate and 85% and 4.9% for paclitaxel, correspondingly. Glioblastoma cellular uptake of these nanoparticles was established by fluorescence microscopy and cell survival rate was examined through the MTT technique after 48 hours of incubation showing IC50 values of 24.5 $\mu g \cdot mL^{-1}$ for paclitaxel and 9.5 $\mu g \cdot mL^{-1}$(82).

PLA nanoparticles for Leukemia treatment

Leukemia is any of several cancers of the bone marrow that prevent the normal manufacture of red and white blood cells and platelets, resulting in anemia, increased susceptibility to infection, and impaired blood clotting(83).

Zhang et al. (20) have advanced a useful drug delivery system using PLA/Polyvinyl alcohol(PVA) nanoparticles for the treatment of leukemia cancer. These nanostructures carry daunorubicin (anticancer agent) and glycyrrhizic acid (a novel nature material lately evidenced operative for leukemia). The mean diameter of nanoparticles was about 90-100 nm. Glycyrrhizic acid and daunorubicin exhibited alike drug release profiles throughout the 96 hours examination. The plots presented more than 90% release at 48 hours and remained approximately steady subsequently. The quantity of free daunorubicin slowly increased during the 10 hours incubation time in parental leukemia K562 cells, to around 1.3% of the whole incubated drug. For the resistant leukemia K562/A02 cells, intracellular daunorubicin decreased from 0.25% at 1 hour to about 0.1% at 10 hours. For the K562 cells, this treatment efficiently inhibited cell proliferation, removing more than 60% of cells after 24 hours incubation(20).

Chronic myeloid leukemia is a kind of hematopoietic stem cell disease. PLA/PEG/arsenic nanoparticles were manufactured for the treatment of this kind of leukemia. These nanoparticles have a diameter size of 200-210 nm. A primary fast release of arsenic (about 20%) from nanoparticles was seen in 30 minutes at pH 7.4. Though, arsenic was released incessantly for up to 48 hours after burst release, getting a proportion of accumulative release close to 43%. The viability of human chronic myeloid leukemia cells decreased from 93% to 13% after treatment(84).

PLA nanoparticles for treatment of the tumor of immature nerve cells

Glioblastoma and neuroblastoma are both solid form tumors. Glioblastomas primarily reside in the brain, while neuroblastomas are found in the sympathetic nervous system(85). Neuroblastoma is a malignant tumor of immature nerve cells that usually starts in the autonomic nervous system or adrenal gland and spreads quickly, most often affecting young children(86, 87).

Pieper et al. designed the PLGA, PLA and PLA/PLGA nanoparticles for delivering doxorubicin molecules. These nanoparticles have a size variety between 73 and 246 nm. These nanoparticles demonstrated similar drug release behavior characterized by a preliminary burst release (about 80% in the first hour). Then followed by a sustained manner up to 24 hours.

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These nanoparticles reduce neuroblastoma cell viability by 50% after 24 hours(88).

In another research, PLA/Temozolomide nanoparticles were formulated for the treatment of glioblastomas and neuroblastoma. These nanoparticles have a diameter size of 160 nm. U138-MG glioblastoma cells, D283 neuroblastoma cells, and DAOY neuroblastoma cells were applied for this work. These nanoparticles resulted in approximate cell viability above 80% in U-138 cells, DAOY cells and D-283 cells when the nanoparticle concentrations were less than 2 mg/mL(89).

PLA nanoparticles for treatment of Adenocarcinoma

Adenocarcinoma is a malignant tumor arising from the secretory epithelium(90). In a different work, PLA/Tocopheryl polyethylene glycol succinate (TPGS) copolymers were produced for the preparation of nanoparticles. The paclitaxel-loaded nanoparticles were used for cancer treatment. in vitro drug release assay exhibited an initial burst of 22.3%, which is followed by an about first-order release later. After 30 days, the accumulative drug release approaches 55–65%. Cancer cells (HT-29 , Caco-2) were applied for imaging and measuring the cellular uptake of PLA/TPGS nanoparticles. HT-29 cell uptake efficiency of nanoparticles reached 53.1% and the Caco-2 cell uptake efficiency of the nanoparticles reached 55.9% after 24 hours culture. in vitro cell viability of paclitaxel loaded nanoparticles was decreased from 45.5% and 61.4% to 39% and 53.2% after 1day incubation with HT-29 and Caco-2 cells, respectively(91).

PLA nanoparticles for treatment of carcinoma

Carcinoma is a malignant and invasive epithelial tumor that spreads by metastasis and often recurs after excision(92).

In an innovative work in 2020, PLA/PEG/Folic acid (FA)/Fe2O3 nanoparticles were synthesized as a potential delivery structure for doxorubicin drug. The nanoparticle size extended between 71.13 and 257.1 nm. The DOX loading level was between 1.73 to 5.14%(93).

Cytotoxicity of nanoparticles was investigated in HeLa (human cervix epithelial carcinoma cells) and CT26 (colon carcinoma cell). These nanoparticles with different w/w ratios can decrease cell viability down to 65.16 ± 5.8% and 61.38 ± 3.2% for HeLa and CT26 cell lines, respectively. The PLA/PEG/FA nanoparticles at w/w ratio 10:1 presented much less toxicity with cell viability 82.83 ± 4.1% and 80.30 ± 2.1% for HeLa and CT26 cell lines, correspondingly. The percentage of apoptotic cells got 57.75± 3.8% and 61.81± 4.1% after 24 hours for HeLa and CT26 cells, correspondingly. The viability of PLA/PEG/DOX nanoparticles (non-targeted) treated cells was alike for both cell lines (33.81± 1.8% and 32.03± 1.1% for HeLa and CT26 cells, correspondingly). The consequences presented that DOX released progressively from PLA/PEG/FA nanoparticles (Around 90% of the whole DOX was slowly released throughout 120 hours in w/w ratio 10:1)(93).

PLA nanoparticles for treatment of colon cancer

Wu et al.,(94) developed PLGA/Epidermal growth factor/5-fluorouracil nanoparticles for colon cancer treatment. The data showed that these nanoparticles had an average size of 200 nm and loading efficiency of 7.29%. These nanoparticles demonstrated a biphasic drug release form with primary faster release followed by a sustained release in 7 days. 45% of 5-fluorouracil was released from nanoparticles within 6 hours, and 80% of 5-fluorouracil was released in 7 days. To estimate apoptosis induced by these nanoparticles, human colorectal cancer cell line SW620 was stained. Antitumor effects showed that treatment with PLGA/Epidermal growth factor/5-fluorouracil nanoparticles (34%) induced a greater rate of apoptosis than that observed in response to PLGA/Epidermal growth factor nanoparticles (15.4%), PLGA/5-fluorouracil nanoparticles (26%). in vivo antitumor effects of these nanoparticles displayed that the tumor weight in tumor-bearing mice decreased from 400 mg to 200 mg after treatment(94).

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In a different work, PLA/PEG/5-fluorouracil nanoparticles were synthesized for colorectal cancer treatment. The loading capacity and encapsulation efficiency of these nanoparticles were 15.39 ± 0.27% and 85.62 ± 0.79%, correspondingly. in vitro drug release displayed that these nanoparticles have a sustained release at both pH 5.0 and 7.4. The accrued release rates of 5-fluorouracil from nanoparticles at pH 5.0 and 7.4 in 120 hours were 77.67% and 28.35%, correspondingly. Treatment with these nanoparticles induced initial apoptosis in about 33% of SW620 cancer cells. in vivo behavior of these nanoparticles evaluated before the combination treatment. The results presented that the circulation in the blood decreased from 70% to 10% after 48 hours. in vivo combined therapy based on these nanoparticles displayed that the tumor growth decreased from 0.5 mm3/day to 0.25 mm3/day after treatment(95).

PLA nanoparticles for liver cancer treatment

Magnetic targeted drug delivery system (MTDDS) is a novel targeted drug system, which can considerably decrease the amount and improve the therapeutic efficiency of the drug. Presently superparamagnetic ferric oxide shows an essential role as a targeted drug in the treatment of tumors, but cytotoxicity was still observed as a side effect in the procedure of the drug(96).

Xiang et al (97) explored the cytotoxicity effect of PLA/$Fe3O_4$ nanomagnetic microspheres as a carrier for normal liver cells (7701) and liver cancer cells (HePG2). The MTT test of nanoparticles for 7701 cells and HePG2 cells indicates that cytotoxicity of nanoparticles does not affect the growth of normal liver cells at low concentrations. The hemolysis test showed that hemolytic data of these nanoparticles was 0.62%, far less than the standard (5%), and presented no hemolysis response. The research proves that compared with liver cell, liver cancer cells (HepG2) are easy to be disturbed with PLA/Fe3O4 nanomagnetic microsphere, which have progressive sensitivity and absorption ability(97).

Xian Zhu et al.,(34) defined novel PLA nanoparticles for encapsulation of small interfering RNA. The in vitro release behavior of siRNA from nanoparticles showed a burst release in the first 24 hours (23% from 1 mg nanoparticles), then a sustained release (32% from 1 mg nanoparticles) after 280 hours. These nanoparticles targeting the Plk1-gene which make significant apoptosis in HepG2 cancer cells and MDA-MB-435s cancer cells(34).

Zhu et al. manufactured the PLA/Docetaxel nanoparticles with a diameter size of 150 nm, zeta potential of -15.4, PDI of 0.144 and EE of 88.68%. The in vitro drug release patterns stated that all these nanoparticles presented a burst release of docetaxel at the primary phase, viz. around 30% of the encapsulated drug was released in the first 2 days. After 14 days, about 55% of drugs were released from these nanoparticles. In vivo anti-tumor effects showed that the liver tumor weight was decreased from 500 mg to 100 mg after treatment. To estimate the cytotoxicity of these nanoparticles, MTT analysis was done with HepG2 cells. The consequences displayed that the cell viability value was decreased from 25.66 ± 1.54 to 3.29 ± 0.56 after 48 hours(98).

PLA nanoparticles for treatment of pancreatic cancer

Pancreatic cancer is the fourth leading cancer with an 85% mortality rate in many countries alone(99-101).

PLGA/gemcitabine nanoparticles were produced for pancreatic cancer treatment. Gemcitabine ($C_9H_{11}F_2N_3O_{4)}$ is approved as the chief chemotherapeutic medicine for pancreatic cancer treatment(102).

These nanoparticles have a diameter size between 360 nm and 395 nm. The best encapsulation efficiency of gemcitabine was 15%. The in vitro gemcitabine release of nanoparticles showed that a biphasic release profile was detected at pH 7.4 with an initial fast release wherever almost 40% of the drug was released in 7 days. Over the next 21 days, a sustained

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release occurred with an additional release of 20% gemcitabine. Past 28 days, a more speedy release of gemcitabine was seeing with the residual 40% gemcitabine being released by 42 days. The uptake of PLGA/gemcitabine nanoparticles in a pancreatic cancer cell line (PANC-1) occurred in 3 hours(103).

In another investigation, PLGA/Chloroquine diphosphate nanoparticles were manufactured as a novel delivery system for DNA (diameter size: 100-150 nm)(104). These nanoparticles intensely improved gene transfection efficiency in HEK293 and presented an accumulative gene transfection for up to 144 hours. The viability of HEK293 cells treated by these nanoparticles decreased from 95% to 75% after 24 hours. The release rate of DNA and chloroquine diphosphate from the nanoparticles was studied. These nanoparticles had no burst release effect of both DNA and chloroquine diphosphate. The DNA released from the nanoparticles presented characteristic pH-dependent release behavior. At pH4.5, the accumulative DNA release in 24 hours was over 30% and ultimately gotten 60% above 28 days. The accumulative release quantity at acidic media was 254 folding to that at neutral media. The DNA releasing at neutral pH was both very low. The accumulative release rate was about 20% (pH~7.4) and 30% (pH~6.8) at 28 days. In brief, it was wondered that only a very minor quantity of the DNA and chloroquine diphosphate was released from the nanoparticles before reaching the object location, and quick release would be activated in an acidic situation in the endosome after endocytosis. The release of chloroquine diphosphate in all situations was much faster relative to the DNA. The tumor size of mice bearing CT26 reached 3700 mm3 and 1000 mm3 after 25 days, without treatment and after treatment with these nanoparticles correspondingly(104).

PLA nanoparticles for treatment of ovarian cancer

Ovarian cancer is a leading cause of death and the third most common gynecologic malignancy in women(105).

PLA/PEG nanoparticles were designed as delivery systems for paclitaxel(PTX) in ovarian cancer treatment. The particle sizes were 167.54 ± 13.80 nm. The drug release rate of this nano-carrier was 6.98% at 4 hours. After 152 hours, paclitaxel releasing reached 30%, which specified that PLA/PEG/PTX nanoparticles presented delayed drug release. Therapeutic in vivo anti-tumor influences of these nanoparticles presented that the final tumor sizes in the treated mice were remarkably reduced after 25 days (from 822.31 ± 43.10 mm^3 to 477.89 ± 4.66 mm^3 , $p < 0.05$). In tumor-bearing animals, the tumor inhibitory rate was 41.88% in the PEG/PLA/PTX group, which was nearly 1.5 times greater than that in the PEG/PLA (25.99%) group(106).

APRPG(Ala-Pro-Arg-Pro-Gly) peptide modified PEG/PLA nanoparticles were manufactured. in vitro tests presented operative inhibition of proliferation, migration and tube formation in human umbilical vein endothelial cells (HUVECs). in vivo antitumor efficiency of nanoparticles was evaluated in SKOV3 cancer-bearing mice. The final tumor size reached from 420 mm^3 to 75.07±38.19 mm^3 after treatment and this size was reduced (Data are represented as the mean ± S.D. (n = 5)). This is confirming an effective antitumor efficiency of these nanoparticles for SKOV3 cancer-bearing mice(107).

Effects of PLA nanoparticles for treatment of osteosarcoma

In a novel study in 2020, PLA/Salinomycin nanoparticles were produced. Theses nanoparticles exhibited good drug EE (98 ± 0.5%), and loading content (8.8 ± 0.1%). The size of empty PLA nanoparticles resulted in smaller (90 ± 3.2 nm) than the PLA/Salinomycin nanoparticles (110 ± 3.8 nm). Their biological activity was evaluated on osteosarcoma bulk cells MG63, healthy osteoblast cell line (hFOB1.19), and enriched osteosarcoma cancer stem cells (CSCs) after 24, 48, and 72 hours. MG63 viability analysis showed a significant decrease after 48 hours (30%) and 72 hours(65%). hFOB1.19 cells viability analysis displayed a noteworthy reduction after 48 hours (65%) and 72 hours(85%). Enriched CSCs viability analysis exhibited a notable reduction after 72 hours(25%)(108).

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Cell viability assays

The viability of cancer cells treated with different PLA nanoparticles will be summarized in Table 1.

Table 1. Viability(MTT assay) of cancer cells treated with the various PLA nanoparticles.

PLA Nanoparticle	Type of Drug/ Gene	Type of Cancer Cells	Cell Viability (According to Number of hours)			
			24	48	72	Ref.
CA/[PCL-ran-PLA]	-	MCF-7 breast cancer cells	95%	95%	-	(70)
pD/CA/[PCL-ran-PLA]	-	MCF-7 breast cancer cells	98%	93%	-	(70)
Apt/pD/CA/ [PCL-ran-PLA]	-	MCF-7 breast cancer cells	97%	97%	-	(70)
CA/[PCL-ran-PLA] +	Docetaxel 0.25(µg/ml)	MCF-7 breast cancer cells	85%	65%	-	(70)
pD/CA/[PCL-ran-PLA]		MCF-7 breast cancer cells	84%	64%	-	(70)
Apt/pD/CA/ [PCL-ran-LA]		MCF-7 breast cancer cells	83%	55%	-	(70)
CA/[PCL-ran-PLA]	Docetaxel 2.5(µg/ml)	MCF-7 breast cancer cells	65%	51%	-	(70)
pD/CA/[PCL-ran-PLA]		MCF-7 breast cancer cells	64%	48%	-	(70)
Apt/pD/CA/ [PCL-ran-PLA]		MCF-7 breast cancer cells	63%	40%	-	(70)

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CA/[PCL-ran-PLA]		Docetaxel 12.5(µg/ml)	58%	45%	-	(70)
pD/CA/[PCL-ran-PLA]	MCF-7 breast cancer cells	MCF-7 breast cancer cells	56%	43%	-	(70)
Apt/pD/CA/ [PCL-ran-LA]		MCF-7 breast cancer cells	55%	28%	-	(70)
CA/[PCL-ran-PLA]		MCF-7 breast cancer cells	58%	33%	-	(70)
pD/CA/[PCL-ran-PLA]	Docetaxel 25(µg/ml)	MCF-7 breast cancer cells	57%	31%	-	(70)
Apt/pD/CA/ [PCL-ran-PLA]		MCF-7 breast cancer cells	48%	20%	-	(70)
CA/[PCL-ran-PLA]+NIR laser irradiation		MCF-7 breast cancer cells	85%	65%	-	(70)
pD/CA/[PCL-ran-PLA] + NIR laser irradiation	Docetaxel 0.25(µg/ml)	MCF-7 breast cancer cells	84%	65%	-	(70)
Apt/pD/CA/ (PCL-ran-PLA]+ NIR laser irradi-ation		MCF-7 breast cancer cells	80%	55%	-	(70)

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CA/[PCL-ran-PLA] + NIR laser irradiation		MCF-7 breast cancer cells	68%	50%	-	(70)
pD/CA/[PCL-ran-PLA] + NIR laser irradiation	Docetaxel 2.5(µg/ml)	MCF-7 breast cancer cells	65%	45%	-	(70)
Apt/pD/CA/[PCL-ran-PLA]+ NIR laser irradiation		MCF-7 breast cancer cells	60%	35%	-	(70)
CA/[PCL-ran-PLA]+ NIR laser irradiation		MCF-7 breast cancer cells	55%	45%	-	(70)
pD/CA/[PCL-ran-PLA] + NIR laser irradiation	Docetaxel 12.5(µg/ml)	MCF-7 breast cancer cells	42%	32%	-	(70)
Apt/pD/CA/[PCL-ran-PLA]+ NIR laser irradiation		MCF-7 breast cancer cells	36%	20%	-	(70)
CA/[PCL-ran-PLA]+ NIR laser irradiation		MCF-7 breast cancer cells	50%	32%	-	(70)
pD/CA/[PCL-ran-PLA]+ NIR laser irradiation	Docetaxel 25(µg/ml)	MCF-7 breast cancer cells	20%	17%	-	(70)
Apt/pD/CA/[PCL-ran-PLA]+ NIR laser irradiation		MCF-7 breast cancer cells	16%	2%	-	(70)

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PLGA (At 53.08µg/mL of PLGA)	ß-Sitosterol	MDA-MB-231 breast cancer cells	20%	-	-	(18)
PLGA (At 26.5 µg/mL of PLGA)		MDA-MB-231 breast cancer cells	30%	-	-	(18)
PLGA (At 13.27µg/mL of PLGA)		MDA-MB-231 breast cancer cells	55%	-	-	(18)
PLGA (At 6.64 µg/mL of PLGA)		MDA-MB-231 breast cancer cells	60%	-	-	(18)
PLGA (At 53.08 µg/mL of PLGA)		MCF-7 breast cancer cells	20%	-	-	(18)
PLGA (At 26.5 µg/mL of PLGA)		MCF-7 breast cancer cells	25%	-	-	(18)
PLGA (At 13.27µg/mL of PLGA)		MCF-7 breast cancer cells	30%	-	-	(18)
PLGA (At 6.64 µg/mL of PLGA)		MCF-7 breast cancer cells	35%	-	-	(18)

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5% PLA		human liver cancer cell: HepG2	-	1.482 ± 0.307	-	(97)
25% PLA		human liver cancer cell: HepG2	-	1.454 ± 0.225	-	(97)
50% PLA	Fe3O4	human liver cancer cell :HepG2	-	1.242 ± 0.093	-	(97)
75% PLA		human liver cancer cell :HepG2	-	1.233 ± 0.158	-	(97)
100% PLA		human liver cancer cell :HepG2	-	1.172 ± 0.103	-	(97)

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PLA/PEG/PLA/ PEI 15%		MCF-7 breast cancer cells	95%	-	-	(69)
PLA/ TPGS (89:11) TPGS(89:11)	Paclitaxel	HT-29 Human colon adenocarci-noma cells	60%	50%	33%	(91)
PLA/ TPGS (89:11) TPGS(89:11) TPGS(89:11)		Caco-2 Human colon adenocarci-noma cells	82%	78%	65%	(91)
PLGA	-	XB-2 keratino-cytes cells	80%	-	-	(49)
PLGA	Curcumin	XB-2 keratino-cytes cells	90%	-	-	(49)
PLA/PVA	-	leukemia cell K562/A02	90%	-	-	(20)
PLA/PVA/DNR	Daunorubicin	leukemia cell K562/A02	45%	-	-	(20)
PLA/PVA/GA	Glycyrrhizic Acid	leukemia cell K562/A02	70%	-	-	(20)
PLA/PVA/DNR/ GA	Daunorubicin + Glycyrrhizic Acid	leukemia cell K562/A02	60%	-	-	(20)

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Release behaviors of therapeutic molecules from PLA nanoparticles in cancer treatment

❖ Therapeutic molecules

A therapeutic molecule in cancer therapy is a molecularly defined chemical entity of low molecular weight (109), which is applied to a patient to heal or palliate primary proliferative disease (110-112). The most important therapeutic molecules in cancer therapy include small molecule drugs, proteins and DNA(113, 114).

❖ Main factors affecting drug release from nanoparticles

The release behavior of therapeutic molecules is the main factor for polymeric nanoparticle use (115). The release rates of therapeutic molecules from polymeric nanoparticles depend on(116):

1.Desorption of the surface-bound/adsorbed molecule(117);

2.Diffusion from the polymeric nanoparticles(118);

3.Polymeric nanoparticle erosion(119);

4.Combined erosion/diffusion process(120).

In most cases, rapid release from polymeric nanoparticles, called " burst release", can be seen primarily(121).

❖ Mechanism of drug loading and release from nanoparticles

It is stated that the release profiles of the therapeutic molecules from polymeric nanoparticles depend upon the nature of the delivery system. In the case of a polymeric nanoparticle matrix, the therapeutic molecule is homogeneously distributed/dissolved in the matrix and the release happens by diffusion or erosion of the matrix. If the diffusion of the therapeutic molecules is faster than matrix degradation, the mechanism of release happens mostly by diffusion(118, 122).

Rapid initial release or burst release is attributed to the fraction of the therapeutic molecules which is adsorbed or weakly bound to the large surface area of the polymeric nanoparticles rather than to the drug incorporated in polymeric nanoparticles(116, 123).

❖ PLA nanoparticles as novel drug delivery systems in cancer treatment

In the next paragraphs, the release behaviors of anticancer drug molecules (like Docetaxel, Paclitaxel, Doxorubicin, Curcumin) from PLA nanoparticles will be designated.

Catechin is water-soluble, astringent yellow compound ($C_{15}H_{14}O_6$) found in Gambier which holds numerous useful possessions such as anti-carcinogenic and anti-inflammatory properties. In addition, they have been exposed producing an important influence on cell viability that makes them a potential therapeutic agent for the treatment of cancers(124, 125).

Catechin was encapsulated effectively with an encapsulation efficiency of 96% in PLA/PEG nanoparticles (35). The average particle sizes were 300nm, while the zeta potential was -22.1mV . in vitro release of catechin displayed that these nanoparticles at great amounts of catechin exhibited a sudden burst in release. In the case of PLA/PEG/Catechin(10mg/ml) nanoparticles, this burst was noted at the 7th hour with the release of 45.58% of catechin from the nanoparticle. After the first burst, sustained release of the catechin from these nanoparticles was noted and about 75.62% of the total catechin was released in 40 hours. Mathematical modeling of release kinetics was also done. Release profiles were fitted to several mathematical models for determining the release kinetics and release mechanism of catechin. Based on the correlation coefficient ($R^2 = 0.9701$) and release kinetic constant values (k_{HC}=0.0035), PLA/PEG/Catechin(10mg/ml) nanoparticles displayed respectable correlation with Hixson-Crowell kinetics. The value of the release exponent (n= 0.0828) presented that the release mechanism followed was Fickian diffusion (35).

In a different study in 2020, PLA/PEG nanoparticles were synthesized as a delivery structure for doxorubicin drugs. These nanoparticles offered a size between 53 and 133 nm, with a drug loading capacity between 1.2 and 4.4 wt%.

These nanoparticles indicated a burst release of doxorubicin in the first 2 hours (40%) and a sustained release up to 70% over 24 hours(126).

In another work, PET/PLA was applied as controlled drug release structures with gold

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nanoparticles in cancer chemotherapy. PET/PLA/Fluorouracil nanoparticles were manufactured in the existence of gold nanoparticles. The size of these nanoparticles was found to be in the variety of 230–260 nm. The release profiles of 5-Fluorouracil (Fu) from the PLA/PET nanoparticles were presented that the drug release was slow (only 15% in the first 24 hours) and sustained (15.5% in 50 hours). The release rate of 5-Fluorouracil for PET/PLA/Fu@Au nanoparticles was slower than that of PET/PLA/5-Fu nanocapsules. PET/PLA/Fu@Au nanoparticles had a slower release behavior mostly for the reason that gold nanoparticles in nanoparticles delayed the diffusion of 5-Fluorouracil away from the nanoparticles(127).

Docetaxel is a common anticancer drug. In a study by Sim et al.(128) in 2018, PEG/PLA/PEG/Docetaxel micelles were formulated. These nanoparticles have the loading content of 7.4, 10.9 and 12.4% docetaxel with a loading efficiency of 81.9, 65.3 and 53.5% and diameter size of 125±2.7, 84±2 and 83±2.2 nm correspondingly. These nanoparticles exhibited sustained docetaxel release with fewer than 50% extreme cumulative drug release in 72 hours. From the pharmaceutical development point of view, these nanoparticles could be considered as an effective nanomedicine for tumor treatment (128).

In a research by Wang et al. (33), poly (d-,l-lactide-co-glycolide) nanoparticles used as delivering anticancer drugs (doxorubicin and irinotecan). The release of irinotecan and doxorubicin was slow/sustained from both the nanoparticles: ~64% of irinotecan and ~30% of doxorubicin was released within 72 hours. The release of both drugs from these nanoparticles was faster at pH 5.0(33).

PCL/PEG/Polycaprolactone(PCL) nanoparticles were used as delivery systems for curcumin (anti-cancer drug). The Z-average and zeta potential of these nanoparticles were determined at about 110nm and -5.58 mv, correspondingly, , with their corresponding PDI being 0.181. The encapsulation efficiency and loading ratio of curcumin molecules loaded to these nanoparticles were determined at 83±1.29% and 17%±1.23%, correspondingly. The in vitro release behaviors of curcumin from nanoparticles showed that in a releasing intermediate of pH=7.4, the fast release was detected in the controlled solution, with 78% of curcumin released in 12 hours. The characteristic two-stage release profile was observed for curcumin release from these nanoparticles; that is, a comparatively fast release in the first phase, followed by a sustained and slow release rate above an extended time of up to 168 hours(129).

Release behaviors of therapeutic molecules from PLA nanoparticles will be described in Table 2 briefly.

Conclusion

Poly (lactic acid) has been demonstrated to be a hopeful biomaterial to be used in clinical applications due to its biocompatibility and biodegradability nature. On the other hand, polymeric nanoparticles can be used in cancer chemotherapy. So, the PLA nanoparticles are the innovative materials that are accomplished as potential nano-systems in cancer chemotherapy.

PLA, PLGA and PLDL nanoparticles loading with various herbal drugs (like Curcumin and Catechin) or anti-cancer drug molecules (such as Paclitaxel, Docetaxel, Doxorubicin and Irinotecan) are used in cancer treatment. Also, therapeutic molecules like DNA and growth factors are loaded in these nanoparticles in cancer chemotherapy. In general, it can be expressed that the PLA nanoparticles can be potential carriers for drug delivery in cancer treatment.

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Table 2. Release behavior of therapeutic molecules from PLA nanoparticles.

PLA Nanoparticles	Therapeutic molecules	Amount of Releasing									Ref
		12 Hours	1	2	5	10	14	21	28		
PEG/PLA/PEG G	Doce taxel	-	40%	50%	9%	-	-	-	-	-	(128)
PLA 50%: PLGA 50%		210 ng	-	-	250 ng						(76)
PLA 100%: PLGA 0%	DNA	60 ng			8ng						(76)
PLA 75%: PLGA 25%		330 ng			20 ng						(76)
PLA/PEG/PLA without PEI		-	15%	-	0%	-	1%	-	23%	25%	27%	(69)
PEI:(PLA/PEG/ PLA) ratio of 5:300 (% w/w)		-	58%	-	5%	-	8%	-	72%	78%	80%	(69)
PEI:(PLA/PEG/ PLA) ratio of 15:300 (% w/w)		-		-	1%	-	3%	-	88%	90%	92%	(69)
PEI:(PLA/PEG/ PLA) ratio of 1:300 (% w/w)		-		-	2%	-	0%	-	52%	55%	60%	(69)
PEI:(PLA/PEG/ PLA) ratio of 10:300 (% w/w)		-		-	3%	-	8%	-	82%	85%	87%	(69)

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0.1HCI-FU-Au/PLA-PET	5-Fluorouracil	-	13%	15%		-		-	-	-	-	(127)
0.1HCI-FU/PLA-PET		-	14%	17%		-		-	-	-	-	(127)
0.1PBS-FU-Au/PLA-PET (pH−7.4)		-	33%	50%		-		-	-	-	-	(127)
0.1PBS-FU/PLA-PET (pH−7.4)		-	60%	69%		-		-	-	-	-	(127)
PLA/TPGS(93:7) Paclitaxel	Paclitaxel	-	-	-		30%		41%	-	45%	51%	(91)
PLA/TPGS(89:11) Paclitaxel		-	-	-		34%		44%	-	50%	55%	(91)
PLA/TPGS(84:16) Paclitaxel		-	-	-		40%		48%	-	60%	65%	(91)
PLGA/Curcumin	Curcumin	-	70%	80%	0%	-	-	-	-	-	-	(26)
PLGA/Curcumin	Curcumin	-	40%	48%	0%	70%	5%	-	-	-	-	(49)
PLGA using E-D	Doxorubicin	-	50%	-		-		-	-	-	-	(88)
PLGA using S-D		-	45%	-		-		-	-	-	-	(88)
PLGA/PEG using E-D		-	70%	-		-		-	-	-	-	(88)
PLGA/PEG using S-D		-	75%	-		-		-	-	-	-	(88)
PLA using E-D		-	80%	-		-		-	-	-	-	(88)
PLA using S-D		-	65%	-		-		-	-	-	-	(88)

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PLA-PEG-Catechin(5 mg/ml)	Catechin	97%	-	-	-	-	-	-	-	(35)
PLA-PEG-Catechin(10 mg/ml)		62%	70%	75%	-	-	-	-	-	(35)
PLA-PEG-Catechin(12 mg/ml)		75%	80%	90%	-	-	-	-	-	(35)
PLA-PEG-Catechin(15 mg/ml)		50%	55%	65%	-	-	-	-	-	(35)

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Conflicts of Interest

The authors declare no conflict of interest.

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