REVIEW ARTICLE

Polylactide-co-glycolic Acid Nanoparticles for Drug Delivery System

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Abstract

Novel drug delivery system, an area of present research is used to carry pharmaceutical ingredients to a targeted site of action in a body, without affecting the nature of the drug. Nanoparticles are too small in size; it has a drug size of 10–100 nm due to its drug size a large amount of drug is absorbed through blood. Polylactide-co-glycolic acid (PLGA) is a synthetic polymer; it has several lactic acids in the unit and several glycolic acids in the unit. PLGA is used with the drug for improved bioavailability and it works on the targeted site of action. It is used as a polymer with the drug which is having less half-life period. The PLGA has been approved by the department of FDA. The PLGA nanoparticles are prepared by the nano-emulsion method and nanoprecipitation method. The PLGA-loaded nanoparticles are administered through various routes of administration such as oral, parenteral, nasal, and transdermal. It is used to treat several diseases such as Alzheimer's, diabetes, and cancer. The evaluation of PLGA nanoparticles has been done with Fourier transform infrared, differential scanning calorimetric, scanning electron microscopy, transmission electron microscopy, etc. PLGA is a biodegradable polymer possessing superiority over other polymers in targeting the disease. This review aims in pooling the nanoparticles prepared using the biodegradable PLGA polymer and its efficiency in targeting the drug.

Key words: Differential scanning calorimetric, Fourier transform infrared, Nanoparticle, Polylactide-co-glycolic acid, Scanning electron microscopy, Transmission electron microscopy

INTRODUCTION

Nanotechnology is the method used to make a particle in a consistent size. Nanotechnology has a different way to make physical, chemical, mechanical, thermal, and biological products.[1] Due to its pore size, it plays a vital in the medical field. Silver nanoparticles have exclusive detection, catalytic, optical, and antimicrobial properties. Gold nanoparticles are used for the management of cancer due to their superior physicochemical properties.[2] Pharmaceutical industries always meet new ideas to plan new drugs with less toxicity and cheaper rate having a greater biological effect. For meeting the above principle, nanotechnology is a very interesting approach to promote the drug delivery system. In the pharmacy field, nanotechnology is used to make a nanosized particle.

NANOPARTICLE

Nanoparticles are nanosized particles, which has a three-dimensional particle with <100 nm. The two-dimensional particles having a size below 100nm are commonly referred as nanotubes or nanofibers.[3] The nanosize has several mechanical, physical, and chemical properties. For example, place two drops of water in a drug size of 0.1–1.0 μm form a thermodynamically non-stable emulsion and it is completely dispersing with each other. Due to gravity, it also gets separated. The nanostructures are obtained in many different forms and also be used in different methods of the formulation.

If a new drug is launched in a market, it should have a non-toxicological effect and it should have a biological effect. The nanoparticle has the lymphatic drug delivery system in oral administration of the drug it has a targeted site of action.[4] The drug size of 10–100 nm is only absorbed by the lymphatic

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node and the dimension range of <10 nm is absorbed by the blood capillary. Some of the parenteral (intradermal injection) has an adverse effect; it leads to more health issues and biological waste to the patient. However, nanoparticles are examined clinically and preclinically to identify the therapeutic effect of the drug substances. Compared to other size ranges, nanoparticle has large surface area so a large number of the drug gets absorbed in our body and it gives the better result to the patient. Administration of the drug to the targeted site is orally or by parenteral administration.

Polylactide-co-glycolic acid (PLGA)

PLGA is a synthetic polymer; it has a high purity level, high molecular weight, and high reproduction level than other natural polymers. The structure of PLGA has several lactic acids in the unit and the number of glycolic acid in the unit.[5] The different types of two monomers are used to produce a PLGA by the ring-opening polymerization method. When the polymerization is happening, the fine monomers get the formation of PLGA by linkage of ester. The PLGA nanoparticles are biodegradable; it has the degradable ability in lactic acid and glycolic acid it will be metabolized by the Krebs cycle.

The PLGA nanoparticles were also reported to exhibit reliable beneficial results in delivery of protein based drugs. In the nanoemulsion method, the PLGA has a biphasic method. It is soluble in numerous organic solvents such as water, ethanol, acetone, and also in ethyl acetate. It can be stored at a room temperature of 37°C. It has a definite controlled size and shape of the polymer.[6] The scientists have a report related to a PLGA-loaded nanoparticle that had a drug with 50–100 nm has larger accumulation in renal, hepatic, and pulmonary systems. This method is safe and has a low toxicity level when compared to other techniques.

The European Medicine Agency and Food and Drug Administration (FDA) has approved this for use in the human body.[6] This method has many advantages in the drug delivery system. Due to the more stability against the hydrolysis of the polymer, the PLGA has more effect than PLA and PGA making it suitable for its usage in continuous drug delivery systems.

In recent studies, this method plays a key role in the drug carrier method. It acts as a vehicle; it carries a drug and reaches a targeted site of action without losing the drug. It is physically strong so it has a prolonged action for its usage in the sustained drug delivery system.[7] It is used with minerals, aqueous vitamins, DNA, RNA, and also with nanoparticle drugs. The emulsification-solvent evaporation technique has overcome with PLGA used polymeric nanoparticles; it is a very commonly used method to prepare a solid nanoparticle.

PLGA FOR PREPARATION OF NANOPARTICLE

Nano-emulsion method

The PLGA nanoparticles are formulated under the method of emulsion evaporation method and it is one of the most familiar methods. The emulsification method has oil in water type or water in oil type. The method of emulsification can be changed according to the solubility level of the drug in water.[8] For the PLGA polymer, the single emulsion method is used; the drug and surfactant are dissolved in an organic solvent, and the emulsion is formed by adding water. Continuously, stirring is also used to prevent emulsion droplet formation when using sonication or a high shearing process.

Using the double emulsion (w/o/w) evaporation process, polymeric nanocarriers are stabilized by PLGA and non-ionic or cationic surfactants for coencapsulation of a therapeutic, as well as a diagnostic and therapeutic agent (both in the initial concentration of 130 M). In general, the homogenizer is set to 25,000 rpm for 5 min to emulsify an aqueous internal phase in the drug (with the drug, PLGA at a concentration of 5 mg/mL, and at a 1:4 ratio). To make the w/o/w emulsion, the primary water-in-oil (w/o) nanoscopic emulsion was poured into a 1% hydrophilic surfactant, homogenized for 10 min at 25,000 rpm, and immersed in an ice-water bath. The organic solvent was then evaporated under reduced pressure in a rotary evaporator (Hei-VAP Value Optical, Heidolph Instruments, Schwabach, Germany) with a rotating speed of 150 rpm and polymeric Nanocarriers with a PLGA, PEG-PLGA, or FA-PLGA shell for 30 min at 25°C. On the next day, the hybrid cargo was picked up.[9]

NANOPRECIPITATION METHOD

It is a method the nanodiffusion or displacement takes place. In this, the PLGA polymers get dissolved in water such as polar solvents. During the continuous stirring of an aqueous solution, the PLGA is added drop-wise constantly. The organic solvent gets diffused continuously by the precipitation of nanoparticles. The balanced amount of nitrogen or air blowing is reduced by a pressure evaporation method.[10] The encapsulation of nanoprecipitation is done by both hydrophobic and hydrophilic drugs. The hydrophilic drug has low drug loading efficiency.

DRUG LOADED PLGA NANOPARTICLES

Tacrine-loaded PLGA nanoparticles were prepared using a nanoprecipitation method for the treatment of Alzheimer's disease.[11] It was used to treat brain targeting diseases and increases memory power. In a non-clinical study, amnesic mice recovered memory faster when given PLGA

nanoparticles instead of giving the pure drug tacrine. This research indicates that tacrine is delivered to a greater degree in the brain of mice and that tacrine has good clinical effectiveness in the treatment of Alzheimer's disease. The evaluation of tacrine-loaded PLGA nanoparticles was done by particle size, TEM, and drug content, *in vivo* studies.

Using the emulsification solvent diffusion technique, ansamycin-loaded PLGA polymeric nanoparticles were developed.[12] It was used to treat the disease bacterial meningitis. The formulation and evaluation carried out by drug release studies in nanoparticles *in vitro* showed a 36-h sustained release. These findings suggested that the polymeric nanoparticles obtained in this study could be used as a carrier *in vivo* with an initial dose and a sustained plasma level when therapeutically needed. Ansamycin-loaded PLGA nanoparticle gives a better result in surface methodology central composition rotatable design when compared to other results.[13]

To enhance the drug's bioavailability in the brain, the gemcitabine-loaded PLGA nanoparticles were made using a modified nanoprecipitation process. Particle size analysis, encapsulation performance, zeta potential, and *in vitro* release studies were used to characterize the nanoparticle formulation.[14] Sprague–Dawley rats were used to study the pharmacokinetics of gemcitabine-loaded PLGA nanoparticles. As compared to plain gemcitabine solution, the formulation study shows that the Cmax and Tmax concentration and drug clearance were lowered in the brain and blood.[15] These findings indicated that PLGA nanoparticles significantly improved gemcitabine transport across the blood-brain barrier (BBB).

PLGA and Pluronic F68 were used to make a nanosuspension of Pramipexole dihydrochloride using a modified nanoprecipitation method.[16] It is used as a brain-targeting drug. The prepared drug was evaluated using a Fourier transform infrared (FTIR) spectrophotometer; the FTIR spectrum of Pramipexole dihydrochloride, polymer, and a mixture of both drugs and the polymer was obtained using the KBr pellet technique. A differential scanning calorimeter (DSC) was used to conduct the DSC experiments. After selecting the appropriate field and magnification, the scanning electron microscopy (SEM) analysis of the polymeric nanosuspension was carried out. Internal structures such as morphology, crystallization, tension, and even magnetic domains can be seen in TEM images. As a result, PLGA-loaded Pramipexole nanoparticle was selected as the best formulation for treating brain targeting disease because it releases faster than other formulations.

The parenteral drug PLGA-loaded risperidone was formulated using the nanoprecipitation method.[17] Risperidone was used as an anti-psychotic drug. The formulated drug was characterized using the photon correlation spectroscopy and atomic force microscopy method for particle size determination. By adding PLGA with the risperidone gave a prolonged action of a drug for 72 h and gave good bioavailability of a drug. The cold method was done in this process to control the initial release of a drug. The dose regimen is fixed by the formulated method.[18] The drug administration was subcutaneous so it gets direct contact with the blood. The PLGA-loaded risperidone gave a better result in psychotic treatment by dose reduction.

PLGA-loaded baclofen was formulated by the nanoprecipitation method.[19] The drug was used for the treatment of neuropathic pain. It had a prolonged action because of PLGA (50% of a drug gets dissolved in 2.5 h). The high-speed homogenizer and ultrasonicator were used for the formulation of work carried out.[20] The release of baclofen-loaded PLGA nanoparticles carries sustained release of drug delivery system. The administration of drug carries through orally, parenteral, and nose-brain route. The compatibility study showed less toxicity of the drug while using PLGA-loaded baclofen instead of using other polymers. From the study, the PLGA nanoparticle serves as a potential carrier for the drug baclofen and it gives better results in neuropathic pain instead of using plain baclofen.

PLGA-loaded zidovudine nanoparticle was formulated using nanoprecipitation method, the coated tablet was formulated for brain targeting.[21] The prepared formulations were characterized using IR and DSC, to check the interaction between drug and excipients. This study was carried out using tween 80 to attain a maximum concentration of drug in the brain. Zidovudine had a good particle size and shape and it has a high concentration in the brain due to the particle size.[22] The effectiveness of the drug was improved by PLGA nanoparticles for brain targeting diseases.

The double emulsion method was used to prepare a PLGA-loaded bevacizumab for the treatment of antiangenogenic.[23] The prepared nanoparticle was analyzed using fluorescence spectroscopy. The physical structure of the drug is noted by the SEM and TEM the morphology of the drug is seen clearly. The lyophilization method is carried out to maintain the physical and chemical study of the nanoparticle-loaded bevacizumab. Hence, the drug has passed all the evaluations it has a therapeutic effect with less toxicity was compared to other antiangiogenic drugs. It has a controlled release of drug delivery system because of PLGA as a polymer.

Irritable bowel syndrome with diarrhea was treated with eluxadoline, a newly approved orally administered drug.[24] PLGA-loaded eluxadoline was prepared by the single emulsion evaporation method. Eluxadoline is a water-insoluble compound with a low dissolution rate and low oral bioavailability. The formulation work was carried out by several plain PLGA, it was prepared and optimized for particle size, polydispersity index (PDI), zeta potential, and percent drug entrapment efficiency. As compared to the standard suspension, the bioavailability of plain and coated

nanoparticles was increased by 6.8–18.5 times respectively.[25] This result indicated that the produced coated eluxadoline-loaded PLGA nanoparticles could be administered orally for the treatment of Irritable Bowel Syndrome with diarrhea.

The formulation and evaluation of the drug diazepam-loaded PLGA were used for the treatment of brain targeting disease.[26] The formulation of the drug was done using the nanoprecipitation method. The administration of the drug occurs through the nasal route of the drug delivery system. The drug crosses the BBB to attain a required amount of drug to the brain. The formulated drug was evaluated using DSC to analyze the particle size of the drug. FTIR shows the interaction between the drug and the polymer, the stability study was done to know the physical-chemical stability of the drug nanoparticle it was done using DSR. The different evaluations were made to check the adverse effect of the drug.[27] Among these, the drug was safe and has less toxicity while compared to other brain targeting drugs available on market. The use of PLGA polymer had a prolonged action on the drug.

The formulation and evaluation of PLGA-loaded Irinotecan hydrochloride were used for the treatment of glioblastoma.[28] The preparation of PLGA-loaded irinotecan was done using an ultrasonic probe. FTIR is used to see the interaction between the drug and the polymer. The TEM is used to check the particle size while is it in a compressed form of size and shape.[29] Because of PLGA, the drug irinotecan had a prolonged action of drug release. It was safe and the drug had less toxicity. Compared to other drugs, the PLGA-loaded irinotecan gave an excellent report.

PLGA nanoparticle-loaded Odorranalectin was formulated by solvent evaporation double emulsification method. The PLGA-loaded Odorranalectin was used for the treatment of anti-Parkinson diseases.[30] The drug was administered through the nose, the drug inhaled by the patient and it gets into the systemic circulation. It was a brain-targeting drug it can cross the BBB using PLGA as a polymer, it enhanced the strong prolonged release of a drug. Beckman coulter was used to evaluate the prepared drug.[31] Odorranaletin-loaded PLGA nanoparticles showed an excellent result for the treatment of anti-Parkinson disease.

PLGA-loaded rhynchophylline nanoparticle was formulated by nanoprecipitation method. It was used for the treatment of brain targeting disease it crosses the BBB and acts on the targeted site of action.[32] The formulation of nanoparticles was centrifuged at the rpm of 2000 rpm at 4°C for 15 min using a magnetic stirrer. For the evaluation test, TEM has used to analyze the particle size of the drug. The PLGA had a good result in bioavailability it had a prolonged action of the drug. PLGA-loaded rhynchophylline nanoparticles had a very good result for the treatment of Alzheimer's disease when compared to other existing drugs.[33]

The gefitinib-loaded PLGA nanoparticle was a brain targeting drug for the treatment of brain tumors. It can pass the BBB with the strong polymer PLGA.[34] The preparation of the drug was done under the method of nanoprecipitation. The administration of gefitinib-loaded PLGA was by an intravenous method. Due to PLGA, it had a prolonged action and good bioavailability of a drug. Using magnetic stirring the formulation work was carried out. The evaluation of prepared nanoparticles was done using SEM and FTIR. The structure of the particle was analyzed by SEM, the particle interaction and drug compatibility were seen under FTIR.[35] Gefitinib-loaded PLGA nanoparticles showed a better result in treating Glioblastoma (brain tumor) instead of using other polymers.

PLGA-loaded vancomycin nanoparticles were prepared under the double-emulsion solvent evaporation method.[36] It was an orally administered drug, has a good biodegradable, and was used as an antibiotic. The formulated drug was evaluated using FTIR; the particle size was analyzed using DSC. The drug had a sustained release of action due to the PLGA as a polymer.[37] It had good biodegradable and less toxic while compared to other drugs. Among these results, the vancomycin-loaded PLGA nanoparticle showed a better result in treating intestinal permeability.

Curcumin naturally occurs from plant resources and it belongs to the family *Curcuma longa* (*Zingiberaceae*). The most common name for curcumin is *Turmeric.* Curcumin has many pharmacological activities such as antioxidant, anti-tumor, and anti-inflammatory.[38] The Curcumin-loaded PLGA nanoparticle was prepared by the nanoprecipitation method. The schistosomicidal activity of curcumin-loaded PLGA nanoparticles was determined. It was used to decrease motor activity and partial alterations in the tegument of adult worms. It was characterized by dynamic light scattering (DLC) and field emission SEM. Curcumin has many beneficial activities such as antioxidant and anti-amyloid and it is used for the treatment of neurodegenerative disease such as Alzheimer's disease.[39] The curcumin has poor solubility to overcome this problem, PLGA nanoparticles were used to enhance the better absorption. Curcumin-loaded PLGA nanoparticles were prepared by the single emulsion solvent evaporation method and it was evaluated by TEM, SEM, and particle size.

The atorvastatin calcium encapsulated PLGA nanoparticles were used to maintain the level of cholesterol.[40] The atorvastatin calcium encapsulated PLGA nanoparticles were prepared by evaporation method and a probe ultrasonicator was used for the formulation of the drug. It was characterized by particle size, drug loading, and encapsulation efficiency. The atorvastatin calcium-loaded PLGA nanoparticles gave a better result in the treatment of cholesterol.[41] From this report, they enhanced an orally administered drug of PLGA-loaded atorvastatin nanoparticle was prepared.

Drug	Polymer	Preparation methods	Activity	References
Capecitabine	Poly (D, L-Lactide-co-glycolide) (PLGA)	Solvent displacement method	Antineoplastic and antimetabolite prodrug	[52]
Metformin Hydrochloride	PLGA	Double emulsion solvent diffusion method	Antihyperglycemic agent	[53]
Pioglitazone	Poly (lactide-co-glycolide)(PLGA)	Emulsion-evaporation method	Anti-diabetic	[54]
Paclitaxel/ methotrexate	Poly (lactide-co-glycolide) (PLGA)	Nanoprecipitation method	Antitumor and antimetabolite	[55]
Zidovudine	Poly (lactide-co-glycolide)(PLGA)	Nanoprecipitation method	Antiretroviral	[56]
Erlotinib	Poly (lactide-co-glycolide) (PLGA)	single emulsion solvent evaporation method	Antitumor	[57]
Endostatin	Poly (ethylene glycol) PEG, poly (DL-lactide-co-glycolide) PLGA	Double emulsion technique	Anti-angiogenic activity	[58]
Cabazitaxel, Curcumin	poly (ethylene glycol) PEG, poly (DL-lactide-co-glycolide) PLGA	Nanoprecipitation method	Anticancer and metastatic castration resistant prostate cancer	[59]
Spirulina	PLGA , poly-β-hydroxybutyrate (PHB)	Nanoprecipitation method	Antioxidant activity and anti-aging agent activity	[60]
5-Fluorouracil, Chrysin	poly (ethylene glycol) PEG, poly (DL-lactide-co-glycolide) PLGA	Double emulsion Method	Anticancer agent and antineoplastic	[61]
Levodopa	PLGA	Double emulsion solvent evaporation method	Anti-cancer agent	[62]
Callistemon citrinus	Poly (lactic-co-glycolic acid)	Nanoprecipitation method	Antioxidant, anticancer and antidiabetic activities	[63]
Methotrexate	PLGA and PEG	Emulsification-solvent diffusion method	Antimetabolite and Anti-tumor	[64]
Rasagiline	Chitosan and PLGA	Double emulsification-solvent evaporation	Monoamine oxidase-B inhibitor and neuroprotective activity.	[65]
Tenofovir	PLGA and chitosan	Solvent evaporation method and ionotropic gelation method	Antiviral activity	[66]
Doxorubicin	PLGA	Nanoprecipitation method	Anticancer activity	[67]
Pralidoxime	PLGA	Double emulsion solvent evaporation method.	Anticholinesterase agents	[68]
Chlorambucil	PLGA	Solvent evaporation method	Alkylating agents and antineoplastic activity	[69]
Cisplatin and paclitaxel	PEG and PLGA	Double emulsion (W/O/W) method	Anticancer and anti-tumor activity	[70]
Diclofenac	PLGA	Emulsion-diffusion-evaporation technique	Anti-inflammatory agents	[71]
Acyclovir	PLGA	Solvent deposition method	Antiviral activity	[72]
Bicalutamide	PLGA and chitosan	Nanoprecipitation method	Anti-neoplastic hormonal agent and anti-androgen	[73]
Noscapine	Methoxy poly (ethylene glycol)-poly (lactide-co-glycolide) (mPEG-PLGA)	Nanoprecipitation method	Anticancer agent	[74]
Paclitaxel	PLGA	Interfacial deposition method	Anti tumoral activity	[75]

Temozolomide incorporated into superparamagnetic PLGA nanoparticles was used for brain glioma.[42] It is used to improve drug loading and encapsulation efficiency and sustained drug release. It was used for brain targeting diseases. Temozolomide-loaded PLGA nanoparticles were prepared by emulsifying solvent evaporation method and it was evaluated by particle size, SEM, transmission electron microscopy, and DLC.[43] The report says that the PLGA-loaded temozolomide nanoparticle plays a multifunction in the brain and it has a good effect on the treatment of brain glioma.

Donepezil encapsulated PLGA nanoparticles were used for the treatment of brain delivering such as Alzheimer's disease.[44] Alzheimer's disease was a numerous neurodegenerative disorder. Donepezil-loaded PLGA nanoparticles were used to increase the drug efficiency in brain targeting and it improved the bioavailability of the drug. Donepezil encapsulated PLGA nanoparticles were prepared by emulsification diffusion evaporation method and it was characterized by particle size, zeta potential, entrapment efficiency, and drug loading, *in vivo* studies.[45] High concentrations of drugs were achieved in the brain because of the polymer PLGA so the drug had good effectiveness for the treatment of Alzheimer's disease.

Cisplatin-loaded PLGA was prepared by emulsification and solvent evaporation method.[46] Cisplatin is one of the anti-cancer agents and it was used for the treatment of malignant and ovarian, bladder, small cell, and non-small cell lung cancer. It increased the biocompatibility, biodegradability and bioavailability, and anti-tumor activity of the drug. It was evaluated by *in vitro* studies. According to the formulation and evaluation study carried out by the drug, it had high effectiveness of treatment of cancer. Hence, the drug was used clinically.[47]

Letrozole encapsulated PLGA nanoparticles were prepared by the nanoprecipitation method.[48] PLGA nanoparticles enhancing the tumor uptake of letrozole. The formulation of the drug was carried out by the DTAP challenge test. The prepared drug was evaluated by TEM, PDI, and zeta potential.[49] The above report says that the PLGA-loaded letrozole nanoparticle was could fight against breast cancer cells. Hence, it can be used as an anti-cancer agent, the laboratory work is in progress using a normal mouse.

Docetaxel-loaded PLGA nanoparticles were prepared by the solvent displacement method.[50] PLGA is a biodegradable polymer and it increases the bioavailability and biocompatibility and absorption rate of the drug. Docetaxel had a low solubility, poor absorption so we encapsulating PLGA nanoparticles to increase solubility and absorption rate. The prepared docetaxel-loaded PLGA was evaluated by SEM, zeta-potential, and particle size.[51] It gave a sustained release of the drug delivery system while used PLGA as a polymer with the drug. It is administered intravenously; the nanoparticle gave a better result in the systemic circulation of the drug, so the drug had a better bioavailability to be used as an anti-cancer drug.

CONCLUSION

PLGA polymers are efficient delivery vehicles for medications, peptides, and proteins. It has good biocompatibility and biodegradability. Greater hydrophilicity will speed up the degradation of PLGA and the rate at which drugs are released. PLGA formulated nanoparticles gave an excellent result with fewer adverse effects instead of using other polymers. Even though PLGA nanoparticles have shown great promise as drug carriers, there are still many issues to address before they can be used in clinical practice. Recent successes and the importance of using PLGA nanoparticles for drug delivery systems are addressed in this paper paving the way for more research on this topic.

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