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A Recent Review of PLGA-PEG Hybrid Nanoparticles for Anticancer and Anti-Inflammatory Applications

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ABSTRACT

Numerous synthetic polymers have been investigated to be used in nanomedicine over the past few decades, particularly in drug delivery systems. Necessitating properties including non-toxic, biodegradable, and biocompatible. Among these, polylactic-co-glycolic acid (PLGA) which stands out due to its complete biodegradability and ability to self-assemble into nanometric micelles. However, their large diameter (150–200 nm), poor stability in aqueous media, and their removal from the bloodstream by the liver and spleen hindering the *in vivo* treatments. Polyethylene glycol (PEG) is the most widely used polymer in drug delivery systems, and the first PEGylated product has been on the market for over 20 years. PEG has a stealth behavior; therefore, it will not be recognized by the immune system. Further, PEG is hydrophilic polymer that could stabilize nanoparticles through steric rather than ionic effects. In this review article, the important of utilizing PLGA-PEG nanoparticles as polymeric drug carriers has been revised and the advantages of employing PLGA-PEG copolymer to form stable and well-defined, nanoparticles for drug delivery applications have been summarized. Moreover, the review aimed to shed light on the various methods employed in their preparation. Additionally, recent advancements in PLGA-PEG copolymer preparations for anti-cancer and anti-inflammatory therapies, are discussed in detail. The other applications of PGA-PEG have been extensively reviewed in other publications. Therefore, it was not addressed in this review.

Keywords: Nanotechnology; PLGA NP; Medical application; Cancer; Anti-inflammatory.

1. INTRODUCTION

In recent years, biomaterials research has been intensively growing, particularly in utilizing the nanoparticles (NPs) as a drug delivery system, which possess great potential for technical breakthroughs in the field of drug delivery. The use of nanoparticles has been evaluated in-depth and has been driven by the ability to deliver a wide range of materials, including hydrophilic and hydrophobic drugs, vaccines, and biological macromolecules. Nanoparticles also allow targeted delivery of drugs to specific organs or site within the body [1-3]. Polymeric NPs have shown promise as an innovative approach for drug delivery application. It is worth noting that approximately >80% of new drug candidates are categorized as poorly water-soluble, as reported by Wulff-Pérez et al. In 2014.[4].

Consequently, these drugs often face challenges such have a low absorption, short circulation time and un-wanted side effects. However, using polymeric NPs can effectively address these issues. In addition, NPs exhibit various properties depending on their size and hydrophilicity. Their small size enable them to penetrate deep into tissue, reaching the target site (Table 1) [5]. Furthermore, polymeric NPs have the ability to selectively bind to site of action with minimal side effects as well

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avoiding harming to other cells. This can be achieved by functionalizing their surface with specific proteins, peptides, monoclonal antibodies thus enhance their efficiency [6-8].

It is important to note that polymers utilized in nanomedicine must adhere with a standard set by the Food and Drug Administration's (FDA) including various criteria including biocompatibility, safety, good drug loading efficacy, good mechanical properties, and well-characterized structure. Whilst numerous synthetic polymers have been employed to create NPs, it's noteworthy that not all are appropriate for application in the nanomedicine [9]. Among these synthetic biodegradable polymers are polyamides, polyesters, poly (amino acids), polyurethanes which have been increasing utilized in the past two decades due to their controllable properties in terms of molecular weight and shape [3, 10].

Table 1: Comparison of Smart PEG-PLGA Hybrid NPs with Different Nanoparticles [11, 12]

Criteria	PEG-PLGA Hybrid NPs	Liposomes	Polymeric NPs	Metallic NPs
Composition	PEG-PLGA	Lipid bilayers	Various polymers (PLGA, PCL, PVA…)	Gold, silver…
Size Range	50 - 200 nm	50 - 200 nm	10 - 200 nm	1 - 100 nm
Surface Functionalization	PEGylation, Ligand Conjugation	Phospholipid functionalization	Polymer coating	Surface modification
Drug Loading Capacity	High	Variable	High	Moderate to High
Controlled Release	Yes	Yes	Yes	Yes
Biocompatibility	High	Generally high	Variable	Variable
Stability	Good	Moderate to High	Variable	Moderate to High
Targeting Capabilities	Active and Passive Targeting	Active and Passive Targeting	Active and Passive Targeting	Active Targeting
In Vivo Performance	Efficacy and Safety	Proven efficacy	Varied depending on polymer	Variable
Imaging Modalities	Fluorescent, MRI, CT, etc.	Limited imaging capabilities	Limited imaging capabilities	CT, MRI, Photoacoustic
Toxicity	Low	Generally low	Variable	Variable
Clinical Translation	Promising	Established in some cases	Under investigation	Limited
Challenges and Limitations	Limited Payload, Manufacturing	Stability, Batch Consistency	Burst release, Biodegradability	Aggregation, Biodistribution
Future Perspectives	Advancements and Innovations	Integration with imaging	Tailoring for specific drugs	Combined therapies

Among these biodegradable polymers is poly (lactic-co-glycolic acid) (PLGA), which is made up of two cyclic dimers of glycolic and lactic acid copolymerized randomly by ring-opening (Figure 1) [3, 13]. The mole ratio of glycolic to lactic acid in the polymer chain has a crucial role in determining the properties of PLGA, such as the degree of crystallinity, mechanical strength, swelling behavior, and hydrolyzing capacity. This, in turn, affects the rate of biodegradation [14]. However, their large diameter (150–200 nm), poor stability in aqueous media, and their removal from the 2bloodstream by the liver and spleen hindering in vivo treatments.

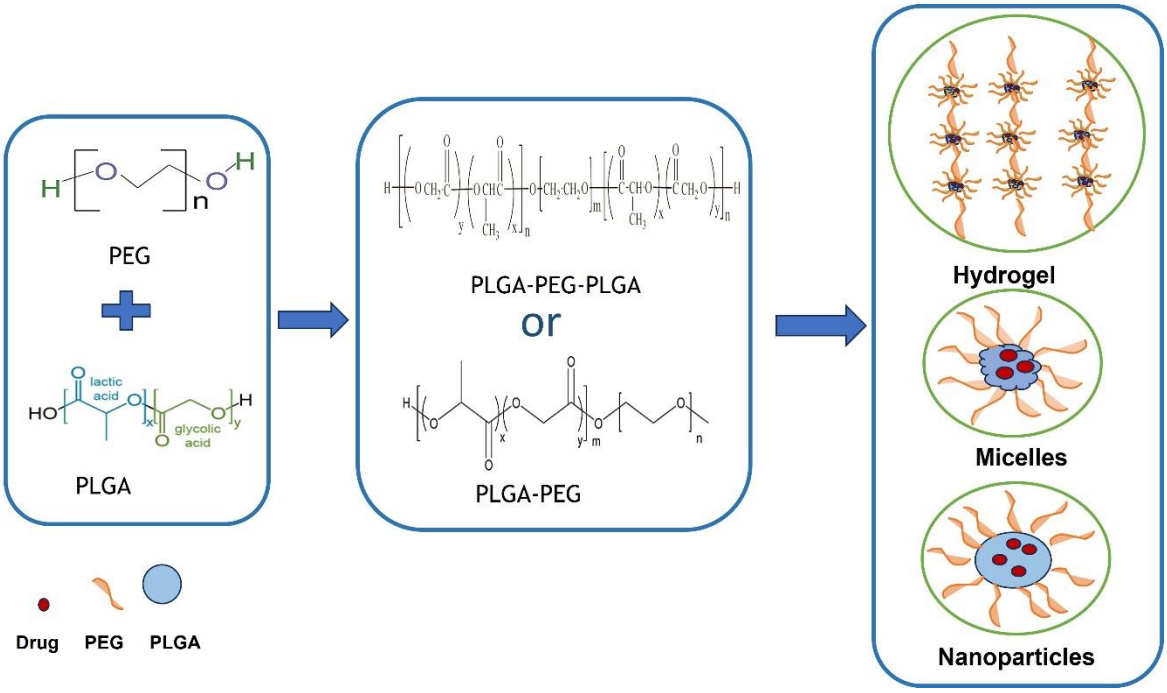

Figure 1: Scheme represents PLGA-PEG nanoparticles formation technique using probe sonication

The biodegrading process of PLGA starts in an aqueous medium, where PLGA completely biodegrades to its original monomers, lactic and glycolic acids, which then the body can either excrete them unchanged in the kidney or metabolize them and eliminate carbon dioxide and water ensuring a safe clearance of PLGA out of the body [14].

PLGA-derived systems, and the first PEGylated product has been on the market for over 20 years. can be encapsulate various drugs, proteins, and peptides that are released gradually, in a time -dependent manner in the body [15]. However, it should be noted that these systems come with significant limitations. Firstly, a stabilizer such as poly (vinyl alcohol) must be used to ensure stability of nanoparticles achieving small diameter with uniform distribution. Additionally, PLGA NPs are readily recognized by reticulo-endothelial system (RES) which is composed of the liver and spleen. This identification leads to eliminate PLGA NPs from blood circulation and significantly shortens their circulation residence time thereby NPs delivered to specific organs or tumor tissues [16].

To date, the potential applications of polyethylene glycol (PEG) with molecular weight of 300 to100,000 Da is highly encouraging, since PEG is not a biodegradable polymer, PEG has a stealth behavior; does not accumulate

in tissue and is eliminated from the body without undergoing biodegradation processes [17]. This particularly comes with those with low molecular weight chains. Furthermore, PEG is widely used in medicine for a variety of purposes such as a laxative agent, excipient in drug formulation as well a coating agent particularly in capsule formulations [18, 19]. Moreover, PEG's hydrophilicity enhances solubility, prevents aggregation, and stabilizes nanoparticles in aqueous media could stabilize nanoparticles through steric rather than ionic effects thereby its worthy to use. Currently many researchers focused on finding new candidate drugs encapsulated within PLGA PEG based NPs due to their ability to encapsulate a variety of hydrophilic and hydrophobic agents [20-22] [23].

Interestingly, several studies investigated the possibility of conjugating the nanoparticles with linear PEG through a process known as PEGylation [24], aiming to improve their pharmacokinetic profile and lessen their toxicity. PEG is considered a promising candidate for adsorption or grafting on NP surfaces to escape clearance by the body's mononuclear phagocytic system (MPS), since they are neutral, hydrophilic along with their strong spatial repulsion characteristics [25, 26].

In this review article, the important of utilizing PLGA-PEG nanoparticles as polymeric drug carriers has been revised and the advantages of employing PLGA-PEG copolymer to form stable and well-defined, nanoparticles for drug delivery applications have been summarized. Moreover, the review aimed to shed light on the various methods employed in their preparation. Additionally, recent advancements in PLGA-PEG copolymer preparations for anti-cancer and anti-inflammatory therapies, are discussed in detail along with its role in the disease.

2. Synthesis of PLGA-PEG copolymer

Several synthetic approaches were developed to prepare different kinds of PLGA-PEG copolymers with various block structures and compositions. The biodegradation rate and hydrophilicity of PLGA-PEG copolymers can be modulated by adjusting the ratio of its hydrophilic and hydrophobic constituents. The properties of PLGA-PEG block copolymers are typically very different when compared to their constituent polymers, so they are developed into a new class of biomaterials with distinctive qualities of their own, including water solubility, crystallinity, microphase separation, and biodegradability[27].

Gref et al. (1994) initially described the synthesis of PLGA-PEG, featuring a covalent linkage between a PLGA chain carrying a free carboxylic acid at one end (PLGA-COOH) and a PEG chain functionalized at both ends with an amino. The resulting product undergoes repeated washing with organic solvent. This process leads to the formation of an amido group in the middle of the copolymer, which remains stable when stored in a freezer for several months [28, 29].

3. Preparation Methods for PLGA-PEG Nanoparticles

Various methods have been identified for PLGA-PEG NPs fabrication including double emulsion, nanoprecipitation, single-emulsion solvent-evaporation, solvent displacement technique, and the emulsification-solvent diffusion technique [30].

PLGA-PEG NPs can be prepared by double emulsion method. In this method PLGA–PEG was dissolved in ethyl acetate forming the organic phase. Simultaneously, the drug was dissolved in deionized water preparing the aqueous phase. The primary emulsion (w_1/o) was formed by using sonication energy (Figure 2). Subsequently, ultrasonic energy was used to produce a secondary emulsion ($w_1/o/w_2$), where the primary emulsion (w_1/o) was distributed in deionized water of polyvinyl alcohol (PVA). Following the evaporation of the solvent, the formed NPs were subjected for washing by centrifugation [31, 32].

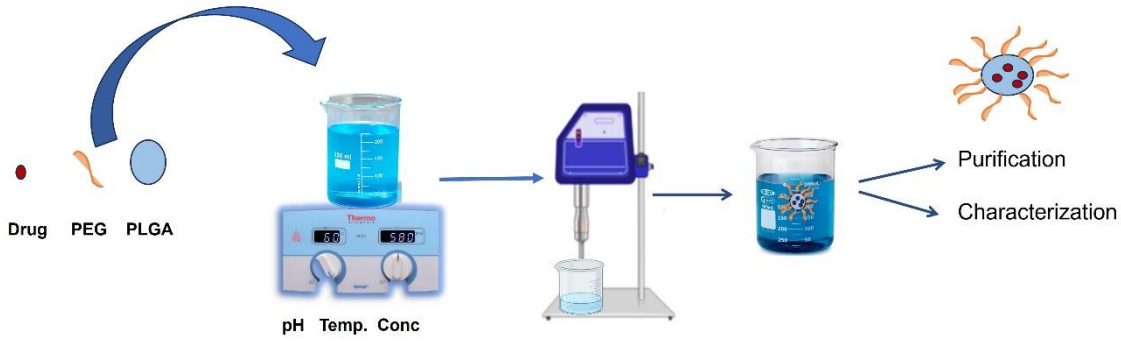

Figure 2 : Scheme represents PLGA-PEG nanoparticles formation technique using probe sonication

Nanoprecipitation is a versatile method that enabling the encapsulation of various therapeutic agents within the nanoparticles, making it suitable for drug delivery functions [30]. In this technique the drug was dissolved in organic layer that are miscible with water along with PLGA–PEG was dissolved and mixed with the drug by stirring. Subsequently, NPs were centrifuge and resuspended in water [33].

Likewise, PLGA–PEG NPs can be prepared by single-emulsion solvent-evaporation method. In this method the NPs were prepared by dissolving the drug, PLGA with PEG at room temperature. This organic phase was rapidly poured into PVA aqueous solution and then emulsified through sonication to form an oil-in-water (O/W) emulsion. Consequently, the organic solvent rapidly evaporated under the vacuum. The particles were then recovered by centrifugation and washed with water to eliminate the surfactant residue (PVA). The NPs were dispersed in the cryoprotectant sucrose, and the resulting nanosuspension was subjected to freeze-drier [34, 35].

Solvent displacement is another technique that can be used in PLGA-PEG NPs preparation. Initially, PLGA-PEG polymer was dissolved in acetone and the solution was gradually transferred dropwise into a stirred solution of sodium cholate in phosphate buffered saline. Subsequently, the acetone allowed to evaporate, and the resulting suspension of NPs was condensed in a rotary evaporator. Gel permeation chromatography was employed to purify the formed NPs [36].

At the men time, PLGA-PEG NPs can be prepared through-solvent diffusion technique. In this technique the polymer was dissolved in a suitable solvent while the drug was dissolved in water containing an emulsifying agent. This solution was slowly dropped at constant speed into liquid paraffin presented as an external phase. This process was conducted under homogenization utilizing high-speed homogenizer at various agitation speeds. The formed NPs were isolated by ultracentrifugation and the separated NPs were washed with n-hexane to remove residual liquid paraffin. Ultimately, a fine powder of NPs was obtained by lyophilization of the formed suspension [37].

4. Benefit and toxicity consideration of PLGA-PEG NPs:

PLGA-PEG polymer is considered a potent platform esteemed by scientists due to its biocompatibility, making it a valuable material for medical application. Although various materials are available for utilizing NPs, the majority of these still require FDA approval; in contrast, PLGA and PEG have already received this recognition, allowing their use in preclinical and *in vivo* testing. Furthermore, the PLGA-PEG copolymer can readily form micelles with well-controllable sizes and high encapsulation efficiencies without the aid of surfactant agents, which are frequently toxic and poorly tolerated by cells and organisms [38]. PLGA and PEGylated NPs were demonstrated the ability to improve the pharmacokinetic

profiles and biodistribution of several drugs. For instance, it was reported that the association of docetaxel with PLGA and PEGylated PLGA NPs modified the pharmacokinetics and biodistribution of docetaxel. Loading of docetaxel in NPs contributed to an increased blood residence time of docetaxel fulfilling NP's role as a long-circulating sustained-release drug delivery system. Also, surface modification of NPs, contributed to more pronounced blood concentrations of docetaxel, confirming the role of PEG in facilitating NPs escape from clearance out of the body [39].

Despite numerous benefits of using PLGA-PEG, some drawbacks have limited their widespread use. Primarily, the synthesis process of PLGA-PEG is considered costly and time-consuming. Both PLGA and PEG are synthetic polymers that require several steps for preparation, including industrial processes, purification procedures, and the use of costly building blocks. In contrast, natural polymers like chitosan may offer simpler and potentially more cost-effective alternatives. [40], are derived from natural waste material and do not require lengthy artificial processes for preparation. In addition, the autocatalysis of PLGA at low pH where the carboxylic end groups of degraded products can accelerate the degradation and decrease the local pH. Hence, this acidic environment limits their protein delivery and typically requires the incorporation of antacids, such as Mg $(OH)_2$, into the polymers for protein stabilization [41]. Moreover, heavy metals like stannous, which are used during the polymerization step of lactic and glycolic acid, must be eliminated from the polymer chains to mitigate any toxicity or organ damage [42].

5.1 PLGA-PEG NPs for cancer treatment:

Recently, there have been reports on the use of (PLGA-PEG NPs) for cancer targeted therapy. Interestingly, it was found that these delivery vehicles, designed to transport drugs precisely to specific targets within the body[43]. The PLGA part provides a substantial structure, while the PEG component ensures stealth-like properties, preventing the immune system from recognizing and attacking them Figure 3.

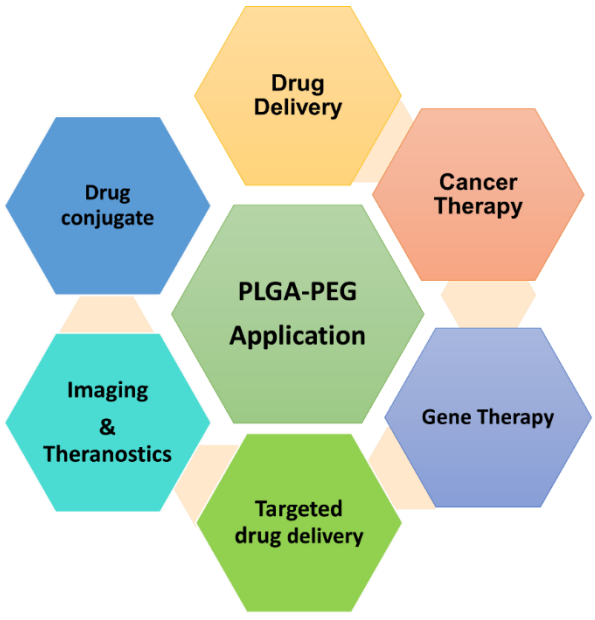

Figure 3: Representative scheme of PLGA-PEG hybrid copolymers applications.

This dynamic couple makes PLGA-PEG NPs versatile tools in the field of medicine, enabling more effective and targeted drug delivery with minimal side effects (Table 2). In essence, they act as microscopic superheroes, navigating our bloodstream to deliver the right medicine to the right place at the right time [44] [45].

Table 2: Examples of different drugs encapsulated into PLGA: PEG nanoparticles.

Drug	Composition and Ratio of PLGA: PEG	Indication	Study type	Refences
Docetaxel	PLGA (lactide/glycolide ratio of 50:50, carboxylic acid end group, molecular weight, 17,000 Da) PEG polymer with terminal amine and carboxylic acid functional group (NH2-PEG-COOH)	Prostate Cancers	In vitro Cytotoxicity and uptake	[46]
Docetaxel	PLGA– PEG diblock copolymer (50:50 PLGA attached to mPEG 5000, 15%. wt)	Cancer	In vitro In vivo (Kinetics)	[47]
Curcumin	PLGA-PEG (50:50 lactide:glycolide, PVA (1%, w/w	Breast cancer	In vitro MCF7 breast cancer cell line	[48]
Dactolisib	blend of poly(D,L-lactide-co-glycolide) (PLGA) and poly(D,L-lactide-co-glycolide)-poly(ethylene glycol)-2000 (PLGA-PEG)	Targeted delivery of the mTOR/PI3kinase inhibitor to inflamed endothelium	In vitro, tumor necrosis factor-α (TNF-α) activated endothelial cells	[49]
Cisplatin	PLGA-PEG (50:50 lactide:glycolide, PVA (1%, w/w	cancer cells	In vitro A549 lung	[50]
Doxorubicin and Tetrahydrocurcumin	PLGA-PEG (50:50 lactide:glycolide)	Glioma	In vitro, MTT Ex vivo DOX fluorescence imaging. The in vivo tumor orthotopic C6 mouse models	[51]
Metformin and Silibinin	poly (D, l -lactide-co-glycolide)-polyethylene glycol	Breast cancer	In vitro T47D breast cancer cell line	[52]
Cyclodextrin-Peganum harmala Alkaloid Complex and Ascorbic Acid	Poly (D,L-lactide-co-glycolide) (PLGA) and polyethylene glycol 6000 (PEG), Polyvinyl alcohol (PVA; 98% MW ≈ 13,000)	Cancer	In vitro Cytotoxicity	[53]
Honokiol	PLGA-PEG (50:50 lactide:glycolide)	Anti-tumour activities	Stability study	[54]
Ciprofloxacin	(Average MW of PEG 2000 g/mol), PLGA (average MW of 11,500 g/mol) (lactide: glycolide=50:50	Bactericidal activity was observed against Enterococcus faecalis	In vitro	[55]
The A10 PSMA aptamer for in vivo targeted drug delivery	Carboxy-terminated poly(D,L-lactide–**co**–glycolide)–**block–** poly(ethylene glycol) (PLGA–**b**–PEG–COOH)	Prostate cancer	The in vivo (xenograft mouse model of prostate cancer)	[56]

Table 1 provides a summary of *in vitro* and preclinical studies that utilized PEG-PLGA in cancer application. Starting with breast cancer, metformin an anti-hyperglycemic agent was encapsulated into folate-functionalized PLGA- NPs, showing a higher cytotoxic effects with remarkable down-regulation of hTERT, Bcl-2 and up-regulation of Caspase7, Caspase3, Bax, and p53 gene expression in breast cancer MDA-MB-231 cell line, therefore these NPs are suggested as an appropriate approach to elevate the anticancer properties of metformin for improving the treatment effectiveness of breast cancer cells [57]. Similarly, treatment with metformin and Silibinin co-loaded in PLGA-PEG NPs resulted in synergistic anticancer activity against T47D breast cancer cells. Also, this dual drug-loaded NPs revealed a significant changes in the expression levels of Bax, Bcl-2, caspase 3 and hTERT compared to the single drug-loaded NPs. As a result, treatment with PLGA-PEG NPs based on combination therapy might have a significant potential to improve the efficiency of breast cancer treatment [58].

In another study, curcumin was loaded into epidermal growth factor receptor (EGFR)-targeting GE11 peptides conjugated with PLGA nanoparticles. This loading was revealed to reduce phosphoinositide 3-kinase cascade and decrease cancer cell proliferation, attenuated drug clearance from the blood circulation, and repressed tumor burden compared with free curcumin or non-EGFR targeting nanoparticle.

In case of colon cancer, S. Khaledi et al (2020) was prepared PLGA-PEG-PLGA NPs loaded 5-FU and Chrysin, a natural compound using double emulsion method. The study reported that the 5-FU and Chrysin with PLGA-PEG-PLGA copolymer exhibited a remarkable uptake in HT29 cells and were found to have significant effect on the cell proliferation compared with NPs loaded with each drug alone in HT29 cell line. In addition, the synergistic anticancer effects of 5-FU and Chrysin in NPs were loaded with a clearance value of 0.35 [59].

For prostate cancer, Dhar et al. (2008) utilized a PLGA-PEG copolymer to create cisplatin-loaded nanoparticles, which were specifically targeted using a prostate-specific membrane antigen (PSMA) aptamer. The study demonstrated that these targeted nanoparticles effectively impacted human prostate cancer cells overexpressing PSMA (LNCaP and PSMA-PC3) while having no effect on normal cells. Additionally, the targeted nanoparticles increased cell death by ten times compared to non-targeted nanoparticles. [60]. In a related study, Farokhzad et al. (2006) developed PLGA-PEG nanoparticles designed to target PSMA and loaded with docetaxel. These nanoparticles specifically bound to prostate cancer cells and demonstrated an increased cytotoxic effect of docetaxel. Furthermore, in vivo experiments with xenograft nude mice bearing tumors showed that a single injection of these nanoparticles resulted in complete tumor volume reduction. Remarkably, 100% of the treated mice survived after 109 days, compared to only 14% of the untreated mice. [61].

Another study involved a lung cancer model using Calu-6 lung adenocarcinoma cells. In this study, siRNA was encapsulated into iron magnetic nanoparticles (MNPs) modified with PLGA and PEG. The results showed that the expression of the telomerase gene was significantly lower in the cells treated with siRNA-magnetic copolymers compared to those treated with free siRNA in the lung cancer cell line. [62]

5.2 PLGA-PEG NPs as a delivery system for anti-inflammatory:

Recently, PLGA-PEG nanoparticles have shown significant potential in enhancing the therapeutic efficacy of anti-inflammatory drugs, making them a promising delivery system for treating inflammatory conditions and diseases. For example, PLGA-PEG polymers can be used to synthesize nanoparticles for targeted delivery to specific cell types within the airways, particularly in obstructive lung diseases [63]. Additionally, Vij et al. (2016) encapsulated ibuprofen into PLGA-PEG nanoparticles, which were further modified with a maleimide-capped PEG to reduce the neutrophil-mediated inflammatory response in COPD. This approach leverages

the mucus inertness of PEG and the coupling properties of maleimide to achieve effective penetration and targeting of the required tissue. [64]. The findings indicated that these nanoparticles, following airway transport, could specifically bind to and release the drug into neutrophils, thereby controlling COPD inflammation. This formulation significantly reduced inflammation compared to the saline serum control 210 minutes after inflammation initiation. Additionally, it reduced ocular inflammation, suggesting it could be a promising candidate for topical application. [65].

The PLGA-PEG polymer has also been utilized for the controlled delivery of anti-inflammatory drugs. Gusperimus, an immunosuppressive drug used for autoimmune diseases and to prevent organ transplant rejection, was encapsulated in PLGA-PEG nanoparticles to enhance drug stability and bioactivity. [43, 66]. In a similar study, Li et al. prepared dexamethasone-loaded PLGA-PEG nanoparticles. These nanoparticles improved the pharmacokinetic properties of dexamethasone and reduced its side effects. When combined with ultrasound (US), dexamethasone-PLGA-PEG nanoparticles may offer a promising drug delivery system to enhance the therapeutic effects of dexamethasone. [67]. Another finding supported that PLGA-PEG nanoparticles exhibit increased interaction with Caco-2 cells and show superiority in inflamed cells. This interaction was further enhanced by increasing the particle size and polydispersity index. [68].

Table 3 summarizes the *in vitro* studies of the role of PLG-PEG in inflammatory diseases.

Drug	Design study	Main finding	Reference
BRP-201	PEG–Lipid–PLGA were prepared using DSPE–PEG–Lipids	It tested on the pro-inflammatory M_1-MDMs and mmn g shown to inhibit 5-LOX product formation and thus inflammation by delivering BRP-201 to the intracellular in 15 min or less.	[69]
Gusperimus	PLGA-PEG NPs	PLGA-PEG/Gusperimus nanoparticles were taken up by macrophages and exerted anti-inflammatory effects as it is indicated by nitric oxide reduction and cytokine suppression in LPS-induced inflammatory macrophages model.	[70]
PS-341 (bortezomib)	PLGA-PEGPS-341	The drug release in CF mice lungs was established by quantifying the changes in proteasomal activity with~2 fold decrease and capability to rescue the Pseudomonas aeruginosa that induced inflammation, which proved the rescue of CF lung disease in murine model.	[71]
Licochalcone-A	PLGA have been utilized PEG and cell penetrating peptides (Tet-1 and B6).	Reduce inflammation compared to the saline serum control in a significant manner after 210 min of inflammation initiation, also it was reducing the ocular inflammation.	[72]

Drug	Design study	Main finding	Reference
Magnolol polyphenol extracted from magnolia plant	magnolol-encapsulated (PLGA-PEG) nanoparticles	This formulation significantly reduced airway hyperresponsiveness, lung tissue eosinophil infiltration, and levels of IL-4, IL-13, TGF-β1, IL-17A, IgE and IgG1 in OVA-exposed mice compared to control-treated mouse also it prevented mucus overproduction and collagen deposition *in vivo* .	[73]
Teicoplanin	mPEG-PLGA hydrogel copolymer as a sol-gel drug delivery system for treating bone infection.	Implantation of the mPEG-PLGA hydrogel containing teicoplanin was effectively treating osteomyelitis in rabbits using histological staining and immunoblotting test.	[74]
recombinant Amb a (*Ambrosia artemisiifolia)*	Amb a 1 -loaded PLGA-PEG nanoparticles.	These nanoparticles enhanced the secretion of T-helper 1 (Th1) cytokine Interferon-gama (IFN-γ) and the production of immunoglobulin G, inhibited the secretion of T-helper 2 cytokine Interleukin 13, 4 and the level of IgE.	[75]
Dactolisib (mTOR/PI3 K inhibitor	Dactolisib nanoparticles composed of (PLGA-PEG) prepared by an oil/water emulsion solvent evaporation method	Dactolisib nanoparticles have a high potential reaching inflamed endothelial cells. E-selectin targeted nanoparticles loaded with Dactolisib had a pronounced effect on inflammation-activated endothelial cells as compared to the non-targeted NPs.	[49]
etoricoxib	PEG-PLGA-Nps using emulsion solvent evaporation approach	In-vivo study shows that PEG-PLGA etoricoxib decreases the swelling index and number of writhes in rat model. Also it remarkably increased the bioavailability of etoricoxib through oral dosage form.	[76]

6. The limitations and challenges of using PLGA-PEG nanoparticles

Despite the remarkable widespread use of PLGA-PEG in drug delivery applications several challenges remain. However, they face several challenges and limitations. One major issue is the potential for burst release, where a large amount of the encapsulated drug is released rapidly, reducing therapeutic efficacy and increasing side effects [77]. Additionally, the biodegradation rate of PLGA can be inconsistent, influenced by factors like particle size, copolymer ratio, and environmental conditions, complicating controlled drug release [78]. PEGylation can improve circulation time but may induce an immune response or accelerate clearance in some cases Manufacturing these nanoparticles at scale while maintaining consistency and reproducibility also poses significant technical hurdles [79, 80]. Understanding and addressing these challenges is crucial for the successful

clinical translation of PLGA-PEG nanoparticles [81]. Indeed, it's important to understand the biodegradation kinetics profile of PLGA-PEG *in vivo* to ensure their efficacy and confirm their safety. Also investigating the synergistic effect for combination therapies using NPs, that offer potential effects and minimizing toxicity should be explored.

To mimic the effects of nanoparticles (PLGA-PEG NPs) on cancer tumors or inflammation in patients, clinical studies involving regulatory agencies are crucial for addressing toxicity and efficacy. However, performing clinical trials is challenging and costly compared to *in vitro* studies. Scale-up and manufacturing steps of PLGA-PEG nanoparticles production is crucial but its cost-effective and required scalable production approaches to be widespread. Overall while PLGA-PEG nanoparticles hold a great value in drug delivery and biomedical applications, further interdisciplinary research and studies with different drugs and cell lines still required to explore and more understand their role in different cancer cell types.

7. Summary and Future Directions

In summary, this review underscores the promising role of PLGA-PEG nanoparticles (NPs) in drug delivery, especially in treating cancer and inflammation. These nanoparticles offer benefits like being safe for the body, releasing drugs in a controlled way, and improving how drugs move in the body. Studies show they can effectively deliver various drugs, enhancing treatment results in lab and animal tests.

However, challenges remain. One big concern is how quickly drugs are released from PLGA-PEG NPs, which can affect how well they work and their side effects. Also, how quickly PLGA breaks down and possible immune reactions to PEG need careful consideration for use in people. Making these nanoparticles on a large scale and keeping them consistent are also tough.

Looking ahead, future research should focus on solving these challenges and making PLGA-PEG NPs even better. Improving how drugs are packed into these nanoparticles, controlling how drugs are released, and making sure they target the right cells are key goals. It's also important to study how these nanoparticles work with different diseases and cell types.

To make PLGA-PEG NPs available for patients, more studies in people are needed to check safety and how well they work. This step is crucial for getting approval from health regulators and using them in real medical treatments. Teamwork between scientists, doctors, and companies will be crucial to overcome challenges and fully use PLGA-PEG nanoparticles to treat diseases more effectively.

In conclusion, while PLGA-PEG nanoparticles show great potential for improving drug treatments, ongoing research and new ideas are vital to make them work even better and solve current problems.

The important hallmarks of PLGA-PEG NPs are drug loading capacity, chemical targeting potential, and improved circulation time, which makes this material very attractive in the drug delivery industry. In summary, PLGA-PEG nanoparticles stand as established nanocarriers suitable for several nanomedicine purposes. These NPs have substantial attention, particularly for emerging anticancer and anti-inflammatory applications. This is largely due to their remarkable physicochemical properties. Various techniques have been involved for the preparation of PLGA-PEG NPs.

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مراجعة حديثة للجسيمات النانوية الهجينة (PLGA-PEG) للتطبيقات المضادة للسرطان والمضادة للالتهابات

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ملخص

تمت دراسة العديد من البوليمرات الاصطناعية لاستخدامها في الجسيمات النانوية على مدى العقود القليلة الماضية، وخاصة في أنظمة توصيل الأدوية. تتطلب خصائصها بما في ذلك غير سامة، والقابلة للتحلل، ومتوافقة حيويا. ومن هذه العناصر، حمض الجليكوليك المتعدد PLGA الذي يتميز بقابليته للتحلل البيولوجي الكامل وقدرته على التجميع الذاتي في الجسيمات النانوية. ومع ذلك، فإن قطرها الكبير (150–200 نانومتر)، وضعف ثباتها في الوسائط المائية، وإزالتها من مجرى الدم عن طريق الكبد والطحال، يعيق العلاجات داخل الجسم الحي. يعد البولي إيثيلين جلايكول PEG هو البوليمر الأكثر استخدامًا على نطاق واسع في أنظمة توصيل الأدوية، وأول منتج مصنوع من البولي إيثيلين موجود في السوق منذ أكثر من 20 عامًا. PEG لديه سلوك خفي. وبالتالي لن يتعرف عليه الجهاز المناعي. علاوة على ذلك، فإن PEG عبارة عن بوليمر محب للماء يمكنه تثبيت الجسيمات النانوية من خلال التأثيرات الاستاتيكية بدلاً من التأثيرات الأيونية. في هذه المقالة المراجعة، تمت مراجعة أهمية استخدام الجسيمات النانوية PLGA-PEG كحاملات للأدوية البوليمرية وتم تلخيص مزايا استخدام البوليمر المشترك PLGA-PEG لتشكيل جسيمات نانوية مستقرة ومحددة جيدًا لتطبيقات توصيل الأدوية. علاوة على ذلك، هدفت المراجعة إلى تسليط الضوء على الأساليب المختلفة المستخدمة في إعدادها. بالإضافة إلى ذلك، تتم مناقشة التطورات الحديثة في مستحضرات البوليمر المشترك PLGA-PEG للعلاجات المضادة للسرطان والمضادة للالتهابات بالتفصيل. تمت مراجعة التطبيقات الأخرى لـ PGA-PEG على نطاق واسع في منشورات أخرى. ولذلك، لم يتم تناولها في هذه المراجعة.

الكلمات الدالة: تقنية النانو، PLGA NP، التطبيقات الطبية، السرطان، مضادات الالتهاب.

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