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Review Article

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Harnessing the Potential Role of PLGA Nanocarrier for Cancer Therapeutics

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Abstract

Cancer treatment has been a major focus of research due to the various treatment options available and the severe side effects of medications. In recent years, nanotechnology has become a fascinating area of study for using nanoparticles (NPs) to deliver medicine for cancer treatment and diagnosis, as well as tissue repair. Poly lactic-co-glycolic acid (PLGA) NPs are a promising option due to their adaptability, biodegradability, and biocompatibility. They can be used in drug delivery systems for medical therapies, including targeted medicine distribution for cancer treatment. However, the particle size, surface charge, and other physicochemical properties of NPs must be carefully controlled to ensure desired pharmacological activity, drug release profile, and target selectivity. Changing one property may affect others and altering the ratio of single units (monomers) in the polymers may impact hydrophobicity and crystallinity. Designing optimal NPs is like solving a complex Rubik's cube, where each side is interconnected, and changing one aspect affects the overall outcome.

Keywords

Cancer, Poly lactic-co-glycolic acid, Nanotechnology, Hydrophobicity, Crystallinity

Introduction

"Cancer is a wound that doesn't heal" [1]. Cancer begins as an uncontrolled growth of cells produces a lump or an aggregate inside their original tissue. When one, a few, or a group of cells begin to divide and are unable to stop, this causes the cells to continue growing indefinitely. The failure of cellular systems first compromises the growth arrest process, after which the enlarging cells form a tumor and seize control of the surrounding environment. The cancer cells take control of our body cells and use our cells as workforce to continue growing and spreading to other body regions. It is a common challenge for the Oncologist to detect and eliminate the cells that start this abnormal division and form a tumor, taking over the body's immune system and start to invade other body tissues and organs. The advanced scientific approach to deliver the drugs to the tumor spot (tumor microenvironment) using nanotechnology and modifying the NPs to our advantage. For the administration of the medicine, biopolymers are preferred as NPs. In this review paper, we'll talk about one of these NPs' application.

The most often used biodegradable polymer to produce nanomedicines is PLGA [2, 3]. The two biodegradable single repeating units (monomers) of PLGA are lactic acid and glycolic acid, which are efficiently processed by the body, and as a result, their systemic toxicity for drug administration is extremely low. These two biodegradable monomers can subsequently be metabolized via the Krebs cycle to give the harmless byproducts H_2O and CO_2. The fact that PLGA

has received USFDA (United States Food and Drug administration) and EMA (European Medicines Agency) approval for pharmaceutical applications gives it a significant advantage over other polymers and puts PLGA-based NPs in a superior position for clinical trials [4, 5].

PLGA NPs: Structure and Properties

Composition of PLGA

Highly adaptable and readily adjustable, PLGA is a polymer that may be manufactured into any form or size [6]. PLGA can be modified to obtain suitable properties for a scaffold matrix or regulate bioactive payload. It may be given some functional qualities by chemically modifying it with various polymers or bioconjugating it with other molecules [7]. Lactic and glycolic acid monomers are directly polymerized during the direct polymerization method of producing PLGA. The use of a catalyst is optional, and then the monomers react when the solution is stirred or melted. Direct polycondensation-produced PLGA copolymers, however, often have a low molecular weight ROP [Ring-Opening Polymerization] has attracted a lot of attention in PLGA synthesis, primarily because it is the most frequent method for producing high molecular weight copolymers [8]. The two primary forms used in the production of polymers is l-lactide and the 1:1 combination of d- and l-lactides, known as d and l lactide or racemic lactide [9].

The simplest linear aliphatic polyester, polyglycolic acid, is derived from glycolic acid, which is arranged as building blocks. polyglycolic acid only has a few biological functions because of its rapid breakdown, which results in acidic by-products, and poor solubility [10]. The process for making glycolide, the cyclic diester of glycolic acid, is like that used to make lactide. First, an oligo(glycolate) is formed, and then this glycolate is thermally unzipped to create glycolide [11]. In PLGA is a linear aliphatic polyester by-product where vit is comprised of subsequent monomeric units of glycolic acid/lactic acid are connected by ester linkages during polymerization [12].

Structure of PLGA

PLGA (Figure 1) is biodegradable polymer that has extensive use, typically created by the ring open co-polymerization of lactide and glycolide. PLGA is employed as therapeutic materials because as a polyester of two-hydroxy acids (Figure 2), it could be broken down into its component monomers and was entirely absorbed by the body. The medication, PLGA(s), and solvent(s) are the three crucial elements of the formulation and drug release kinetics from microparticles (MPs) are impacted by the components. Molecular weight (M.wt.), lactide and glycolide (L:G) ratio, end-group, and the linear or branching molecular shapes are the typical characteristics of PLGAs. For duration of action formulations, a variety of PLGAs with varying M.wt., L:G ratios, and molecular architectures are mixed. In 5% molar increments, PLGA polymers having L:G ratios ranging from 50:50 to 100:0 is available, such as 55:45, 60:40, 65:35, etc. [13].

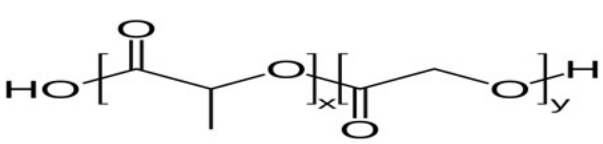

Figure 1: Diagrammatic representation of the chemical structure of PLGA. Here, x represents the number of units of lactic acid and y represents the number of units of glycolic acid.

Desirable properties for drug delivery

Biodegradability

PLGA is biodegradable polymers which is very useful for developing nanomedicines as it undergoes hydrolysis in the human body and produces lactic acid and glycolic acid, biodegradable metabolite monomers. These monomers are metabolised through Krebs cycle thereafter excreted as CO_2 and H_2O, there is virtually no systemic toxicity associated with their use [14]. It can be claimed that simple compounds can catalyze the nucleophilic nitrogen of the ester bond scission, accelerating the breakdown of polymers [15].

Biocompatibility

PLGA is regarded as biocompatible, which means it does not trigger any potent immune response in the body. The tendency of PLGA to interact with the living tissue without significantly causing any adverse consequences or immunological reactions is referred to as biocompatibility. This characteristic trait of PLGA makes it appropriate for several biological uses and is a preferred for medication delivery and tissue engineering. On the other hand, plasmid DNA, oligonucleotides, and siRNA are just a few examples of the therapeutic DNA/RNA molecules that have been delivered using PLGA MPs/NPs due to their excellent biocompatibility [15].

Protection of drug from degradation

Clathrin-mediated endocytosis and fluid phase pinocytosis plays a major role in the internalisation of PLGA NPs in cells. These PLGA NPs quickly exit the endo-lysosomes and reach the cell's cytoplasm within few minutes of incubation, this helps the NPs to easily in contact with vesicular membranes, causing localised and temporary membrane destabilisation and allowing the particles to escape into the cytosol [16].

Ability to change surface characteristics

It is possible to coat NPs with chemicals that provide a layer to the surface which has affinity towards water and masking the hydrophobicity. Polyethylene glycol (PEG) is a polymer with its characteristic affinity towards water and it exhibits a non-ionic behavior, making it the most preferred moiety for surface modification. Additionally, the study of the usage of materials such as poloxamer, poloxamines or chitosan

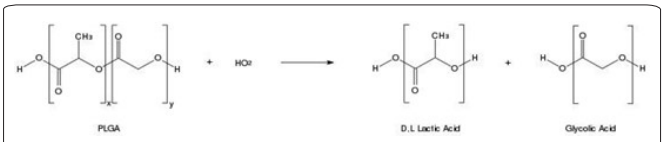

Figure 2: Diagrammatic representation of the hydrolysis of PLGA.

for surface modification of the PLGA NPs are also explored for various functionality change in PLGA [17]. The interaction and uptake of NPs with cells are significantly influenced by their surface charges. Because of the ionic connections that have been formed between positively charged NPs and cell membranes (negatively charged), allows greater level of permit to the NPs for cellular internalisation. Additionally, it appears that this internalisation of the NPs (positively charged) can easily escape from lysosomes and display perinuclear localisation, whereas the negatively or neutral charge carrying NPs prefer to colonize with the lysosomes. The surface modification allows the PLGA NPs to attain charges from negative, neutral to positive from negative to neutral/positive charges.

Site specific targeted therapy

Surface modifications made in PLGA NPs aid in the targeting organs with tumors to improve binding to specific cells at various sites, supporting the internalization of these NPs through receptor-mediated endocytosis. On the surface of the NPs, a linkage of PEG chains which target specific ligands is often grafted granting the NPs a ligand mediated pathway to the tumor site [18].

Controlled drug delivery

The process of releasing a drug from a drug loaded PLGA particle is made possible by the bulk mixing of diffusion and erosion on the surface of the NPs, and this process may be customised based on the specific the physicochemical properties of the PLGA polymers [19]. The M.wt., lactide/glycolide ratio, size, shape of the particle and the conditions of the environment in which the drug is released, these important characteristics of the PLGA can be modified to edict the release of the drug and its patterns of release [20]. The controlled release of medications from PLGA carriers allows a prolonged and gradual release of drugs, leading to consistent drug presence and reducing the potential for harmful effects on the entire body.

Various other properties include tuneable degradation rate that can be useful for treating cancer effectively over time. Also, we can enhance the targeted drug delivery using PLGA NPs by increasing medicine effectiveness and minimising negative effects and enabling the use of combination therapies to treat many aspects of cancer and overcome drug resistance [19]. These attributes make PLGA an adaptable and promising platform for developing cancer therapeutics, boosting patient quality of life, and enhancing treatment results. However, for the implementation to be effective thorough consideration of elements such particle size, drug loading, release kinetics, and targeting techniques is crucial.

Mechanism and Uptake of PLGA

The systemic release of drugs from PLGA MPs and NPs

The physical and chemical properties of the PLGA polymers can be used to adjust the diffusion and erosion processes that take place at the surface of the nanocarrier and in the bulk release of the drugs from PLGA NPs (Figure 3). As soon as the PLGA polymer is exposed to water or delivered *in vivo*,

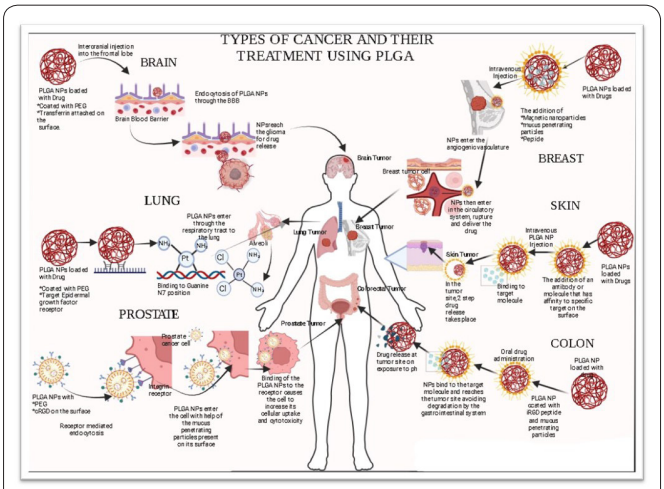

Figure 3: Demonstration of the procedures required to deliver drug-loaded PLGA NPs to several tumor-ridden areas of the human body (tumors shown: brain, lung, breast, skin, prostate, and colon) (Created with BioRender.com).

it starts to absorb water [19]. As a result of the water-filling process, the polymer matrix generates pores because of the water-filling process, and these pores increase in size and number over time, generating a porous interconnected network that permits medicines to permeate from the polymer matrix [21]. The release of the protein molecules from the particle surfaces is another method of drug release that has been documented [22]. When PLGA is exposed to water, it begins to degrade right away due to hydrolysis, which results in the breaking of the backbone ester bonds and a consequent drop in molecular weight. The breaking down of PLGA on reaction with H_2O results in the formation of carboxylic groups [23]. According to reports, this auto-catalytic activity results in heterogeneous degradation inside PLGA matrices, the centre of the matrix degrades faster than the external surface area. As the M.wt. of any polymers drops, they become less hydrophobic and eventually water-soluble at a molecular weight of about 1.1 kDa [19]. This causes the polymer of PLGA particles to lose mass, as they diffuse into the releasing media of the biological sample. The phenomenon of diffusion, surface diffusion, bulk erosion, and surface erosion when work together contribute to the breakdown of the PLGA copolymer [24]. PLGA particles often release the drugs in a traditional triphasic fashion [19]. Phase I begins with an early burst referred to as phase I caused by unencapsulated drug on the particle surface or close to the surface after getting readily hydrated [25]. The drug released subsequently diffuses into the media either through some of the already present pores or through the denser polymers. Phase II of the delayed release process occurs as the polymer hydrates and breaks down. Phase III, the swiftly releasing phase, is often referred to as the second burst release and is brought on by polymer breakdown. Furthermore, it has been demonstrated that not all PLGA particle's release follow the conventional tri-phasic pattern. If the second phase is rapid, for example, phase III may discharge more slowly [26, 27] (Table 1).

Preparation of PLGA MPs and NPs

Emulsification-solvent evaporation process i.e., the double-emulsion for NPs loaded with biomacromolecules, is the

Table 1: Modification of PLGA NPs in cancer drug delivery to various organs.

Organ	Ligand	Size (nm)	Coating	Structure	Approach	Ref.
Brain	Transferrin (Protein)	~150	PEG	Elongated or rod-shaped	Active Targeting through BBB receptor-mediated transcytosis	[28]
Lung	Target EGFR	~210	PEG	Stick to the mucus of respiratory tract	Modification to navigate the lung's complex branching airway system	[29]
Breast	HER2/nue or CD44 markers	~124	PEG	Delivers immunotherapeutic agents checkpoint inhibitors, cancer vaccine	Addition of multiple therapeutic agents e.g., chemo-therapeutic drugs, for synergistic effects	[30]
Skin	Target melanocortin-1 receptor	~210	PEG	Usage of permeation enhancers, microneedles, or sonophoresis in combination	Ability to penetrate and accumulate in the hair follicle orifices	[31]
Prostate	Prostate specific membrane antigen markers	~123	PEG	Optimization of drug encapsulation within PLGA NPs to achieve high drug loading efficiency	Lyophilized surface	[32]
Colon	EGFR, CD44 Cells	~330	Chitosan	Designing based sensitivity of NPs to the microbiota of colon, Azo-reductase	Combination of chemotherapeutic agents, immunomodulatory agents	[33]

most popular methodology for producing solid, polymeric NPs [25]. Nanoprecipitation is also a popular method for creating PLGA NPs. Using this technique, polar, water-miscible solvents (dimethyl sulfoxide, acetone, or ethanol) are used to dissolve both polymers and medicines. Drop by drop, the solution is released into the aqueous solution containing the surfactant. This rapid diffusion of the solvent into the solution causes the nanoparticles to form instantly. Also, ease of processing, reproducibility [34], and mild processing conditions of the approach allow the pharmaceuticals to be encapsulated without being subjected to shearing stress or high temperatures [35]. The fact that the technique was first created for the encapsulation of hydrophobic compounds is a significant issue [36]. To distribute hydrophilic biomacromolecules, variations of nanoprecipitation have been devised. To include enzymes like lysozyme and α-chymotrypsin into PLGA NPs, the development of two-stage nanoprecipitation method was adopted where the first step is a protein nanoprecipitation and polymer nanoprecipitation is the second step [37]. This technique can result in high residual enzyme activity >90% and encapsulation efficiencies >70%. Additionally, dextran sulphate and lysozyme were hydrophobically ion-paired before the complex was nano precipitated into PLGA NPs, which gave the proteins great encapsulation efficiency and preserved the enzyme's biological functioning [38]. Additionally, block copolymers containing polycations are used to create PLGA core-shell NPs, which operate as a stable vehicle for the delivery of negatively charged proteins through electrostatic interactions [39].

Use of PLGA in Therapeutic Antibodies

Muromonab-CD3, the first monoclonal antibody drug, authorized by the USFDA in 1985 to treat transplant rejection, since then there have been over 70 antibody-based medications authorized by the USFDA as of 2017, making them the largest segment of the biopharmaceutical market [40]. These antibodies either disrupt the action of specific antigens or block the ability of signalling molecules to attach to cell surface receptors, both of which may have therapeutic benefits [41]. Given the high cost of these pharmaceuticals, the antibodies released under controlled circumstances can reduce the number of registered injections and the associated dosages. As a result, PLGA-based MPs and NPs might be the best vehicle for the antibodies. A monoclonal antibody (anti-VEGF) called bevacizumab is used for the treatment of age-related macular degeneration [42]. Bevacizumab's ocular administration needs to be released slowly for treatment to be successful. PLGA-based MPs with PLA NPs loaded with bevacizumab, a group of scientists invented a unique procedure using supercritical carbon dioxide fusion and pressure quench [43]. The distinct structure of NPs-encapsulated MPs allowed *in vitro* maintenance of antibodies for 2 months then the NPs were delivered into the rat's eyes through intravitreal injection for one month, according to standard therapy. Additionally, PLGA NPs loaded with bevacizumab were administered into the host body who had undergone laser photocoagulation-induced Bruch's membrane rupture [44]. The inhibition of choroidal neovascularization after two weeks of drug release further demonstrated the potential of PLGA MPs/NPs-based delivery for the treatment of eye diseases. To encapsulate infliximab, TNFα an antibody, it was created 75:25 PLGA NPs [45]. The test conducted in cell culture revealed that fibroblast viability was higher when TNF-α was present and that cell movement in rates were higher in a cell wound model. This exploratory work may culminate in PLGA NPs-based delivery approach for the treatment of Crohn's disease, even if *in vivo* findings were not shown. While the majority of monoclonal antibodies are included in PLGA MPs/NPs as direct treatments, they reported that coating PLGA NPs with cetuximab, targets EGFR (Epidermal growth factor receptor), to help direct the specific delivery of paclitaxel in cancer cells with over expression of EGFR [46]. Although an *in vitro* investigation revealed that EGFR on cancer cells had a high binding affinity, NPs treatment into mice with generated lung cancer substantially inhibited the tumour's growth and increased the animals' survival time.

PLGA Based Vaccines

The well-established biocompatibility of the PLGA polymers in combination with their natural abilities to tune the

rates of bioerosion and release led to the early development of PLGA-based vaccines being primarily technologically driven [47]. Other properties, such the adjuvancy of PLGA-MS, have recently grown to be just as appealing or more so. For a polymer that is typically approved for slow release injectables. In addition to the antibody responses seen initially in the very early investigations, PLGA-MS can generate cellular effector responses, also known as cytotoxic T-cell responses [48-50].

Conclusion

Nanotechnology is an effective weapon for overcoming the challenges faced by various researchers as well as oncologists, especially in combating targeted drug delivery into the tumor microenvironment. The use of PLGA is this process holds a very bright future due to its unique properties such as biocompatibility, biodegradability, and control on the release rate of drug release (especially the control over enhanced permeation and retention effect). In this review paper we have investigated various processes in which the modifications of the PLGA NPs are done to fit our needs, the mechanism of how the NPs interact with the body tissues and the tumor cells of various organs and the possibilities it holds in improving drug delivery in tumor microenvironment. As PLGA was approved by the USFDA, in the 1970s, extensive research has been done on its applications not only on its use in cancer treatment, but also in delivery of various biological particles in various systems in our body. The technological advancements in recent years have made it very easy to make chances for nanoparticles to suit our needs. However, keeping the physiochemical properties is a challenge, which is still being pursued by researchers today.

Acknowledgements

None.

Conflict of Interest

None.

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