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Review Article

Latest research about active pharmaceutical ingredient loaded Poly Lactic Acid-co-Glycolic Acid (PLGA) based drug delivery system in Türkiye

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ABSTRACT

Some of the most well-engineered and produced biomaterials are polyesters based on polyglycolic acid (PGA), polylactic acid (PLA), and their copolymers, polylactic acid co-glycolic acid (PLGA). In controlled release systems, PLGA is the most extensively used and popular polymer. Because of its biodegradability, biocompatibility, and favorable release kinetics, but also because of the reliability of protein delivery issues, this synthetic polymer has been found to be very successful. PLGA is approved in various human drug delivery systems by EMA and FDA. In this review, first, PLGA and historical development, usage, physico-chemical structure, drug release properties, degredation specifications, solubility, crystallinity, thermal stability, release properties, types of PLGA will be mentioned. In the last stage of the review, studies conducted in Türkiye are included. In conclusion, we believe that this review is a resource for researchers doing research with PLGA.

Keywords: PLGA, Drug Delivery Systems, Drug Carrier, Nanotechnology

1. INTRODUCTION

Polylactic acid (PLA), polyglycolic acid (PGA) and their copolymers, polylactic acid co-glycolic acid (PLGA) based polyesters are some of the approved, optimized, well-designed and manufactured biomaterials. Lactic acid contains an asymmetric R-carbon, usually defined in classical stereochemical terms as the D or L shape and sometimes as the R and S form [1].

Because of its methyl side group, PLA is a hydrophobic polymer and is more resistant to hydrolysis than PGA due to methyl group steric hindrance. Semi-crystalline poly (L-lactide) (about 37 percent crystallinity) while poly (DL-lactide) is amorphous due to structural irregularities. PLA has brittleness and low thermal stability. PGA does not contain methyl side groups and has a crystalline structure of 45-55 percent. As a result, a lot of organic solvent is insoluble. Glycolide copolymerisation is used for PLGA L-lactide or DL-lactide. The differentiation of the glycolide/lactide ratio of the PLGA crystallinity can be controlled [2].

Because lactic acid and glycolic acid, two biodegradable metabolite monomers, are hydrolyzed by the body, PLGA is one of the most often utilized

biodegradable polymers for the development of nanomedicines. During the Krebs cycle, the body simply metabolizes these monomers and removes them as carbon dioxide and water. This results in a minimal toxicity to the system. PLGA is approved in various human drug delivery systems by EMA and FDA. Polymers are available commercially with a variety of molecular weights and compositions of copolymers. Depending on the ratio of molecular weight copolymer, the time of degradation might range from several months to many years [3].

In this study, firstly an introduction about PLGA is made and the history of PLGA is mentioned. Then brief information about usage, physico-chemical structure, drug release, degradation, solubility, cristallinity, thermal stability, release properties and types of PLGA are presented. Finally, pharmaceutical Research & Development work done with PLGA in Türkiye have been included.

2. HISTORICAL DEVELOPMENT

First used as a matrix in 1967 was copolymer PLA/PGA. This copolymer has a surgical thread under the trade name Vicryl® [4]. To date, PLGA is the most popular polymer in controlled release systems and is widely used. This synthetic polymer has been proven to be particularly effective because to its biodegradability, biocompatibility, and favorable release kinetics, as well as the reliability of protein delivery difficulties. PGA and PLA together with copolymer PLGA are biodegradable synthetic polymers used in the 1960s as surgical sutures. These polymers were successfully developed as surgical sutures, which led to an increase in their application as polymeric biomaterials. The copolymer has since been developed for usage in controlled release systems and is regarded as the most efficient and extensively researched polymer for controlled delivery systems of biodegradable polymers. PLGA has been utilized to release a variety of small-molecule drugs, peptides, and proteins, such as steroid hormones, insulin, anti-inflammatory drugs, cytokines, growth hormones, chemotherapeutics, antibiotics, and narcotic antagonists, as well as hormones that control fertility [5].

3. USAGE

One of the most important uses of PLGA is that it is a polymer used in nanoparticle production technology. PLGA has different weights and copolymer technologies available on the market. When the literature is examined, one of the important parameters in the preparation of PLGA nanoparticles is the water solubility of the drug to be loaded into the nanoparticle system. While preparing PLGA nanoparticles of drugs with low water solubility, double emulsion solvent evaporation technique is generally used, while nanoprecipitation method is used for drugs with low water solubility. In the literature, it is seen that many active pharmaceutical ingredients are encapsulated into PLGA nanoparticles. Examples of these active ingredients are: paclitaxel, nitrocamptothecin, cisplatin, haloperidol, estradiol [6-8,12]. Another carrier system in which PLGA is frequently used is scaffold, fiber, microbubble [9-13].

Biological targeting ligands such as cytokines, hormones, chemotherapeutic drugs and other agents can be conjugated to PLGA nanoparticles or microspheres to target tumors. Early diagnosis and imaging of cancer can be done with PLGA nanoparticles used in the field of radiopharmacy [14]. One of the most extensively researched polymers for vaccines is PLGA. Systems prepared with PLGA as a controlled release system can deliver antigens or adjuvants to the target site [15].

4. PHYSICO-CHEMICAL STRUCTURE

PLGA is able to be shaped into virtually any size or form and can hold practically any quantity of molecules. The inherent viscosity of PLGA polymers that are commercially accessible on the market is often correlated with their molecular weights. The PLGA polymer's crystallinity directly influences its mechanical strength, swelling characteristics, hydrolysis propensity, and ultimately the rate of biodegradation [16].

The mechanical strength of the polymer and its capacity to be designed as a tool for drug delivery are influenced by physical parameters like molecular weight and polydispersity index. Such characteristics

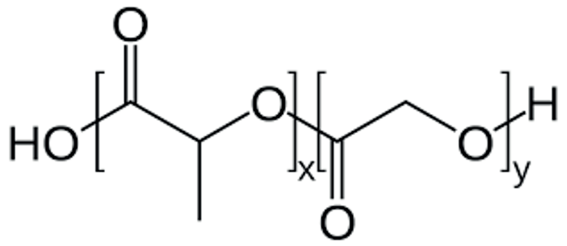

Figure 1. Chemical structures of PLGA

can control how quickly polymers hydrolyze and degrade biologically [16]. These qualities can also be used to design a drug delivery system and regulate how quickly the system degrades and hydrolyzes [17]. The chemical structure of PLGA is presented in Figure 1.

5. DRUG RELEASE PROPERTIES

When the PLGA polymer undergoes biodegradation or hydrolysis, the ester bonds in the polymer chain are broken and split into oligomers and then monomers. The two main release mechanisms associated with drug release from PLGA-based delivery systems are diffusion and degradation/erosion. It is reported that release rate of the drug is initially controlled by diffusion followed by the last phase of release by degredation/erosion. Direct correlation between the release rate and nanoparticle size can be seen. The fact that large microspheres degrade faster than small microspheres was shown in the literature. This is presumably because of the expanded collection of acidic items in huge polymeric microspheres. Hydrolysis occuring in PLGA systems starts immediately after being in contact with water; hydrolysis produces acids which catalyze hydrolysis. This autocatalytic process leads to a faster degradation at the center of PLGA matrix rather than from the surface [17-20].

6. DEGREDATION SPECIFICATIONS

Understanding the variables that affect PLGA's degradation is crucial for improving its desirable qualities and designing a drug delivery system that considers each of these variables will increase its effectiveness and efficiency. The most crucial element in determining the hydrophilicity and rate of degradation of a delivery matrix is its polymer composition. Numerous studies have shown how to conduct an organized analysis of polymer composition and degradation [21]. These findings indicate that the weight loss of polymers is accelerated by an increase in the amount of glycolic acid in oligomers. Degradation rate is indirectly impacted by copolymer composition, which also influences crucial attributes like glass transition temperature and crystallinity. There are conflicting reports right now on how crystallinity affects the rate of degradation [22].

The copolymer's rate of degradation is influenced by its molecular weight. Higher molecular weight polymers typically showed slower rates of degradation. The length of the polymer chain and molecular weight are directly correlated. Longer polymer chains in higher molecular weight polymers require longer to degrade than small polymer chains to do so [17].

Large system degradation has been demonstrated to be significantly influenced by the surface-to-volume ratio. Higher surface area ratio causes the matrix to degrade more quickly [23].

Both alkaline and highly acidic environments increase speed polymer degradation, as shown by *in vitro* PLGA biodegradation and hydrolysis.

7. SOLUBILITY

Solubility in common organic solvents has a substantial impact on how easily polymers can be processed, applied, and characterized. Less than 50% of the glycolyl units in many common organic solvents, including halogenated hydrocarbons (chloroform and dichloromethane), acetone, ethyl acetate, dioxane, and tetrahydrofuran (glycolic acid units). Only a few organic solvents, like hexafluoroiso-propanol, can be used to characterize and process PLGA with high glycolyl unit content (50 percent and greater) because it is insoluble in most of them [7]. By hydrolysis, PLGA biodegrades the ester associations in water. Due to the presence of methyl side groups in PLA, it is more hydrophobic than PGA; as a result, lactide copolymers high in PLGA are less hydrophilic, absorb less water, and degrade more slowly [17].

8. CRYSTALLINITY

Cristallinity affects the rate of degradation and mechanical characteristics of PLGA. The lactide to glycolide ratio and the stereoisomeric composition of the lactide units in the copolymer affect the poly(lactidecoglycolide) crystallinity. Amorphous poly(DL-lactide-co-glycolide) has 0–75 percent glycolyl units. With 25-75 percent glycolyl units, poly(L-lactide-co-glycolide) is also amorphous [7].

The molecular weight of the polymer and its melting point are both directly correlated. According to reports, the PLGA copolymers' Tg (glass transition temperature) is higher than the physiological temperature of 37°C, making them glassy by nature and providing them a very robust chain structure. Depends on the polymer having a specific mechanical strength in order to be produced as a drug delivery system. Tg of PLGAs decreases with a reduction in the molecular weight and lactide concentration of the copolymer composition [16].

9. THERMAL STABILITY

In the absence of moisture, PLGA copolymers are thermoplastic materials with adequate thermal stability. As a result, these materials can be melted down to produce sutures, orthopedic fixation devices, and drug delivery systems. Poly(lactide-co-glycolide) degrades to lactide and glycolide under nitrogen or vacuum after being heated for a long time over 200°C. Thermal degradation occurs at lower temperatures as a function of time, temperature, and is accelerated by impurities, residual monomers, and humidity [7].

Table 1. Glass transition temperatures of PLA and PLGA [24]

Polymers	Tg (°C)
PLA 100	45.3
PLGA (90:10) (Lactide:Glycolide)	48.7
PLGA (75:25) (Lactide:Glycolide)	36.5
PLGA (65:35) (Lactide:Glycolide)	42.8
PLGA (50:50) (Lactide:Glycolide)	35.7

10. RELEASE PROPERTIES

A drug delivery system based on PLGA may release drug molecules in only three different ways:

-Transport by water-filled pores,

-Transport by polymer,

-Transport by dissolution of the encapsulating polymer (which does not involve the transfer of drugs).

Because the encapsulated product is often a biopharmaceutical, such as a peptide or protein, which is too large and too hydrophilic for transportation through the polymer process, transportation through water-filled pores is the most popular mode of release [25].

11. TYPES

Monomer ratios and PLGA forms are generally categorized as PLGA 50:50 and PLGA 25:75. A copolymer composed of 50% lactide and 50% glycolide is known as PLGA 50:50. As a result, PLGA 25:75 (lactide: glycolide) and PLGA 80:20 (lactide: glycolide) both have amorphous structures. PLGA is hydrolyzed by ester linkages when there is water present. They are hydrolyzed into monomeric acids and eliminated through the creb cycle as CO_2 and water in the urine. The biodegradation of PLGA is influenced by its molecular weight, lactide: glycolide ratios, glass transition temperature (Tg), and degree of crystallinity. High lactide concentration PLGA is less hydrophilic, less water absorbing, and hydrolyzes more slowly. Properties of PLGA, such as molecular weight, lactide: glycolide ratio (rate of the active substance extracted from the carrier system: 50:50 > 65:35 > 75:25 > 80:20), and factors affecting the release of the active substance, such as particle size and surface properties of the prepared carrier systems [17].

Table 2. The pharmaceutical Research & Development studies with PLGA in Türkiye

Drug	PLGA type	Type of drug delivery system	Method of Preparation	Ref
-	PLGA (50:50) (Lactide:Glycolide) [2A (14 kDa), 3A (46 kDa), 4A (58.8 kDa) Medisorb®]	Nanoparticles	Spontaneous Emulsification Diffusion	[11]
-	PLGA (50:50) (Lactide:Glycolide) with molecular weights of 30,000–60,000 Da (High) and 24,000–38,000 Da (Low)	Nanomicelles	Oil/Water Emulsification-Solvent Evaporation	[13]
1,1'-dioctadecyl-3,3,3',3'-tetramethyl-indocarbocyanine perchlorate	Resomer® RG 503	Nanoparticles	Nanoprecipitation	[14]
5-fluorouracil	PLGA (74:26) (Lactide:Glycolide) PLGA (73:27) (Lactide:Glycolide)	Nanoparticles	Nanoprecipitation-Solvent Displacement	[26]
20-S-Camptothecin	PLGA (50:50) (Lactide:Glycolide)	Nanoparticles	Nanoprecipitation	[27]
Antisense oligonucleotides (ODNs) (5' CTT CAT CTT CAG CTA GTC GG)	Resomer® RG 503 Resomer® RG 503 H	Nanospheres	Emulsification-Diffusion	[28]
Atorvastatin, Alpha-lipoic acid	PLGA (50:50) (Lactide:Glycolide)	Microspheres	Spray-Drying	[29]
Betamethasone-17-valerate	PLGA (50:50) (Lactide:Glycolide)	Nanoparticles	Emulsion–Diffusion–Evaporation	[30]
Bovine Serum Albumin	Resomer® RG 502 Resomer® RG 503	Nanoparticles	Double Emulsion-Solvent Evaporation	[31]
Carvedilol	Resomer® RG 502 Resomer® RG 504	Nanoparticles	Nanoprecipitation	[20]
Clarithromycin	Resomer® RG 502 H Resomer® RG 503 H Resomer® RG 504 H	Nanoparticles	Nanoprecipitation	[32]
Curcumin (diferuloylmethane)	Resomer® RG 503	Hybrid Nanoparticles	Emulsion Sonication	[33]
Dexamethasone	Resomer® RG 502 H	Nanoparticles	Emulsification-Solvent Evaporation	[34]
Dexketoprofen trometamol	Resomer® RG 504 H	Nanoparticles	Double Emulsion-Solvent Evaporation	[35]
Dexpanthenol	Resomer® RG 756 S	Nanofiber Mats	Electrospinning	[36]

Table 2. Continued

Drug	PLGA type	Type of drug delivery system	Method of Preparation	Ref
Diclofenac sodium	PLGA (50:50) (Lactide:Glycolide) (34000 Da) PLGA (50:50) (Lactide:Glycolide) (88000 Da)	Microspheres	Solvent Evaporation	[37]
Diclofenac sodium	Resomer® RG 503 H	Nanoparticles	Nanoprecipitation	[38]
Docetaxel	Resomer® RG 502 Resomer® RG 502 H Resomer® RG 503 Resomer® RG 503 H	Nanoparticles	Emulsification-Solvent Evaporation	[39]
Doxorubicin	PLGA (50:50) (Lactide:Glycolide)	Hybrid Nanoparticles	Oil/Water Emulsion-Solvent Evaporation	[40]
Eletriptan hydrobromide	PLGA (50:50) (Lactide:Glycolide)	Nanoparticles	Sonication Evaporation	[41]
Epidermal Growth Factor	Resomer® RG 503 H	Microspheres	Double Emulsion-Solvent Evaporation	[42]
Etodolac	PLGA (50:50) (Lactide:Glycolide)	Nanoparticles	Nanoprecipitation	[43]
Flurbiprofen sodium	PLGA (50:50) (Lactide:Glycolide) (69 kDa), PLGA (50:50) (Lactide:Glycolide) (63 kDa), PLGA (75:25) (Lactide:Glycolide) (130 kDa), PLGA (75:25) (Lactide:Glycolide) (92 kDa), PLGA (85:15) (Lactide:Glycolide) (149 kDa)	Microspheres	Solvent Evaporation	[44]
Flurbiprofen, Folic Acid	Resomer® RG 504 H	Nanoparticles	Nanoprecipitation	[45]
Gemcitabine hydrochloride	PLGA (50:50) (Lactide:Glycolide)	Nanoparticles	Modified Double Emulsion-Solvent Evaporation	[46]
Gemcitabine hydrochloride	PLGA (50:50) (Lactide:Glycolide) PLGA 65:35 (Lactide:Glycolide)	Lipid Polymer Hybrid Nanoparticles	Emulsion-Solvent Evaporation	[47]

Table 2. Continued

Drug	PLGA type	Type of drug delivery system	Method of Preparation	Ref
Heparin	Resomer® RG502 Resomer® RG503 Resomer® RG504	Microparticles	Spray-Drying	[48]
Ibuprofen	Resomer® RG 503 H	Nanoparticles	Nanoprecipitation	[49]
Imatinib mesylate	PLGA (50:50) (Lactide:Glycolide) PLGA (75:25) (Lactide:Glycolide) PLGA (85:15) (Lactide:Glycolide)	Microspheres	Water/Oil/Water Double Emulsion-Solvent Evaporation	[50]
Interleukin-2	Resomer® RG 502	Microparticles	Double Emulsion-Solvent Extraction	[51]
Ketoprofen lysine	Resomer® RG 504 H	Nanoparticles	Spray-Drying	[52]
Lamivudine	Resomer® RG 504 H	Nanoparticles	Double Emulsion-Solvent Evaporation	[53]
Meloxicam	PLGA (50:50) (Lactide:Glycolide)	Nanoparticles	In Situ Coating Technique-The Surface Adsorption	[54]
Meloxicam	PLGA (50:50) (Lactide:Glicolyde)	Nanoparticles	Using Salting-Out-Emulsion-Evaporation	[55]
Meloxicam	PLGA (50:50) (Lactide:Glycolide)	Nanoparticles	Ultrasonication-Solvent Evaporation	[56]
Metformin HCl	Resomer® RG 502	Nanoparticles	Ultrasonication-Solvent Evaporation	[57]
Nifedipine	Resomer® RG 756 S	Nanoparticles	Nanoprecipitation-Emulsion-Solvent Evaporation	[58]
Nimesulide	PLGA (50:50) (Lactide:Glicolyde)	Nanoparticles	Ultrasonication-Solvent Evaporation	[59]
Ondansetron	Resomer® RG 502 Resomer® RG 503	Microspheres	Emulsification-Spray-Drying	[60]
Paclitaxel	Resomer® RG 502 H	Nanoparticles	Oil/Water Emulsification-Solvent Evaporation	[61]
Paclitaxel	Resomer® RG 503	Nanoparticles	Nanoprecipitation	[62]
Paclitaxel, Flurbiprofen	PLGA	Nanoparticles	Nanoprecipitation	[63]
Phenyl Butyl Nitrone (α-phenyl-N-tert-butyl nitrone)	Resomer® RG 502 H	Nanoparticles	Homogenization-Solvent Evaporation	[64]
Plasmid DNA (pDNA)	Resomer® RG 502 Resomer® RG 503 Resomer® RG 503 H	Microspheres	Water/Oil/Water Double Emulsion-Solvent Evaporation	[65]

Table 2. Continued

Drug	PLGA type	Type of drug delivery system	Method of Preparation	Ref
Recombinant Human Interleukin-2	Resomer® RG 502 Resomer® RG 502H Resomer® RG 504 Resomer® RG 752H Resomer® RG 756S	Microparticles	Double Emulsion-Solvent Evaporation	[66]
Recombinant Human Interleukin-2	Resomer® RG 502 Resomer® RG 502 H Resomer® RG 504 Resomer® RG 752 H Resomer® RG 756 S	Microparticles	Double Emulsion- Solvent Evaporation	[67]
Salmon calcitonin	Resomer® RG 502 H	Nanoparticles	Nanoprecipitation	[68]
Small interfering RNA (siRNA)	PLGA (50:50) (Lactide:Glycolide) [2A (14 kDa) and 3A (46 kDa) Medisorb®]	Nanoparticles	Emulsification Diffusion	[69]
Sodium fusidate	PLGA (50:50) (Lactide:Glycolide)	Microspheres	Double Emulsion Solvent Evaporation	[70]
Terbinafine hydrochloride	Resomer® RG 502 H	Nanoparticles	Emulsification-Solvent Evaporation	[71]
Vancomycin	PLGA (75:25) (Lactide:Glycolide)	Microspheres	Oil/Water Emulsion-Solvent Evaporation	[72]
Vancomycin	PLGA (90:10) (Lactide:Glycolide) PLGA (70:30) (Lactide:Glycolide)	Microcapsules	Water/Oil/Water Double Emulsion-Solvent Evaporation	[73]
Vancomycin	PLGA (90:10) (Lactide:Glycolide) PLGA (70:30) (Lactide:Glycolide)	Polymer disks	Solvent Evaporation	[74]
Vascular Endothelial Growth Factor	PLGA (50:50) (Lactide:Glycolide)	Microspheres	Water/Oil/Water Emulsification	[75]
Vascular Endothelial Growth Factor	PLGA (50:50) (Lactide:Glycolide)	Microspheres	Water/Oil/Water Emulsification	[76]
Vincristine, ε-Viniferine	PLGA	Nanoparticles	Nanoprecipitation	[77]
Diclofenac sodium	Resomer® RG 502 H	Nanoparticles	Double Emulsion Solvent Evaporation	[78]
Flurbiprofen	Resomer® RG 502 H Resomer® RG 503 H Resomer® RG 503 H	Nanoparticles	Nanoprecipitation	[79]
Ketoprofen lysine	Resomer® RG 504H	Nanoparticles	Spray drying technique	[80]
Cefaclor Monohydrate	Resomer® RG 504H	Nanoparticles	Nanoprecipitation	[81]
Lamivudine	Resomer® RG 502 H	Nanoparticles	Double Emulsion Solvent Evaporation	[82]

12. CONCLUSION

Drug delivery systems and polymers used in drug delivery systems are a very important issue today and studies are continuing [81,83-87]. Different drug delivery systems prepared with polymers are more advantageous and more promising than traditional drug delivery systems [81,85-93]. Table 2 shows pharmaceutical R&D studies with PLGA in Turkey. PLGA is widely using as a polymer for long time and it is approved in various human drug delivery systems by the FDA and the EMA. This review shows that there are latest studies on medicine industry about beneficial usage of PLGA and also traditional usage of PLGA in Türkiye. In addition because of its good biodegradable properties and able to controlled release PLGA is a very important polymer technology. We can make inference that PLGA is continue to be used for human health and medicine industry.

Author contribution

Concept: AAÖ; Design: AAÖ; Supervision: AAÖ; Data Collection and/or Processing: BK, FDŞ, KKB, ME, AAÖ; Analysis and/or Interpretation: BK, FDŞ, KKB, ME, AAÖ; Literature Search: BK, FDŞ, KKB, ME, AAÖ; Writing: BK, FDŞ, KKB, ME, AAÖ; Critical Reviews: AAÖ.

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Conflict of interest

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