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## Biomedical applications of polyglycolic acid (PGA)

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### ABSTRACT

Biodegradable polymers have a great potential and widely used in biomedical applications due to their biodegradability and biocompatibility. Biodegradable polymers contain hydrolytically unstable functional groups (such as esters, anhydrides and etc.) in their backbone. These hydrolytically unstable functional groups can be hydrolyzed, or eaten by microorganisms, and degradability happens. Biodegradable polymers can be effectively used for several biomedical applications such as drug delivery, dental, orthopedic and tissue engineering. Polyglycolic acid (PGA) is a desired material for physicians due to its excellent degradation behaviour. However, limited research based on PGA polymers has been studied in biomedical applications due to insolubility of PGA in most of the solvents and rapid degradation of PGA. This review will focus on the improvements made in the development of hydrolytically degradable PGA in biomedical fields.

**Keywords:** Biodegradable polymers, polyglycolic acid (PGA), biomedical applications, biodegradability, biocompatibility

### Poliglikolik Asit' in (PGA) Biyomedikal uygulamaları

#### ÖZ

Biyobozunur polimerler, biyobozunurluk ve biyoyuymululuk özelliklerinden dolayı biyomedikal uygulamalarda büyük potansiyele sahip olup yaygın şekilde kullanılmaktadır. Biyobozunur polimerler yapılarında hidrolitik olarak kararsız fonksiyonel gruplar (örneğin, esterler, anhidritler vd.) içerirler. Bu hidrolitik olarak kararsız gruplar kolayca hidroliz olabilmekte, veya mikroorganizmalar tarafından yenilebilmektedir. Bu sayede polimerlerin bozunması gerçekleşir. Biyobozunur polimerler birçok biyomedikal alanda (örneğin; ilaç salınımı, dişçilik, ortopedi, ve doku mühendisliği) etkili bir biçimde kullanılabilir. Poliglikolik asit (PGA) oldukça iyi bozunma davranışından dolayı tıp alanında yaygın şekilde kullanılan bir materyaldir. Ancak, PGA polimerlerinin biyomedikal uygulamaları alanında sınırlı sayıda araştırma mevcuttur. PGA birçok çözücü içerisinde çözünememekte ve hızlı bir şekilde bozunmaya uğramaktadır. Bu derleme hidrolitik olarak bozunabilen PGA' nın biyomedikal alanda kullanımındaki yenilikleri açıklayacaktır.

**Anahtar Kelimeler:** Biyobozunur polimerler, poliglikolik asit (PGA), biyomedikal uygulamalar, biyobozunurluk, biyoyuymululuk

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## 1. INTRODUCTION

In recent years, research into biodegradable and biorenewable plastics to replace petroleum-based products has increased dramatically [1]. Large portions of trash in landfills are mostly petroleum based polymer materials, such as plastic bags and bottles [2]. The degradability of these petroleum based materials takes a very long time, like thousands of years. One of the reasons of increasing global pollution is the expanding use of these non-degradable materials [3]; therefore, a switch from petroleum-based polymers to biodegradable polymers is necessary. The difference between biodegradable and petroleum based polymers is that biodegradable polymers contain hydrolytically unstable functional groups (such as esters, anhydrides, etc.) in their backbone but petroleum based polymers mostly not. Esters, anhydrides, orthoesters and amides have possessed these unstable functional groups. Because of hydrolytically unstable functional groups, these linkages can be hydrolyzed, or eaten by microorganisms, and degradability happens [4]. Degradation rate of any polymer mainly depends on its chemical structure (functionality) and physical properties (morphology, thermal and mechanical properties and etc.). Biodegradable polymers can be effectively used for several biomedical applications such as drug delivery, dental, orthopedic and tissue engineering [5].

All biodegradable polymers can not be used for biomedical applications. There are some important criterias for selecting a material to use it in a pharmaceutical application. Biodegradable materials must have required mechanical properties and degradation time to the needs of the application. The ideal biodegradable material would have following properties to be used in pharmaceutical applications [6,7];

- 1) Biodegradable materials must produce nontoxic degradation products that can be readily resorbed or excreted, and they would be metabolized in the body after fulfilling its purpose with leaving no residues.
- 2) They must have appropriate mechanical properties to be easily processed into the desired form and easily sterilized.
- 3) Their degradation time should be acceptable to accordance with their function.

- 4) They should not cause a sustained inflammatory/toxic response.
- 5) They should also possess appropriate permeability and processability for their intended use.

Nowadays, polyglycolic acid (PGA) is of interest among scientists due to its biodegradability and environmentally safe properties. PGA is the simplest linear aliphatic polyester (Figure 1) and has highly crystalline structure (amorphous-55%) [8]. Its  $T_g$  (glass transition temperature) is around 35-40 °C, and  $T_m$  (melting temperature) ranging from 224-227 °C [9]. There are four main types of processes to produce PGA: polycondensation of glycolic acid, ring-opening polymerization glycolide, solid-state polycondensation of halogenoacetates and Brønsted acid catalyzed polymerization of carbon monoxide and formaldehyde [10]. Polycondensation methods give rise to polymers of low molecular weights; however, higher molecular weights can be obtained via ring-opening polymerization of glycolide, the cyclic dimer form of glycolic acid [10,11].

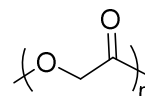


Figure 1. The chemical structure of polyglycolic acid (PGA).

PGA was marketed as the first biodegradable synthetic suture, trade name was DEXON in 1960s [12,13]. Kureha Corporation is currently pursuing PGA for larger scale packaging applications under the trade name Kuredux® [14]. PGA was also offered as an internal bone pin under the name Biofix from 1984 to 1996 [6]. Sutures must have special properties to be conveniently used by surgeons. They must have good knot strength that can be tied, and have better handling characteristics that can be easily placed it where surgeon desires [15]. Fibers of stretched PGA have shown good knot strength, non-toxic behaviour, and absorbability characteristics which are desirable properties of collagen sutures for surgical operations. PGA sutures lose almost 50% of their strength after two weeks and 100% at four weeks. PGA sutures are completely absorbed in 4-6 months [16].

Polyglycolic acid is a desired material for physicians due to its degradation behaviour. As mentioned above, the main reason to have biodegradable devices is to use them as implants

in surgical applications [17]. Biodegradable implants mostly will not require a second surgical operation for removal on the contrary of the stainless steel implants. The second surgical operation potentially causes the psychological stress for patients. In addition to that, after fractured bones were fixated with stainless steel implants, there would be a tendency for re-fracture of the bones during the removal of the implant. When stainless steel implants are used to heal the fractured bone, the load is carried by the implant. However implants prepared from biodegradable materials can degrade and slowly transfer load to the healing bone [18,19]. PGA implants for fracture fixation have indicated no apparent adverse effects on the healing of the fracture. Some complications including minor displacements of fracture (about 10%), inflammatory sinus (about 7%) and fixation failure (about 5%) have been reported for using PGA rods and screws [20,21].

The physical properties and biodegradable behavior of PGA based materials have been studied since 1960s, and these materials have been found as attractive for developing delivery vesicles, grafts and scaffolds for tissue regeneration. The chemical and physical properties of PGA materials can be delineated to address the desired requirements. PGA based materials are expected to be used as fibres and composites to help for healing of tendons, ligaments and bones [22]. In addition to that, PGA polymers are also used in other biomedical applications for resorbable implants in the shape of rod, plate, fibre and beads for bone. PGA exhibits biodegradability, biocompatibility, non-toxicity and ease of fabrication properties [23].

### 1.1. Packaging and Sterilization

Since PGA is hydrolytically unstable under aqueous conditions, moisture must be eliminated during the packaging to prevent degradation. PGA materials should also be sterilized before using them in biomedical applications before the surgical revision to prevent the possible infections and complications by any micro organisms or deleterious materials [22].

$\gamma$ -radiation, ethylene oxide (EtO), plasma etching or electron beam irradiation techniques can be used to sterilize PGA materials. PGA devices should not be sterilized by dry heating and autoclaving, because PGA can be degraded under these conditions. The temperatures above the thermal transition temperatures of PGA can alter

its physical and mechanical properties. A high dose of  $\gamma$ -radiation is also known to decrease in molecular weight of PGA since it causes chain scission in the polymer chain [24].

Ethylene oxide (EtO), a gaseous sterilizing agent, exposure is the common method for the sterilization of PGA. EtO gas can be absorbed into the polymer. Since EtO is a highly toxic gas, the concentration of residual EtO must be reduced to acceptable levels in the PGA implant before the packaging. Therefore, the process takes very long time due to degassing of EtO residue [25].

### 1.2. Degradation

Degradation of the PGA occurs in two phases. In the first phase; water penetrates in the amorphous region and attacks the ester functional groups of the polymer chains. Thus, long polymer chains are converted to shorter chains. In the second phase; shorter chains are attacked by enzymes and metabolized [26]. Polymer degradation rate depends on the following properties [27,28];

- 1) Possessing more hydrophilic repeat units
- 2) Having more hydrophilic, acidic end groups
- 3) Having reactive hydrophilic group in the backbone
- 4) Less crystallinity
- 5) Smaller device size

### 1.3. Biocompatibility

Biocompatibility of a biodegradable polymer depends on its physical properties (such as durability, permeability and degradability) and surface properties (such as hydrophilicity, smoothness and surface energy). Ideal biodegradable polymer implants are not expected to show an inflammatory or toxic response. Degradation products (degradants) must be metabolized in the body after fulfilling its aim with leaving no residue. Degradation of PGA by hydrolysis and esterases generates glycolic acid. Glycolic acid can be either excreted in urine or used to form glycine for further transformations to enter tricarboxylic acid cycle [29].

### 1.4. Tissue Engineering

Tissue engineering is a growing biotechnological area for the aim of the regeneration of diseased tissues or organs. Tissue and organ failure is known to be destructive and costly problems in

medicine [30]. Tissue engineering is potentially an alternative solution for tissue and organ failure by implanting synthetic tissue and organ mimics. This method has an important advantage to reduce the number of operations needed, and results in a shorter recovery time for patients [31].

Biocompatible scaffolds are attracted more attention for tissue engineering due to their porous and degradable structures. Scaffolds can be produced from using either natural materials (including starch, chitin/chitosan, alginate and etc.) or synthetic polymers (polyglycolic acid, polylactic acid and etc.) [32].

A scaffold can be used to culture and seed the cell populations and it accommodates to grow and proliferate new cells in three dimensions. In order to repair damaged tissues, the scaffold should selectively interact with the target cells in surrounding tissues. Scaffolds must possess essential physical properties including high porosity, uniform porous structure, large surface area and pore size. Degradation ability in response to enzymes released by cells is also required for the scaffolds to progress tissue repair [33-35]. Molecular weight, crystallinity and geometry affect the degradation rate of the polymer [36]. As mentioned previously, tissue scaffolds must also be sterilized to prevent infection in the body [37].

### 1.5. Drug Delivery Systems

Controlled drug delivery systems are one of the most rapidly expanding areas in biochemical applications, and biodegradable materials have been extensively researched in the area of controlled release of drugs. Biopolymers and drug delivery systems provide improvement for the efficiency of drug formulations and treatments. These systems generally use synthetic biodegradable polymers as drug carriers [38]. Many synthetic biodegradable polymers, including polyesters, polycarbonates, polyphosphazenes, polyanhydrides and etc., have been studied for their usage as a drug release matrix. Natural polymers have some drawbacks to be able to use for drug delivery systems. One of the biggest problems for natural polymers is microbial contamination. The natural polymers possess 10% or more moisture, therefore there is always a chance for microbial contamination when they are exposed to the environment [39]. However, biodegradable polymers are more convenient to use them as drug carriers. They provide localized and sustained drug delivery,

steady release rate of drug with time, and stabilization of drug [40].

Traditional drug delivery methods using pills or injection is not suitable and not preferred for new protein, DNA, and other therapies [41,42]. Controlled release of drugs has been achieved using biodegradable polymer matrix which encapsulate drugs and release them by diffusion and polymer erosion [43]. Advantages of controlled drug delivery systems over traditional drug delivery are explained below [39,44,45]:

- 1) Occurrence of undesired side effects and toxicity is reduced
- 2) Usage of the drug is better and dosage application is decreased
- 3) Drug concentration in the circulation is sustained
- 4) Patient compliance is better
- 5) Therapeutic effect is more reliable

Biodegradable polymeric implants have mainly a triphasic release pattern; the first initial phase, the diffusional phase, and the final phase. The initial phase consisted of the rapid release of the drugs deposited on the surface of the matrix. The diffusional phase has been resulted in slowly released drugs by the degradation of polymer. The final stage is considered as suddenly occurred release of the drugs due to swelling and disintegration of the matrix. Drug release rate depends on the molecular weight of the polymer, the surface area of the matrix, and drug loads [46-49].

PGA as a degradable polymer can also be used in drug delivery systems. Since ester bonds in PGA backbone can be cleaved under physiological conditions (around pH 7.4), PGA has a special interest in drug delivery applications [50]. Polymers used for controlled drug delivery systems should provide following properties [39];

- 1) Versatility
- 2) Wide range of mechanical, physical and chemical properties
- 3) Non-toxic and good mechanical strength
- 4) Inert to host tissue and compatible with environment.
- 5) Inexpensive and easy to construct

## 2. CONCLUSION

In conclusion, PGA polymers have a big potential in biomedical applications by replacing traditional polymers. PGA in the fields of pharmaceutical and orthopedic applications appears to be very promising. PGA can also contribute in formation of composites, and blends to obtain different properties for different applications especially for drug delivery systems. The use of PGA based biodegradable implants is also expected to grow for development of supplement traditional treatments.

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