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Biodegradable Poly (lactic-co-glycolic acid) Microparticles Controlled Delivery System: A Review

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ABSTRACT

Microparticles represent a promising drug delivery system as they offer a definite amount of drug to the site of action and provide protection for unstable drugs before and after administration. Poly lactic-co-glycolic acid (PLGA) is a polymer approved by Food and Drug Administration (FDA) that has been among the most attractive polymeric candidates intended for controlling drug delivery. PLGA is biocompatible, biodegradable, and has been extensively utilized for the development of devices for delivery of small molecules, proteins, and macromolecules. This manuscript describes the various development techniques for PLGA-based microparticles and the factors affecting their degradation and drug release. The effectiveness of using biodegradable PLGA polymer in microparticles formulations and the application of this strategy through several routes of administration has been discussed.

Keywords Microparticles, controlled delivery system, poly (lactic-co-glycolide), biodegradability, small-molecule drugs.

Abbreviations NSAIDs: Non-steroidal anti-inflammatory drugs, IM: Intramuscular, SC: Subcutaneous, PCL: Poly(caprolactone), PHA: Polyhydroxyalkonates, PPE: Polyphenylene ethylene, KDa: kilodaltons.

1. INTRODUCTION

The selection of a drug delivery system is highly dependent on the drug, disease state, and the location of disease in the body. The controlled release system has been extensively used in the pharmaceutical field. The use of a controlled drug delivery system aims and objectives are: achieving a high blood level of the drug over an extended period of time, enhancing therapeutic efficacy, optimizing pharmacokinetic and pharmacodynamic properties, maintaining drug levels in a favorite range, minimizing the side effects, and improving patient compliance[1-2]. The potential disadvantages of controlled drug delivery systems are the toxicity of the polymer used, by-products of degradation, patient discomfort and the higher cost compared with traditional preparations [2]. Controlled release approach for drug delivery has mostly used encapsulating devices such as polymers to adjust the rate of drug released for specified periods, ranging from days to months. The extended duration of effect depends on the dose, route of administration, and the hydrophobicity of the drug. Generally, the duration will not be more than 48 hours once given orally, but it can last up to several months when given via intramuscular (IM) or subcutaneous (SC) injections [3, 4].

1.1. Polymers

Polymers are considered to be a special class of compounds that are intended for use in controlled release preparations [5]. They are macromolecules with low or high molecular weight and have large chains

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with various functional groups [6]. Polymers can be categorized into biodegradable and non-biodegradable type polymers [7-11]. Biodegradable systems have gained much popularity over non-degradable types since they are absorbed and/or expelled by the body once the required effect is obtained[12-15].

Non-biodegradable polymers are generally stable even after the active agents leach out (Figure 1). Examples of non-biodegradable polymers include cellulose derivative (carboxy methylcellulose), silicon (polydimethyl siloxane), polyvinyl pyrolidine, ethylvinyl acetate, and poloxamine[16, 17].

Biodegradable polymers are degraded in vivo, either enzymatically or nonenzymatically to biocompatible, non-mutagenic, or nontoxic byproducts (Figure 1)[15-16, 18-19]. Their breakdown is mainly affected by temperature, pH, and the surface area of the delivery system [20].

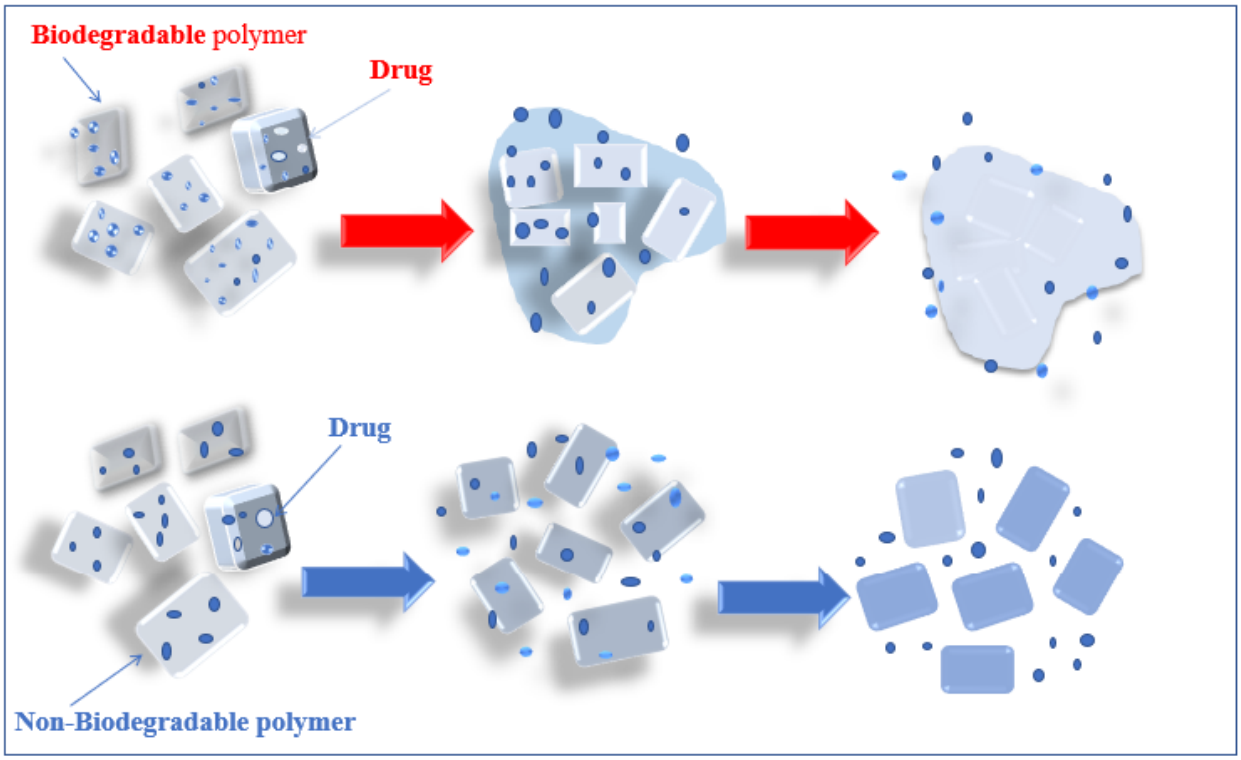

Figure 1. Schematic representation of biodegradable (bioerodible) and non-biodegradable drug delivery device as modified from Imazato *et al.* [16].

Biodegradable polymers used in the preparation of controlled release formulation can be obtained from natural sources as hyaluronan, alginic acid, chitosan, and hydroxyapatite, while synthetic ones include poly lactic-co-glycolic acid and polyanhydrides (Figure 2) [7–9, 21-24]. Polyglycolic acid (PGA), polylactic acid (PLA), polyglycolic-lactic acid (PLGA), polyaspartic acid, and polycaprolactone are the most generally used biodegradable polymers [20, 25].

A biodegradable polymer may release the medication by diverse mechanisms such as erosion, diffusion, and swelling [17, 26-28].

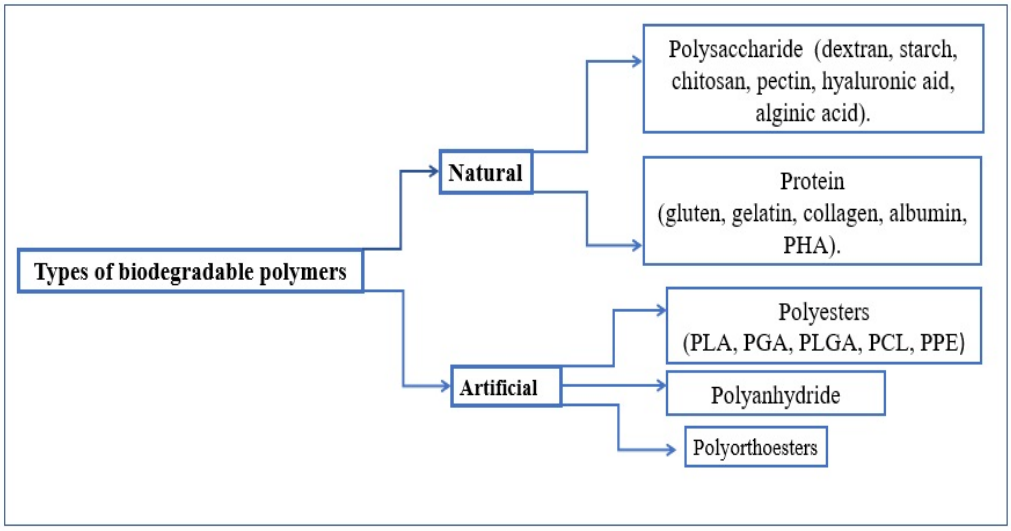

Figure 2. Types of biodegradable (erodible) polymers as modified from Prajapati *et al.* [22].

The monomers in biodegradable polyesters are linked by ester bonds. The breakage of ester bonds usually happens randomly through hydrolytic cleavage and leads to subsequent erosion of the device. The amount of hydrolysis is influenced by molecular weight, copolymer ratio, polydispersity, and crystallinity of the polymer [29]. Poly lactic-co-glycolic acid (PLGA) polymers are a family of biodegradable polymers, FDA-approved, and used as delivery vehicles for proteins and macromolecules (DNA, RNA, peptides) [1–3]. It can be synthesized via polymerization of lactides and glycolide acid monomers (Figure 3).

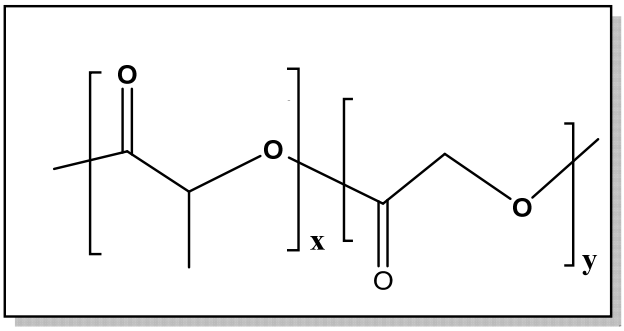

Figure 3. Structure of poly lactic-co-glycolic acid; x is the number of lactic acid units, and y is the number of glycolic acid units [30].

PLGA carriers of different molecular weight (ranging from 10 to more than100 kDa) and various lactide to glycolide molar ratios (50:50, 65:35, 75:25, and 85:15) are available. Usually, the lower amount of glycolide produces a slower rate of degradation. In fact, a ratio of 50:50 lactide/glycolide PLGA copolymer possesses the fastest half-life of degradation of about 50-60 days, while ratios of 85:15, 75:25, and 65:35 lactide/glycolide copolymers exhibit an extended degradation half-life in vivo [25, 31]. The biodegradation periods of various types of PLGA polymers

are shown in Table 1 [27, 32]. This means that the physicochemical properties of PLGA polymers vary by changing the ratio of lactic acid to glycolic acid [31, 32].

PLGA polymers are supposed to undertake surface erosion since they are made from fast degrading functional groups (Figure 4) [25, 30].

Table 1. Summary of biodegradation time of PLGA (lactide/glycolide) polymers [32].

Polymer	Biodegradable time (month)
Poly(l-lactide)	18-24
Poly(dl-lactide)	12-16
Poly(glycolide)	6-12
Poly(dl-lactide-co-glycolide) 90:10	2
Poly(dl-lactide-co-glycolide) 85:15	5-6
Poly(dl-lactide-co-glycolide) 75:25	4-5
Poly(dl-lactide-co-glycolide) 50:50	1-2

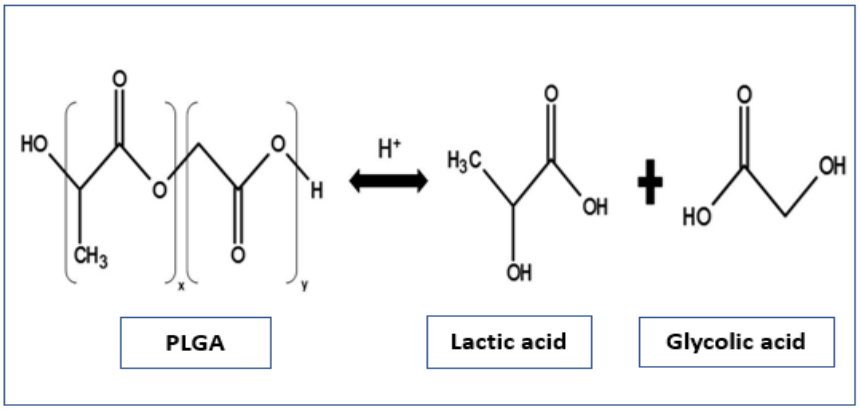

Figure 4. A diagram showing the hydrolysis of the poly lactic-co-glycolic acid polymer [30].

Biodegradable PLGA polymers have been widely used for encapsulation of an extensive range of hydrophobic and hydrophilic molecules [33-35]. Diflunisal, a non-steroidal anti-inflammatory drug, [34] and diclofenac sodium [35, 36] have been incorporated into PLGA microparticles and investigated for the treatment of rheumatoid arthritis and osteoarthritis [36, 37]. PLGA is also used in various other drug delivery applications such as those involving the transport of anticancer agents with low water solubility [33, 38, 39]. However, the problems of low drug loading efficiency, difficulties in controlling drug release rate from encapsulated preparations, and formulation instability have limited the use of PLGA microparticles in pharmaceutical products [40].

2. Microparticles

Microparticles, also known as microspheres, were prepared for the first time in 1997 to control the action of drugs [1]. They can permit accurate delivery of small quantities of the potent drugs to the site of action, improve dissolution rate, offer protection for unstable drugs before and after administration, and manipulate the drug action in vivo [41, 42]. However, there are some potential drawbacks of microparticles use such as dose dumping, low loading efficiency, polymer toxicity, high cost, and complications in the scale-up procedures [40, 43]. Microspheres are mainly

monolithic spherical particles with diameters ranging from 1 to 1000 μm [44]. They are made up of polymers in which drug particles are dispersed [1]. Microspheres could be of three types: porous, hollow core with thin porous shell and solid structures depending on types of organic solvent used [45]. The main advantage of microspheres is their biocompatibility and degradation into substances eliminated by the normal metabolic pathways. Therefore, microparticles based on biodegradable PLGA polymer could be used to deliver a variety of therapeutic constituents as proteins, peptides, NSAIDs, antibiotics and anticancer drugs [46].

2.1. Preparation of PLGA-based microparticles for controlled-release formulations

Numerous methods have been established to prepare drug-loaded microparticles with favorite release characteristics from polymers. These included suspension of solid particles in the polymer solution, solvent extraction/evaporation, solvent diffusion/evaporation, supercritical CO_2, spray drying, coaxial electrospray, and phase separation method. Depending on the method used, drugs can be entrapped in the polymer matrix, enclosed by polymer membrane, incorporated in a liquid core, or adsorbed on particle surfaces [17, 47]. The use of these methods for the preparation of microparticles depends on the physicochemical properties of PLGA polymer and the drug type, the intended use of the system, and duration of the treatment (Table 2) [28, 31, 48].

2.1.1. Emulsification of solvent evaporation by extraction and diffusion methods

This approach depends on the evaporation of the internal phase of an emulsion by agitation. For the preparation of drug-loaded microparticles, many steps are involved: the dissolution of PLGA biodegradable polymers in an organic solvent, dissolution or dispersion of the drug in organic-polymers solution, emulsification of organic phase in a second continuous phase, and evaporation/ extraction/ diffusion of organic solvents, then recovery and drying. However, an organic solvent is very difficult to be removed completely and may harm the encapsulated drug [43, 49].

a) Single emulsion technique (spontaneous emulsion method)

Oil-in-water (O/W) emulsion solvent evaporation technique is favored when drugs are hydrophobic (such as steroids) and soluble in a water-immiscible organic solvent. In this method, PLGA polymer and a drug are dissolved in the same water immiscible volatile organic solvent (dichloromethane) to formulate a single-phase solution. The polymer-drug dispersed solution is then emulsified in a large volume of an aqueous solution containing an appropriate emulsifier (polyvinyl alcohol) [48]. The volatile solvent is then permitted to evaporate or extract to harden the oil droplets. The resultant solid microspheres are then washed and dried under suitable conditions to produce a final injectable microsphere formulation [43].

b) Double emulsion technique

In the double emulsion process, the choice of solvents and stirring rate affect the encapsulation efficiency and microparticle size. This technique involves the preparation of double emulsion either water in oil in water (W/O/W) or oil in water in oil (O/W/O). The W/O/W emulsion method is the most universal method that was developed by Ogawa et al. in 1988 [50]. It comprised four stages: primary emulsification; an aqueous solution of the drug is emulsified into an organic solution containing biodegradable PLGA polymer by vigorous stirring to yield a water-in-oil emulsion (W/O). The primary emulsion is further emulsified into another aqueous phase comprising a surfactant for about a minute at an appropriate stress mixing environment to produce a W/O/W double emulsion. The formed emulsion was then solidified through evaporation or extraction of the organic solvent which yields solid microparticles. The process was followed by separation and purification of microparticles by centrifugation or filtration (Figure 5) [30].

The most important principles for good encapsulation

efficiency in W/O/W method are the insolubility of the drug in the organic polymer solution and the fine dispersion of the aqueous drug solution into the organic polymer solution to produce a W/O emulsion [51]. For example, Ivermectin containing microspheres were prepared by a solvent evaporation technique using polymers as a matrix [52].

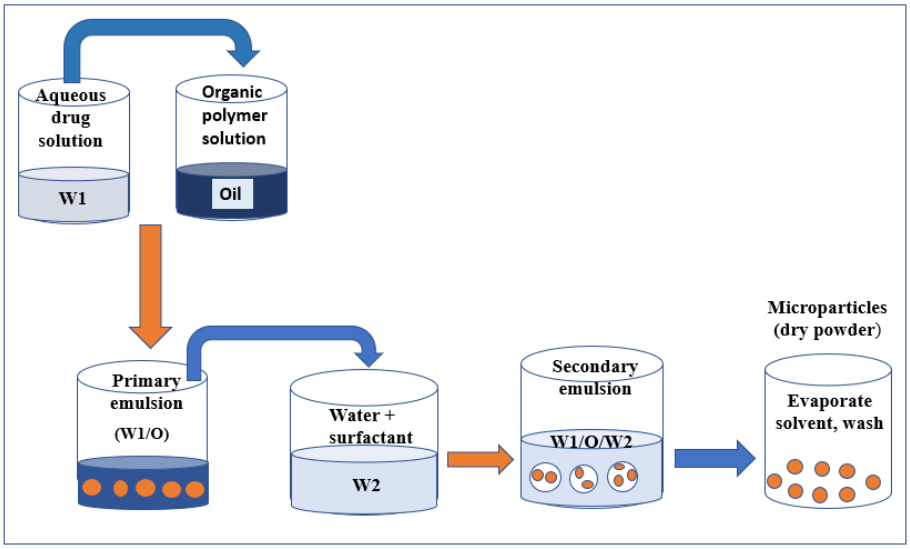

Figure 5. Scheme of the preparation of microparticles through encapsulating aqueous drugs by the double emulsion-solvent evaporation method (this figure is modified from Giri *et al.* [53]).

c) Suspension method

It can be used for the encapsulation of proteins by the solid/ oil /water (S/O/W) or solid /oil /oil (S/O/O) method. The S/O/W has been developed to protect protein from denaturation or adsorption at the aqueous/ oil interface during microspheres formation [49]. It involves a fine dispersion of a solid protein/excipient mixture in an organic solvent. Thus, this strategy has been employed for encapsulation of many proteins such as tumor necrosis factor (TNF-a), recombinant human growth hormone (rhGH), and bovine serum albumin (BSA). In addition, it could be used for other hydrophobic drugs like haloperidol, Levonorgestrel, and β-estradiol [54, 55]. The drawbacks of this technique comprise the need for small size materials and the partial solubility of the protein in the organic solvent. Other problems might contain the micronization of lyophilized protein solids which could cause some protein damage, and the tendency of the drug to show floatation or sedimentation during the encapsulation process [56].

2.1.2. Salting out/ phase separation method

Salting out process is also known as simple coacervation, used to precipitate dissolved polymer through attracting water atoms to the salt ions, and thus, decreasing the amount of water available for solvation of the polymer [49, 56]. Coacervation is a procedure of formulating a micrometer-sized PLGA polymer by liquid-liquid phase separation method [56]. The process yields two phases including a dilute supernatant phase and polymer containing dense coacervate phase. This process comprises of three stages; phase separation of the coating polymer solution that holds the coacervate phase, adsorption of the coacervate around the drug particles which are dispersed or dissolved in the polymer solution and quenching of the microspheres. The size and the morphology of the microspheres are influenced by solvent composition, type of polymer, temperature and time. Consequently, coacervation methods produce agglomerated particles and require the removal of large quantities of the organic phase from the microparticle [30].

2.1.3. Melting technique

This method used to encapsulate drugs into biodegradable polymers where a hot mixture of drug and PLGA polymer are emulsified into an aqueous surfactant solution that has been heated above the polymer melting point to form an emulsion [1]. The drug/matrix polymer melt is cooled down and then grounded to form non-spherical particles. Consequently, the melting technique avoids the use of organic solvents to produce microparticles formation [25, 57].

2.1.4. Spray drying method

Spray drying is a rapid and convenient method used for the encapsulation of hydrophobic, hydrophilic substances and heat-labile biomacromolecules. It can also be suitable for large-scale production of microparticles. This technique can overcome the large volumes of solvent-contaminated water that results from emulsion-based encapsulation methods [30, 58]. PLGA polymer is liquified in an appropriate volatile organic solvent. The solid drug is then dispersed in the solution using high-speed homogenizer. The dispersion is atomized in a stream of warm air through a nozzle under different experimental conditions to form small droplets. The solvent is then evaporated instantly leading to the formation of microparticles [59]. The morphology of the particles is affected by the nature of the solvent used, the temperature and feed rate. The main disadvantage of this technique is the adhesion of the microparticles to the internal walls of the spray-dryer [30].

2.1.5. Coaxial electrospray (CES) method

This is a desirable technique to produce microparticles of precise mean particle size. CES can produce microparticles by using an electric field applied to both the PLGA carrier and drug-loaded solutions sprayed at the same time through two isolated feeding channels of a coaxial electrospray [28]. CES utilizes the electrostatic forces to control the size and shape of the particles and to increase drug release characteristics [57].

2.1.6. Supercritical carbon dioxide technique

Supercritical carbon dioxide (CO_2) was used as a foaming agent in the production of PLGA microparticles. In this technique, polymer encapsulated with a drug can be prepared using emulsion techniques and placed into a CO_2 pressure cell immediately after emulsification. Under the high pressure of CO_2, the polymer is dissolved. Following the pressurization and depressurization sequence which lead the molecules to form clusters inside the liquid polymer, and the porous polymer structure is then produced as the CO_2 leaves [30].

Table 2. A summary of methods used for producing PLGA microparticles.

Methods	Advantages	Disadvantages	References
Oil in water (O/W) emulsion	• Simple, economic, and well-controlled procedure. • High entrapment of lipophilic drugs. • Regulate the size of particles by changing homogenization speed, the quantity of stabilizer, the viscosity of organic and aqueous phases.	• The entrapment of hydrophilic drugs is poor. • It is difficult to scale up.	60
Water-in-oil-in-water (W/O/W) emulsion.	•Appropriate for temperature-sensitive compounds. •Control of particle size. •Encapsulation of both hydrophilic and hydrophobic constituents.	•Solvent residuals. • Low yield, accumulation of adhesive particles. •Require controlling the processing parameters. • Protein denaturation due to the presence of an organic solvent. •Large polydisperse particles. •Difficult to scale up.	43

Methods	Advantages	Disadvantages	References
Spray drying	• Encapsulate a wide range of drugs. • The drying step not crucial. •Atomizers enable constant preparation procedures.	•Adhesion of microparticles to inner walls. •Not appropriate for temperature-delicate compounds. •Difficult to control particle size. •Low yield and accumulation of sticky atoms.	[43, 61, 62]
Coacervation method	• Used for thermosensitive drugs. •Inexpensive. •Control shape and size of particles.	• Possible degradation of the components under acidic conditions.	[60, 63]
Supercritical CO_2	•Slight residual of organic solvent.	• Several steps, poor control of size and morphology.	[64]
Coaxial electrospray (CES)	•Nearly 100% encapsulation rate. •Useful for water-soluble molecules •Protects drugs from processing damage. •Control particle morphology.	•Needs additional development process controls. •Not an effective particle collection method.	[30]

2.2. Factors affecting yield, physicochemical characteristics, drug entrapment efficiency, and rate of drug release from PLGA-based microparticles

2.2.1. Chemical Factors

a) Solvents

The choice of organic solvents is considered to be a critical stage in developing successful formulation since solvents can affect size, morphology, drug release and the residual solvent of the microparticles [65]. The encapsulation efficiency is usually improved through a decreasing amount of organic solvent due to an increase in the viscosity of the organic/drug-polymer solution. The most common organic solvents utilized for the preparation of PLGA-based microparticles are acetone, ethyl acetate, dichloromethane, chloroform, and methylene chloride [56, 61, 66].

b) Polymers

The biodegradability and biocompatibility are among the marked properties of the PLGA polymer. PLGA polymer's properties can affect the degradation and release rate of an incorporated drug. This depends upon multiple factors including initial molecular weight, size, constituent's ratio, storage temperature and exposure to water [67-70]. Polymers can erode through surface and bulk erosion mechanisms (Figure 6). Bulk eroding polymers (e.g. PLGA) permit permeation of water into a polymer matrix, and diffusion of the drug out of the sphere into the surrounding medium. Surface eroded polymers (e.g. polyanhydride) resist the penetration of water into the bulk, and thus drug release from the surface occurs as the polymer eroded around it [43].

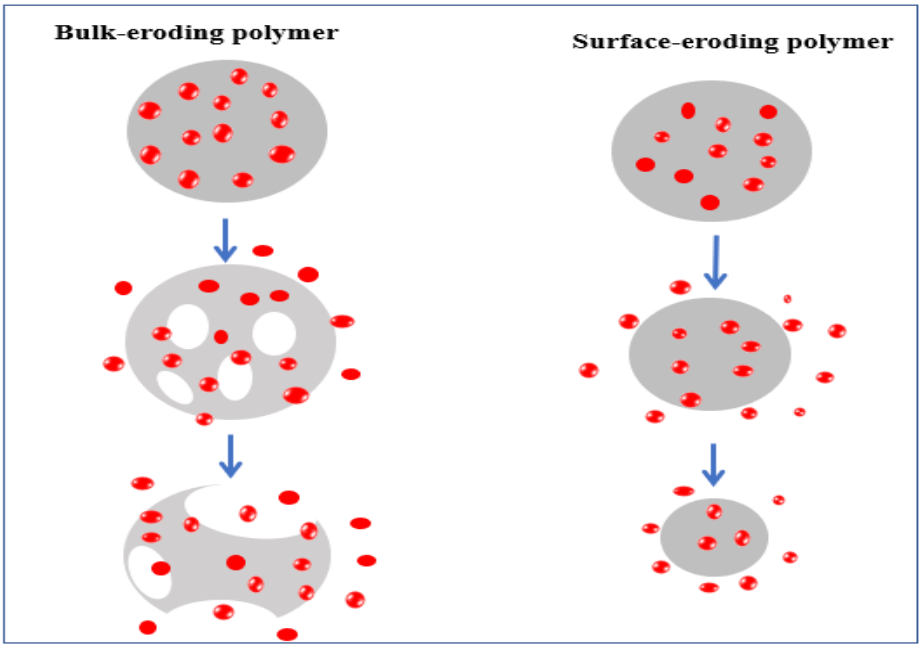

Figure 6. Polymer erosion mechanism: Bulk eroding polymer and surface-eroding polymer as modified from Verde *et al.* [43].

c) Surfactants

The quantity of surfactant is important in the preparation of PLGA microparticles mainly in the emulsification - solvent evaporation process because the surfactant plays an essential role in the protection of droplets against coalescence. The most common surfactants used in preparation of PLGA microparticles are polyvinyl alcohol (PVA), methylcellulose, methylcellulose hydroxyl-propyl methylcellulose, gelatin, cetrimethyl ammonium bromide (CTAB) [43, 71], sodium dodecyl sulphate (SDS), polyoxyethylene sorbitan monooleate (Tween 80), glycerin, dextran derivatives, potassium oleate, didodecyl dimethyl ammonium bromide (DMAB), and d-α-tocopheryl polyethylene glycol 100 succinate (Vitamin E, TPGS) [31, 56].

d) Drug loading

The increase in initial drug loading would presumably increase the mean diameter of microparticles. It was found that a greater amount of drug results in mutual dispersion of the phases and larger particles produced [46].

2.2.2. Physical Factors

a) Agitation speed

The particle size of microparticles decreases with a rise in agitation speed. The geometry of the reactor, the number of impellers and their position, and the viscosity of dispersing and continuous phases must be considered with regard to the agitation speed [72].

b) The ratio between internal and external phases

The stability and size of microparticles in the emulsification-solvent evaporation method can be influenced by the ratio between the external and internal phases of an emulsion. An increase in the volume of internal phase leads to a slight decrease of the microparticle's average size for a given polymer concentration as a result of the prevention of the coalescence of the droplets by a large quantity of organic solvent presented in the oil in water (O/W) emulsion [43].

c) Rate of solvent evaporation

The rate of solvent evaporation depends on its boiling point and vapor pressure and this will affect the

characteristics of the drug-loaded microparticle. The fast rate of solvent evaporation produces smaller particle size and shows lower encapsulation efficiency compared with microparticles that were evaporated by a consistent rate [56, 73-74].

d) Temperature

A gradual increase in the temperature leads to a decrease in the size of microparticles, this is thought to be due to lower viscosity of emulsion at high temperature. However, higher temperature yields a larger size of a microsphere, possibly due to rapid solvent evaporation [75].

e) pH of the external aqueous phase

The type of buffer chosen and its pH can impact on droplet size of the primary emulsion, the microstructure of the microparticles, and PLGA degradation. Increasing the pH of an external aqueous phase causes an increase in the drug entrapment due to a decrease in the degree of ionization and solubility of drugs [43].

f) Pressure

Reducing the pressure exerted throughout the production of microparticle produces smooth surface and smaller size microparticles, and this can improve the encapsulation efficiency [43, 71].

2.3. Methods to enhance drug loading with an acceptable control release rate of PLGA- based microparticles

2.3.1. Physicochemical properties of the drug

The physicochemical properties of the drug including hydrophilicity, molecular size, and charge can markedly affect the loading and release mechanisms of microparticles. The encapsulated drug will be released either through diffusion or bulk erosion of the polymer and the diffusion rate depends on the partition coefficient and drug diffusivity [76]. Hydrophobic drugs can delay water dispersion into microparticulate systems, and this diminishes the rate of polymer degradation [28, 76-78] Thiothixene, haloperidol, hydrochlorothiozide, corticosterone, ibuprofen, and aspirin have the same drug loading, but they have obvious differences in the release rate from PLGA (50:50) microparticles due to the effect of the drug on the polymer degradation and the rate of release [78].

2.3.2. The particle size of the drug

Understanding the relationship between biopolymer composition, microparticle morphology and size are crucial for the formation of materials with pre-determined drug release profiles. Microparticle size and morphology can potentially affect encapsulation efficiency, product injectability, in vivo biodistribution, drug release rate, and efficacy [51, 76, 79-82]. Usually, the best release profiles are attained by microparticles with diameters ranging from 10–200 μm [83]. Therefore, the effect of microparticle size on the drug release rate for certain formulations could be quantitatively predicted [84]. Large diameter particles can diminish the degree of water permeation, polymer degradation, and reduce the rate of drug release [76, 85].

2.3.3. Microparticles degradation mechanisms

PLGA polymer degradation involves diverse mechanisms that drive the release of the drug from microparticles [28]. PLGA is a bioeroding polymer in which the water permeates readily into its matrix and creates pores so that degradation occurs all over the microparticles [43]. There are many factors that affect the biodegradation of microparticles include: chemical structure, molecular weight of polymer, morphology, processing condition, dimension of polymeric device, and site of the application [86].

The degradation mechanism of 50/50 PLGA incorporated in drug-eluting stents occurred heterogeneously. It is started with a rapid decline in the molecular weight of polymer with little mass loss is commenced. This occurs as a consequence of the hydrolysis of ester bonds of PLGA polymer. Subsequently, the size of the polymer becomes smaller and its surface becomes more porous. Degradation products could escape from the matrix and dissolve in the medium. Thus, the mass loss of the 50/50 PLGA begins to be observed [87].

2.3.4. Physicochemical properties of the polymer

The degradation and release rates from PLGA-based microparticles can be achieved by regulating the ratio of lactic acid to glycolic acid of the polymer, the concentration and molecular weight of the polymer in the organic solvent during formulation. Thus, the physicochemical properties of PLGA can influence microparticle morphology [28, 30, 87].

2.3.5. Surfactant type

Distinct types of emulsifiers should be used to maintain the stability and conformation of the droplet and particle during microparticle formulation [88]. The most frequently used surfactant in the preparation of PLGA microparticles is PVA [60], and D-α-tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS). The latter has been found to enhance drug loading at a concentration of 0.3 mg/ml compared to PVA (5mg/ml) owing to higher drug-encapsulation efficiency and cellular uptake compared with the PVA-emulsified preparation [76, 89].

3. PLGA-based microparticles formulations

PLGA is the most commonly used biomaterial for encapsulation and extended delivery of therapeutic agents such as proteins, hormones, antigens, and anticancer drugs [90]. PLGA microspheres were used to encapsulate epigallocatechin-3-gallate (EGCG) using a double emulsion solvent procedure to form a controlled release formulation. The drug loading efficiency of EGCG in PLGA was improved by the complexation of EGCG with beta-cyclodextrin (βCD). This complex can prevent the EGCG from rapidly partitioning to the aqueous phase, thereby improving the drug loading efficiency, slowing the drug release and allowing longer circulation time [91].

A controlled release formulation has been developed with PEGylated human insulin encapsulated in PLGA microparticles, this was found to produce a sustained release formulation in vivo, [92, 93]. Lysozyme was also encapsulated in an unfolded form in biodegradable PLGA microspheres by a double emulsion solvent evaporation method. Urea, an unfolding agent for protein, was added into the incubation medium. The new urea-based formulation exhibited a more sustained lysozyme release profile than the control formulation and presumably was attributed to the suppression of protein aggregation [94].

Recombinant human erythropoietin (rhEPO) loaded onto PLGA microspheres using human serum albumin (HSA) as a stabilizer was prepared by S/O/W technique. The integrity of rhEPO was protected during the encapsulation process and 33 days release period from the polymeric matrices was observed [31]. Biodegradable microparticles for intraocular sustained release of ganciclovir resulted in high ganciclovir loading (95%) and prolonged release of drugs [95].

A modified procedure for the preparation of protein-loaded PLGA microspheres was established by the formation of the lysosome-Zn complex, whereby the complex was loaded into PLGA microparticle using a double emulsion technique. It was observed that the percentage of pelletized lysozyme has reached 80% and the salt type had a marked impact on the magnitude of protein complexation [96].

Rho kinase (ROCK) inhibitor Y-27632, used for the treatment of corneal endothelial disease was incorporated in PLGA microparticles with diverse molecular weights, and different composition ratios of lactic acid and glycolic acid. The microspheres produced have achieved the sustained release of ROCK inhibitor over 7–10 days in vitro and Y-27632 released from PLGA microspheres has significantly encouraged the proliferation of cultured corneal endothelial cells [97].

Villanueva *et al*. have optimized the preparation of small-sized PLGA microspheres encapsulating dexamethasone. The release behavior of dexamethasone was improved by human serum albumin to achieve low burst and sustained release, and this has ultimately improved patient compliance [98]. Parumasivam et al. prepared rifapentine-loaded PLGA microspheres for an inhalation delivery mode by a spray-drying method. PLGA

microspheres with high lactic acid (LA) ratio had a higher tendency for macrophage uptake and encouraged phagocytosis to harbor mycobacterium tuberculosis. In addition, the microspheres obtained have maintained a stable drug concentration in the lung and greatly improved the drug efficacy [99].

Feng *et al.* encapsulated doxorubicin (DOX) and paclitaxel (PTX) at a molar ratio of 2/1 (DOX/PTX) into porous PLGA microspheres. Inhalation delivery of microspheres produced showed high efficiency due to the different drug release rates, and greatly reduced the number of lesions in the tumor-bearing mice [100]. Leuprolide acetate, a luteinizing hormone-releasing hormone analogue (LH-RH), was ion paired with sodium oleate in an aqueous solution. The oleate–leuprolide complex was incorporated into PLGA microparticles based on a single oil-in-water emulsion technique. The formed microparticles demonstrated a lower release time and could be applied for the sustained delivery of other peptides and proteins [45].

The poly-(L-histidine) component of PEG–polyhistidine polymer was attached to the surface of bovine serum albumin (BSA) through ionic interactions. PEG–polyhistidine has significantly improved the stability of BSA in aqueous solutions and PLGA microspheres [101]. Encapsulation complex of cationic lysozyme with variable amounts of anionic polyelectrolyte chondroitin sulfate by a double w/o/w method has generated microspheres with improved encapsulation efficiency and a lower amount of insoluble aggregates related to native lysozyme [101].

Hinds *et al*. established a novel controlled-release preparation with PEGylated human insulin encapsulated in PLGA microspheres that produced a multi-day release polymer in vivo [49, 92]. Guanidinium hydrochloride (GdnHCl) and sodium dodecyl sulfate (SDS) were efficiently complexed using single emulsion and double emulsion methods; microspheres made by the single emulsion method showed a slow release of about 10% during the first five days compared to double emulsion method [49, 102]. Leuprolide was complexed with sodium oleate to form a modified leuprolide–oleate complex which was encapsulated in PLGA microspheres via a single oil-water emulsion method. The microspheres encapsulated with these complexes showed a reduced burst release compared to those encapsulated with free leuprolide which was thought to be due to low aqueous solubility [45, 49].

Conclusion

We have shown that biodegradable microparticles controlled release formulations provide a unique and powerful method to treat chronic diseases due to several factors. They can lower administration frequency, increase compliance of drug therapy, and improve low drug loading. Increasing drug loading using PLGA-microspheres can be achieved by modifying the classical solvent evaporation methods, preparation of multi-layered microparticles, and the development of novel methods for microparticle fabrication including coaxial electrospray, spray drying, and supercritical CO_2. Consequently, PLGA biodegradable microparticles can provide a long-term delivery system of drugs and might help pharmaceutical industry to decide on the fate of new chemical entities with disadvantaged physicochemical properties.

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تحلل جسيمات حمض بولي لاكتيك – جليكوليك (PLGA) المستخدمة في مراقبة أنظمة الايصال للأدوية – (مراجعة)

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ملخص

تمثل الجسيمات المجهرية نظامًا واعدًا لإيصال الأدوية حيث أنها تقوم بتزويد كمية محددة من الدواء إلى موقع العمل فـي الجسم وكذلك توفر الحماية للأدوية غير المستقرة قبل وبعد تناولها. حمض بولي لاكتيك–جليكوليك (PLGA) عبارة عن بوليمر معتمد من إدارة الغذاء والدواء (FDA) والذي كان من بين أكثر المرشحات البوليمرية المستخدمة للسيطرة على توصيل الدواء. يمتاز PLGA بعدة خصائص من أهمها أنه متوافق حيوياً و قابل للتحلل البيولوجي، وقد أستخدم على نطاق واسع لتطوير الأدوية وتوصيل الجزيئات الصغيرة و الكبيرة والبروتينات إلى المكان المراد.

توضح هذه المخطوطة تقنيات التصنيع المختلفة للجسيمات الدقيقة القائمة على PLGA والعوامل المؤثرة على تحللها وإطلاقها، و مناقشة فعالية إستخدام بوليمر PLGA القابل للتحلل في تركيبات هذه الجسيمات الدقيقة وتطبيق التحديث لهذه الاستراتيجية من خلال عدة طرق للايصال الدواء.

الكلمات الدالة: الجسيمات الدقيقة، نظام التسليم المتحكم به، بولي لاكتيك–جليكوليك، قابلية التحلل الحيوي، عقاقير جزيئية صغيرة.

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