



# Poly(lactic acid)/poly(lactic-co-glycolic acid)-based microparticles: an overview

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## Abstract

**Background** Poly(glycolic acid), poly(lactic acid) and poly(lactic-co-glycolic acid) were approved by the United States Food and Drug Administration (FDA) in the 1970s as materials for the manufacturing of bioresorbable surgical sutures, but soon became the reference materials for the preparation of sustained release formulations, especially injectable microparticles. Since the 1986 approval of Decapeptyl<sup>®</sup> SR, the first product based on PLGA microspheres, more than 15 such products have been approved for clinical use.

**Area covered** This article highlights the key steps that brought to the development of injectable poly(lactic acid)/poly(lactic-co-glycolic acid) microparticles for the sustained release of active pharmaceutical ingredients. After a brief history of some pioneering works that opened the field of controlled drug delivery, the key steps that led to the development of these polymers and the approval of the first microparticle-based medicinal products are reviewed. Finally, the general characteristics of these polymers are described and the classical preparation method is explained.

**Expert opinion** Poly(lactic acid)/poly(lactic-co-glycolic acid) microparticles are among the most successful drug delivery systems. The recent approval of new medicinal products based on PLGA microspheres is the proof that pharmaceutical companies have continued to exploit this drug delivery technology. The possible development of generics and the continuous discovery of therapeutic peptides will hopefully further the success of microsphere technology.

**Keywords** Microspheres · Drug delivery systems · Long-acting injections · PGA · PLA · PLGA

## Prologue

Poly(glycolic acid) or poly(glycolide) (PGA), poly(lactic acid) or poly(lactide) (PLA), and poly(lactic-co-glycolic acid) or poly(lactide-co-glycolide) (PLGA) are among the few polymers approved by regulatory agencies for clinical use. Soon after their approval as materials for the manufacturing of bioresorbable surgical sutures, PLA and PLGA become the reference materials for the production of injectable controlled release systems, especially microparticles. Since the 1986 approval of Decapeptyl<sup>®</sup> SR, the first product

based on PLGA microspheres, more than 15 such products based on this technology have been approved and marketed.

Today, research on PLA/PLGA microparticulate systems is experiencing a sort of revival. With many approved products on the market, injectable PLA/PLGA microparticles are considered a consistent drug delivery system (Qi et al. 2018), and hold particular promise for the delivery of therapeutic peptides, a field of discovery in continuous growth (Lau and Dunn 2018). In addition, with the expiration of the first patents, pharmaceutical companies have been interested in the development of generic PLA/PLGA-based products, a difficult process that will require additional academic, industrial and regulatory research. In fact, the demonstration of pharmaceutical equivalence and bioequivalence for PLA/PLGA microparticulate products is much more complicated than that of medicinal products based on conventional oral dosage forms, such as immediate release tablets or capsules (Wang et al. 2017). Last but not least, PLA/PLGA microparticulate products, as part of the drug delivery device market sector, may be profitable for pharmaceutical companies. In

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To the memory of Dr. Patrick P. DeLuca who sadly passed away on May 22 2019.

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fact, in 2016 the global drug delivery device market was valued at more than 330 billion USD and is expected to reach about 930 billion in 2024 (Karlsson 2017).

This article does not offer an extensive review the field of injectable microparticulate systems, but instead describes the key steps that led to the development and commercialization of injectable PLA/PLGA microparticles. Some pioneering works that opened the field of controlled drug delivery are presented, and then the early development of PGA, PLA, and PLGA for bioresorbable surgical sutures and the development and approval of the first microparticle products are briefly reviewed. The general characteristics of these polymers and the classical preparation method are also described.

## Controlled release and microencapsulation

Without a doubt, pharmacological therapies have been having a positive impact on human health and have surely contributed to the postponement of mortality (Vaupel 2010). For many centuries, the medicinal products used by human beings have been exclusively of natural origin, from plants, animals and minerals, and conclusions about their curative properties have been based on empirical evidence. Only in the last century or so has the search for remedies to fight human diseases become an interdisciplinary science-based research field, namely, *drug discovery and development* (Drews 2000; Scheindlin 2001). Nowadays, research towards the development of a new medicinal product requires the contribution of many scientific disciplines including, but not limited to, physics, chemistry, biology, engineering, and medical sciences. Obviously, pharmacology and medicinal chemistry have a prominent role in the long and complex process of drug discovery and development.

The development of the concepts of *bioavailability and bioequivalence* in the 1960s opened the way to a new and more complex vision of the medicinal product. For many decades, and sometimes still now, scientists focused exclusively on the *active pharmaceutical ingredient* (API) and not on the medicinal product as a complex whole. In contrast, now it is clear that even if the pharmaceutical excipients and the formulation itself do not contribute directly to the pharmacological activity of the API, they nonetheless guarantee the quality, the stability and in vivo performance of the medicinal product (Rowland et al. 2012).

Since in general the limiting step for API absorption is its release from the dosage form, it was obvious that the best way to control API absorption and concentration in the systemic circulation is to control its release. In fact, the 1960s saw the rise of a new discipline in the field of pharmaceutical science: *drug delivery science and technology*.

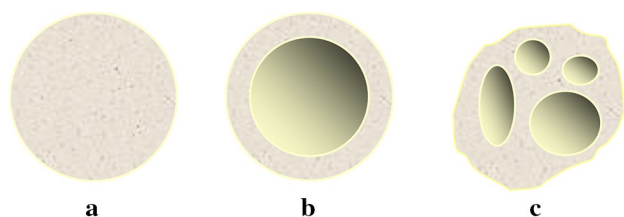
The first controlled release formulation was introduced in 1952 (Helfand and Cowen 1983) and the first patent on microcapsule preparation was issued in 1957 (Ranger 1974), but the 1960s saw three pioneering works that opened the way to drug delivery science and technology.

In 1961, Professor Takeru Higuchi published his seminal paper, “Rate of release of medicaments from ointment bases containing drugs in suspension”. In this now famous work, he derived an equation on the rate of release of solid drugs suspended in ointment bases in perfect sink conditions, since known as the “Higuchi equation” (Higuchi 1961). The possibility of using mathematical models to predict the release of the API from dosage forms opened the way to rationalizing formulation design according to therapeutic needs (Higuchi 1963). In 1964, Professor Judah M. Folkman, together with Dr. David M. Long, published the paper entitled “The use of silicone rubber as a carrier for prolonged drug therapy” (Folkman and Long 1964), demonstrating the possibility of producing devices able to deliver controllable amounts of drugs for long period of times, from weeks to months. Again in 1964 (Chang 1964, 1988),<sup>1</sup> Professor Thomas M.S. Chang reported the successful preparation of enzyme-loaded semipermeable microcapsules, later called artificial cells (Chang 2005), that could be used as enzyme replacement therapy (Chang and Poznansky 1968). Obviously, the same technology could be applied to microencapsulate small organic compounds to take advantage of their diffusion through the membrane, generating controlled release microparticulate systems.

These pioneering works introduced the basic concepts for controlled release and microencapsulation. Some of these early ideas led to the development and commercialization of what has been called the first generation of drug delivery systems (DDSs) (1950–1980), for the most part oral, ocular and transdermal formulations (Yun et al. 2015; Park 2014). Technologies like Ocusert<sup>®</sup>, Oros<sup>®</sup>, or Transderm-V<sup>®</sup> have revolutionized the way of administering active compounds (Zaffaroni 1981; Peppas 2013). In fact, the control of API release/absorption rates offers a number of benefits, such as reduction of fluctuations in API plasmatic concentration, improvement of therapeutic efficacy, limitation of side effects, and reduction of the frequency of administration (Burgess and Wright 2012).

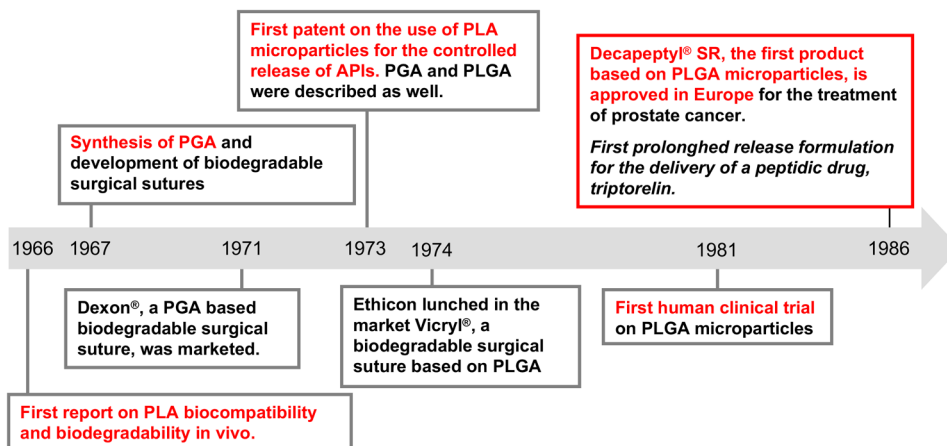
The following three decades (from 1980 to 2010) saw the development of the so-called second generation of DDS (Yun et al. 2015; Park 2014). During these years, research on macroscopic devices was eclipsed by the growing interest in

<sup>1</sup> The method to produce hemoglobin loaded semipermeable microcapsules was originally reported by Chang in 1957 and reprinted in 1988 as part of the 30th Anniversary in artificial red blood cells research.



**Fig. 1** Schematic representation of the internal structures of different kinds of microparticles: **a** microsphere, **b** mono-nuclear microcapsule and **c** a poly-nuclear microcapsule

**Fig. 2** Timeline (1966–1986) indicating the most important scientific breakthroughs that led to the development and commercialization of the first injectable product based on PLGA microspheres



microscopic and nanoscopic systems that could be delivered parenterally. Between the end of the first and the beginning of the second generation of DDS, the *successful story of PLA/PLGA microparticles* began.

## PLA/PLGA-based microparticles

### General considerations

Microparticles measure between 1 and 1000  $\mu\text{m}$  (sometimes 1–800  $\mu\text{m}$ ), whereas nanoparticles or colloids have a mean diameter  $< 1 \mu\text{m}$ . Depending on their internal structure, microparticles may be further classified as microspheres and microcapsules. *Microspheres* are generally formed by a homogeneous matrix in which it is not possible to distinguish a core and a membrane, and the API is dispersed in the polymer matrix either molecularly or as small clusters. The terms *microspheres* and *microparticles* are often used synonymously, as in this article. *Microcapsules* are systems constituted by a central liquid, solid, or semisolid core containing the API, alone or in combination with excipients, surrounded by a continuous polymer coating or membrane. Multiple nuclei may also be present (Fig. 1) (Benita 1996; Burgess and Wright 2012).

Microparticles smaller than 200  $\mu\text{m}$ , ideally in the range 50–100  $\mu\text{m}$ , can be easily administered by injection and generally do not provoke any pain or discomfort (Kissel et al. 1991; Wu 1995; Jain 2000). Injectable polymeric microspheres were studied as controlled release dosage forms to avoid the inconvenient surgical insertion of larger implants characteristic of the first generation DDS (Kleiner et al. 2014). Obviously, to avoid surgical procedures, the polymer material had to be completely biodegradable, a feature encountered in the homo- and co-polymers of lactic and glycolic acids. In fact, the real breakthrough in the development

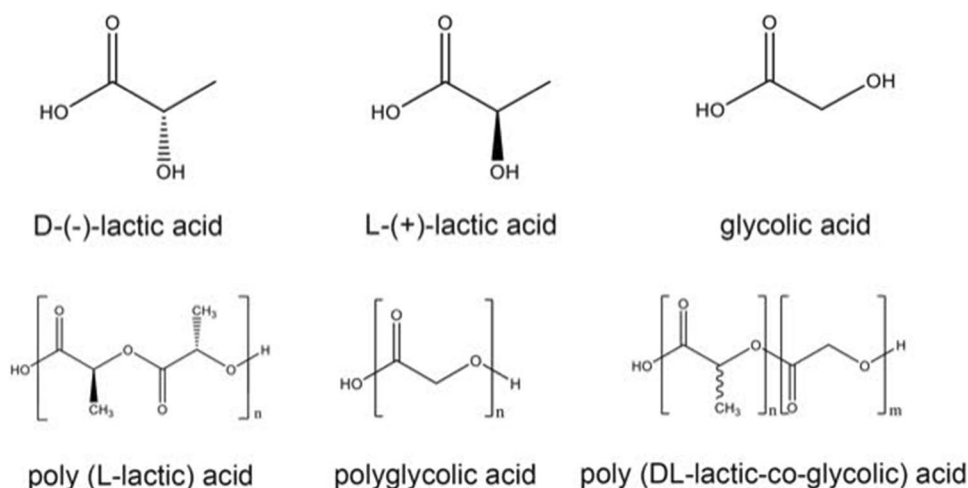
and clinical application of injectable polymeric microparticles has been the development and the clinical approval of these polymers.

### From sutures to microspheres

Homo- and co-polymers of lactics and glycolic acids were studied in the 1950s and 1960s but their clinical approval and commercialization began in the 1970s (Fig. 2). PLA was synthesized in the 1930s, only at the end of 1950s was it obtained at high enough molecular weights to be used in the production of resistant films and fibers (Schneider 1955; Farah et al. 2016). Their potential biomedical applications started to come to light in the following decade when, in 1966, Kulkarni et al. demonstrated that PLA could be used as a material for surgical implants, since it was non-toxic and did not induce tissue reaction. The polymer was also completely degraded in vivo, producing lactic acid that was metabolized in the body (Kulkarni et al. 1966).

In 1967, Schmitt and Polistina patented a method for the production and the application of PGA absorbable surgical sutures (Schmitt and Polistina 1967) that were marketed 4 years later with the trade name of Dexon® (Frazza and Schmitt 1971; Sugar et al. 1974). Researchers at Ethicon

**Fig. 3** Molecular structures of the monomers D-(-)-lactic acid, L-(+)-lactic acid, glycolic acid, of the homopolymers poly(L-lactic acid) and poly(glycolic acid) and the co-polymer poly(DL-lactic-co-glycolic acid)



modified the existing PGA synthesis and, by adding lactic acid, easily obtained PLGA. Vicryl<sup>®</sup>, a bioresorbable suture based on PLGA, was launched on the market by Ethicon in 1974 (Ratner et al. 2013) (Fig. 2).

In the early 1970s, PLA, PGA, and PLGA polymers started to be available in clinics as biodegradable surgical sutures, and their exceptional characteristics of biocompatibility, biodegradability, and mechanical strength could not remain unnoticed by pharmaceutical scientists, who started to glimpse their possible applications in the emerging field of drug delivery. In fact, in 1973, the first patent describing the preparation of PLA-based devices, including microparticles, for the sustained release of APIs (entitled “Polylactide-drug mixtures”) was granted to Boswell and Scribner (1973) (Fig. 2). Shortly after, in the early 1980s, the Swiss based pharmaceutical company Debiopharm started to develop a PLGA microsphere formulation for the sustained release of triptorelin. The therapeutic peptide was successfully microencapsulated by employing a methodology developed by the Southern Research Institute and Syntex Research team for another peptide, nafarelin acetate. In 1986, Debiopharm launched on the market Decapeptyl<sup>®</sup> SR, a triptorelin sustained release formulation based on injectable PLGA microspheres for the treatment of prostate cancer (Sanders et al. 1984; Tice 2017). In 1989 Lupron Depot<sup>®</sup>, a microsphere formulation of leuprolide acetate for the treatment of prostate cancer, was approved, followed by Parlodel LA<sup>®</sup> (bromocriptine mesilate), Sandostatin LAR<sup>®</sup> (octreotide acetate), and many others (Schoubben et al. 2019). As mentioned, more than 15 products based on PLA/PLGA microparticles have been approved and marketed. By considering also different PLA/PLGA formulations, such as preformed and in situ forming depots, more than 35 products have been successfully developed (Tice 2017). A list of the medicinal products based on PLA/PLGA microparticles can be found

in recent reviews (Wischke and Schwendeman 2012; Jain et al. 2016; Zhong et al. 2018; Schoubben et al. 2019).

From this brief historical overview, it is clear that the success of injectable microspheres is substantially due to the development of the lactic and glycolic acid polymer family.

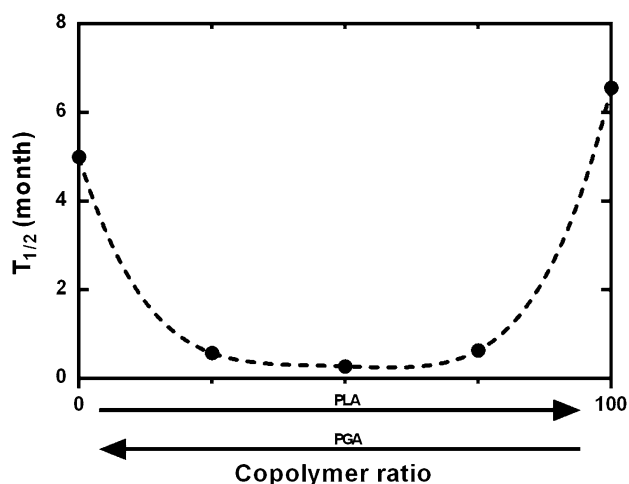
### Polymer features

PLA has two semi-crystalline enantiomeric isomers, poly(L-lactic acid) and poly(D-lactic acid), while its optically inactive racemic form, poly(DL-lactic acid), is amorphous. PGA is a highly crystalline polymer, more hydrophilic than PLA (Fig. 3). Even if PLA and PGA are the “originators” of the field, their use in the formulation of injectable microspheres has been very limited.

PLA has generally long degradation rates and, for this reason, has been employed in the preparation of the 3, 4, and 6-month formulations of Lupron Depot<sup>®</sup>, a microsphere-based leuprolide acetate formulation originally approved in the USA in 1989 (Wischke and Schwendeman 2012). Another marketed product based on PLA microparticles is Sculptra<sup>®</sup>, a cosmetic product for the treatment of facial lipoatrophy, approved in 2004 by the FDA. These microparticles are used as filler and have no encapsulated API (Jain et al. 2016).

PGA is not present in microsphere-based commercialized products. It was studied in the late 1980s as a polymer material for the preparation of injectable microspheres but their characteristics, such as its high hydrophilicity, high degradation rate and the high porosity of the produced particles, did not allow for long-term releases of the embedded therapeutic compounds (Sato et al. 1988; Redmon et al. 1989; Lee et al. 1991).

The real star of this polymer family is PLGA (Fig. 3), the copolymer used for practically all the microsphere based products commercialized. In fact, even Lupron Depot<sup>®</sup> has a



**Fig. 4** Half-life (in months) of various ratios of PLA and PGA as copolymers implanted in rat tissue Reproduced with permission from Miller et al. (1977)

PLGA one-month depot formulation (Wischke and Schwendeman 2012; Jain et al. 2016).

Since PLGA is synthesized from lactic and glycolic acid, it may be customized to obtain the desired features in terms of hydrophilicity/lipophilicity and degradation rate. In fact, copolymers containing a high fraction of lactic acid are less hydrophilic, absorb less water and degrade more slowly than PLGA containing a higher percentage of glycolic acid (Fig. 4) (Miller et al. 1977). PLGA degradation rate is also affected by the polymer molecular weight, the polydispersity index, and the nature of the end-chain (Makadia and Siegel 2011). Additional customization was achieved by the production of a star-like branched PLGA with D-glucose, which enabled a fast degradation rate. This polymer was used to develop Parlodel LAR<sup>®</sup>, a once-a-month bromocriptine microsphere formulation. Parlodel LAR<sup>®</sup> replaced Parlodel LA<sup>®</sup>, the degradation rate of which was too long, thus precluding repeated administration (Kissel and Rummelt 1990).

PLGA may be semi-crystalline or amorphous as a function of its composition. PLGA crystallinity is influenced by the stereochemistry of the lactic acids and the molar ratio of glycolic and lactic acids. In fact, co-polymers composed of L-PLA and PGA are semi-crystalline, while those prepared with D,L-PLA and PGA are amorphous. Since the embedded APIs are generally dispersed more homogeneously in an amorphous polymer than in a semi-crystalline one, D,L-PLGA can be preferable.

Since D,L-PLGA is amorphous, one of its most important physico-chemical properties is the glass transition temperature ( $T_g$ ), at which a highly viscous brittle structure (glass) transitions to a less viscous, more mobile, rubbery state. The rubbery state (achievable at temperatures above the  $T_g$ ) has a liquid-like structure with higher polymer chain mobility than

the glassy state. Polymers in their rubbery state are more prone to physical and chemical changes. For instance, the diffusion coefficient of small molecules through a rubbery polymer is several orders of magnitude greater than in the same polymer at a glassy state (Karlsson et al. 2001), and this can have a profound impact on the release mechanism and kinetics (Albertini et al. 2015). When studying the role of the  $T_g$  on PLGA microparticle degradation and release, it should be always kept in mind that water has a strong plasticizing effect and thus the system has to be investigated in its hydrated state (Passerini and Craig 2001; Blasi et al. 2005). Generally, PLGA  $T_g$  decreases in several conditions: with the reduction of lactic acid content, the reduction of its molecular weight, and the addition of compounds, either excipients or APIs, that act as plasticizers (Jamshidi et al. 1988; Fernández-Carballido et al. 2004; Blasi et al. 2007).

In sum, D,L-PLGA has become the form of choice because it is possible to tailor not only its hydrophilicity and degradation rate, by making changes to its composition and molecular weight, but also its polymer physical state from semi-crystalline to amorphous. In fact, most of the PLGA microparticle products on the market are formulated with D,L-PLGA.

PLGA biodegradability and the formation of by-products compatible with the body are surely two other fundamental features of this polymer.

The degradation mechanism of PLGA is a complex matter in and of itself. Even if it has been studied since the 1960s and 1970s (Kulkarni et al. 1966; Miller et al. 1977) and huge advances have been made in the understanding of in vitro degradation mechanisms (Pitt et al. 1981; Li et al. 1990; Reich 1997; Vert et al. 1998; Siepmann et al. 2005), a complete understanding has yet to be achieved, since many factors affect polymer degradation and the consequent API release.

PLGA co-polymers undergo degradation in the presence of water, both in vitro and in vivo. The ester bonds are cleaved by hydrolytic degradation occurring throughout the whole PLGA microparticle matrix. PLGA degradation can be divided into three phases. In the first phase of random chain scission, the molecular weight of the polymer decreases significantly while the weight loss and soluble monomer formed are not appreciable. During the middle phase there is further decrease of the molecular weight and rapid loss of mass, with the production of soluble oligomers and monomers. In the last step the polymer disappears completely, because of the formation of soluble monomers. Once the monomers are formed, they are eliminated by physiological pathways. Lactic acid enters the tricarboxylic acid cycle and is metabolized and eliminated in carbon dioxide and water, while glycolic acid is excreted unchanged by the kidneys or metabolized by the tricarboxylic acid cycle (Jain et al. 1998; Sinha and Trehan 2003; Elmowafy et al. 2019).

PLGA degradation is probably homogeneous in very small microspheres, while in large microparticles or macroscopic devices, hydrolytic degradation is generally heterogeneous. In fact, during the degradation process, the number of carboxylic end groups increases and acid autocatalysis enhances the PLGA degradation rate (Pitt et al. 1981; Li et al. 1990; Li 1999; Siepmann et al. 2005; Li and Schwendeman 2005). A pH as low as 1.5 has been measured within microspheres of about 40  $\mu\text{m}$  (Fu et al. 2000). This acidic microenvironment is clearly deleterious for fragile molecules like proteins. How it affects the release kinetics from PLGA microspheres has yet to be fully elucidated. Siepmann et al. (2005) highlighted the importance of the autocatalytic effects in PLGA degradation and drug release kinetics from microparticles and, more recently, Mylonaki et al. (2018) called attention to how the accumulation of acidic by-products affects PLGA microparticle porosity (non-homogeneous pore distribution) and internal structure evolution.

The development of an acidic internal microenvironment also depends on the nature of the API and excipients embedded in the system (Li and Schwendeman 2005). For instance, basic molecules may interact with the polymer matrix, and as a result either accelerate or decelerate the degradation, according to two envisioned mechanisms. In the first, basic molecules may behave as catalysts on the ester bond cleavage, enhancing the polymer degradation rate (Cha and Pitt 1989; Selmin et al. 2012). Instead, in the second, opposite mechanism, it is thought that basic molecules shield the polymer terminal carboxylic residues, decelerating the catalytic effect of the acidic end chains on polymer degradation (Mauduit et al. 1993; Miyajima et al. 1998).

### **Microparticle preparation: the solvent diffusion/evaporation technique**

Microparticles may be produced by many different methods, generally classified as chemical and physical according to the processes involved in particle formation. Chemical methods start with polymer monomers or oligomers, and particle formation occurs through chemical reactions in which new covalent bonds form. Practically, the polymer is formed at the same time as the particle for instance in a process of interfacial polymerization. Physical methods generally exploit interactions among solvents, APIs, excipients and preformed polymers. The most widely used are emulsion solvent diffusion/evaporation (including double or multiple emulsions), phase coacervation, salting out, spray-drying, spray congealing, and techniques based on supercritical fluids (Benita 1996; Jain 2000; Lu and Park 2012). All these methodologies were proposed and optimized in the 1990s and early 2000s for the preparation of PLA/PLGA microspheres (DeLuca et al. 1993; Conte et al. 1994; Li et al. 1995; Thomasin et al. 1998; Lee et al. 2006). Now, most

commercialized products are prepared by solvent diffusion/evaporation, solvent extraction, phase separation, and spray drying methods (Schoubben et al. 2019).

The solvent diffusion/evaporation technique has several important advantages. It is low cost, easy to perform at the laboratory scale, and can be employed with virtually all APIs. However, the needs of organic solvents and the difficulty of scale up are the drawbacks that limited its use at industrial level.

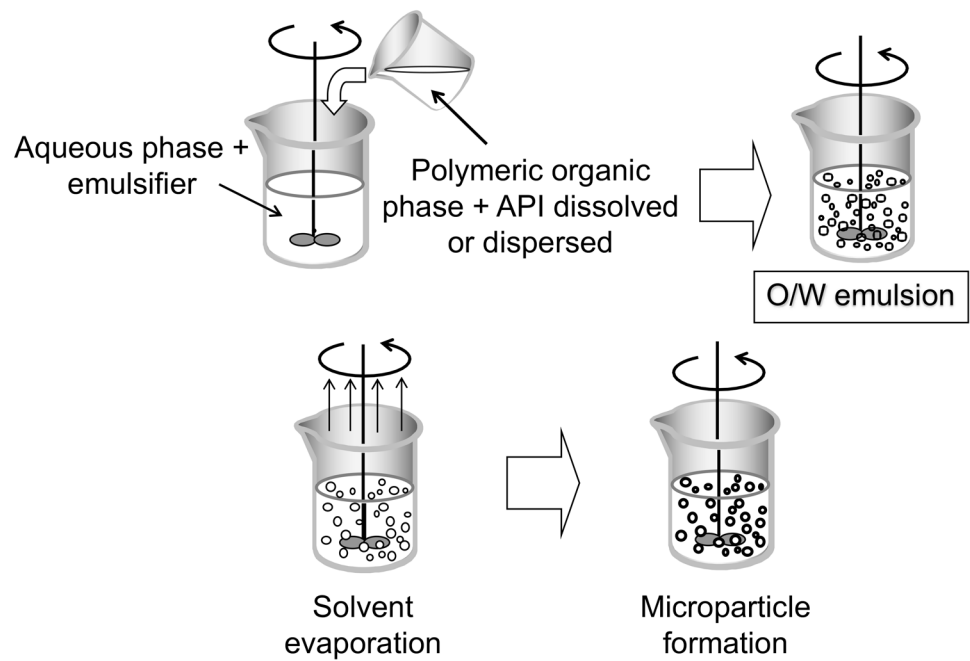
The principle of this method is the emulsification of a polymer solution (methylene chloride is generally used as volatile solvent) in an aqueous continuous phase (oil-in-water emulsion) by mechanical agitation. Figure 5 illustrates the method phases. The API may be either dissolved or dispersed in the polymer solution (oily phase) of the emulsion. Agitation of the system is continued until the solvent partitions into the aqueous phase and is removed by evaporation. This process results in hardened microspheres which are recovered by filtration or centrifugation and lyophilized. Correct evaporation temperature during the procedure allows for better elimination of the volatile solvent and control of particle structure and morphology.

The oil-in-water single emulsion technique has been successfully used to encapsulate poorly water soluble APIs. Instead, with water soluble molecules such as proteins and peptides, a double emulsion technique is employed because otherwise encapsulation of these molecules generally results in rapid partitioning between the internal phase and the external aqueous phase, leading to microparticles with poor loading (Jalil and Nixon 1990). In the double emulsion technique, the water solution of hydrophilic APIs is emulsified with the organic solvent polymer solution, which is then further emulsified with the external phase of water and a stabilizer, generally polyvinyl alcohol. In the case of fragile molecules such as proteins, the encapsulated compound is protected from the denaturing effect of organic solvents and hydrophobic surfaces by the addition of sugars or hydrophilic polymers (Giovagnoli et al. 2004).

Besides the solvent diffusion/evaporation process, an extraction process can be used to eliminate solvent from the emulsion. Extraction can be achieved by using either large volumes of the aqueous dispersing phase or non-solvents. Solid microspheres may be successively collected by filtration or centrifugation, washed to eliminate the stabilizer/emulsifier, and finally vacuum dried or freeze-dried to give a final free flowing powder (Couvreur et al. 1997; Jain 2000; Freitas et al. 2005).

Several methods can be used to achieve the dispersion of the oil phase in the continuous external phase. The most common method is mechanical stirring. As the stirring speed is increased, there is generally a decrease in the size of the dispersed droplets and of the future solid particles. In addition to agitation, other factors that influence the

**Fig. 5** Schematic representation of the solvent diffusion/evaporation technique



physicochemical characteristics, encapsulation efficiency, and release kinetics of microparticles are surfactant concentration, rate of solvent evaporation, temperature, solvent type and volume, polymer molecular weight and organic/water phase ratio (Couvreur et al. 1997; Jain 2000; Freitas et al. 2005).

Ideally, high API encapsulation is desirable so as to maximize its amount in the minimal amount of polymer and thus reduce the quantity of administered microparticles. Therefore, the preparation method has to be optimized in order to achieve a high yield of microparticle recovery, the desired particle physico-chemical characteristics, and the highest API loading in its active form. In addition, the excipients and solvents used during microparticle preparation should be non-toxic or removable. Solvents that have been used to prepare microparticles include dichloromethane, acetonitrile, ethyl acetate, chloroform and benzene (O'Donnell and McGinity 1997). Apart from polyvinyl alcohol, typical emulsifiers include polyvinylpyrrolidone, alginates, methylcellulose and gelatin (Couvreur et al. 1997).

The solvent diffusion/evaporation technique can be considered the *classical preparation method* for polyester microparticles since it has been largely employed for research purposes at the laboratory scale and also in the manufacturing of some commercial products (O'Donnell and McGinity 1997; Schoubben et al. 2019). The solvent diffusion/evaporation technique has been extensively exploited at the laboratory scale and the results published in a wide range of articles have surely contributed to the success of PLGA microspheres as injectable DDSs.

## Concluding remarks

Injectable PLGA microparticles have been in use in clinics for over 30 years and their clinical success is unquestioned. With four new medicinal products approved in the last 5 years (pasireotide pamoate, Signifor Lar<sup>®</sup>; triptorelin pamoate, Triptodur<sup>™</sup>; triamcinolone acetonide, Zilretta<sup>®</sup>; and exenatide, Bydureon Bcise<sup>®</sup>) (Jain et al. 2016; Zhong et al. 2018; Schoubben et al. 2019), PLGA microparticles seem to have a promising future. Most probably, PLGA microparticulate products will continue to be investigated and marketed for the delivery of peptides and, hopefully, proteins that require parenteral administration. However, the development of PLGA microparticles for protein delivery is not an easy task and, at the moment, no products are on the market. In fact, Nutropin Depot<sup>®</sup>, the only microparticulate product ever approved (1999) for the delivery of a protein, somatotropin, has been discontinued (Mohammadi-Samani and Taghipour 2015; Tice 2017).

Surely, the continuation of the general success of PLGA microparticles will also depend on the development of generic products, as medicinal products based on PLGA microparticles tend to be expensive (Wang et al. 2017). This is not an easy task, first, because demonstration of pharmaceutical equivalence is complicated by the complexity of the systems, since small differences in the polymer chemistry or in the particle size and morphology may have significant effects on the API release profile (Klose et al. 2006). Second, the demonstration of bioequivalence is complicated by the lack of consistent *in vitro* release

methodologies able to establish in vitro-in vivo correlation (Shen and Burgess 2015).

PLA/PLGA in situ forming depots will also play a role in the drug delivery arena, especially in small molecule APIs. At the moment, at least 6 products are on the market; the most recent (risperidone, Perseris™) gained FDA approval in November 2018 (American Pharmaceutical Review 2018) and was launched by Indivior at the end of February 2019 (Indivior 2019). It is interesting to note that the formulation of risperidone as in situ forming depot offers some advantages over PLGA microparticles (Risperdal Consta®). Risperidone, being a tertiary amine, accelerates polyester degradation by catalyzing the hydrolytic cleavage of the polymer chain ester bonds. This obviously causes problems during the design, manufacturing and storage of the product (Selmin et al. 2012). In Perseris™, this issue is bypassed because PLGA and risperidone are mixed extemporaneously and come into contact just before injection. In addition, unlike Risperdal Consta®, this formulation is able to release therapeutic concentrations of risperidone for 1 month without the need of loading doses or oral supplementation (American Pharmaceutical Review 2018; Janssen Pharmaceuticals 2019).

In conclusion, the future of PLA/PLGA microspheres, and more in general that of PLA/PLGA injectable DDSs, is very bright. Obviously, this will continue to be the case if academics, industry and regulatory bodies will carry out research to address the open issues that remain to be resolved.

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## Compliance with ethical standards

**Conflict of interest** The author declares no conflicts of interest.

**Statement of human and animal rights** This article does not contain any studies with human and animal subjects performed by the author.

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